Neuroscience at a Glance

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Neuroscience at a Glance

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Introduction

Neuroscience at a Glance is designed primarily for undergraduate medical students as a revision text or review of basic neuroscience mechanisms, rather than a comprehensive account of the field of medical neuroscience. The book does not attempt to provide a systematic review of clinical neurology. However, it should also be of use for those in clinical training and practice wanting a review and synopsis of the science behind the clinical practice.

The changing nature of medical training in this country has meant that rather than teaching being discipline based (anatomy, physiology, pharmacology, etc.), the current approach is much more integrated with the focus on the entire system. Students pursuing a problem-based learning course will also benefit from the concise presentation of integrated material.

This book summarises the rapidly expanding field of neuroscience with reference to clinical disorders, such that the material is set in a clinical context. In general, the later chapters contain more clinical material whilst the earlier ones contain a section towards the end outlining applied neuroscience. However, learning about the organisation of the nervous system purely from clinical disorders is short-sighted as the changing nature of medical neuroscience means that areas with little clinical relevance today may become more of an issue in the future. An example of this is ion channels and the recent burgeoning of a host of channelopathies. For this reason some chapters focus more on scientific mechanisms with less clinical emphasis.

Each chapter presents the bulk of its information in the form of an annotated figure, which is expanded in the accompanying text. It is recommended that the figure is worked through with the text rather than just viewed in isolation. The condensed nature of each chapter means that much of the information has to be given in a didactic fashion, but a list of suggested further reading for each chapter is given at the end of the book. Although the text focuses on core material, some additional important detail is also included.

The book has broadly been divided up into sections on the structure and biophysics of the nervous system (Chapters 1–16); the sensory components of the nervous system (Chapters 17–28); the motor components of the nervous system (Chapters 29–35); the autonomic, limbic and brainstem systems underlying wakefulness and sleep (Chapters 36–39) and finally neural plasticity and clinical disorders of the nervous system (Chapters 40–47). A list of further reading and glossaries of neurological conditions and neuroscientific terms are available free of charge from the Blackwell Science website, see the inside front cover for further details.

Each section builds on the previous ones to some extent, and so reading the introductory chapter may give a greater understanding to later chapters in that section; for example, the somatosensory system chapter may be better read after the chapter on the general organisation of sensory systems.

Acknowledgements

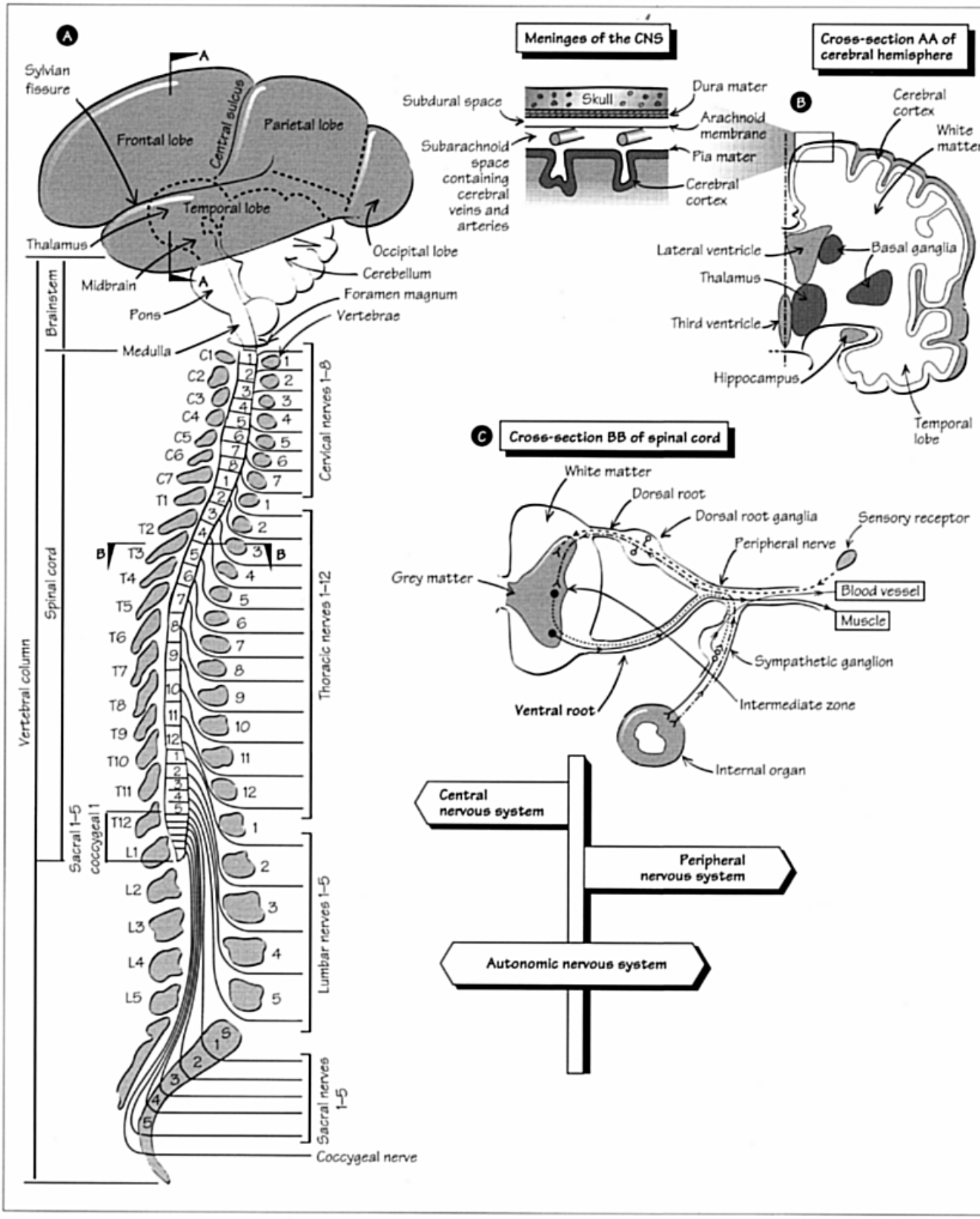
The focus and content of *Neuroscience at a Glance* owes a great deal to the numerous groups of students who have wrestled with the difficult and rapidly changing subject of neuroscience. There are a large number of people we would like to thank for their help in the writing of this book; this includes our colleagues at Cambridge and Cardiff who have patiently read through the various drafts of the manuscript and given their honest opinion. In addition, we would especially like to thank Andrew Larner for diligently correcting the wayward ways of our writing and highlighting errors or poorly formulated explanations and Mike Neal for his important sections on neuropharmacology which have provided valuable additional information.

We would also like to thank Mike Stein and Patricia Hardcastle at Blackwell Science for their endless enthusiasm, support and encouragement for this project. Finally, we would like to thank our families for allowing us to spend so much time on this book.

Roger Barker & Stephen Barasi
Cambridge & Cardiff
May 1998

Part 1 The anatomical and functional organisation of the nervous system

1 The organisation of the nervous system



An overview

The nervous system can be divided into three major parts: the **autonomic** (ANS), **peripheral** (PNS) and **central nervous system** (CNS). The PNS is defined as those nerves that lie outside the brain, brainstem or spinal cord, while the CNS embraces those cells that lie within these structures.

Peripheral nervous system (PNS)

The PNS consists of nerve trunks made up of both afferent fibres or axons conducting sensory information to the spinal cord and brainstem, and efferent fibres transmitting impulses primarily to the muscles. Damage to an individual nerve leads to weakness of the muscles it innervates and sensory loss in the area from which it conveys sensory information. The peripheral nerves occasionally form a dense network or plexus adjacent to the spinal cord (e.g. brachial plexus in the upper limb). The peripheral nerves connect with the spinal cord through foramina in the bones (or **vertebrae**) of the spine (or **vertebral column**), or with the brain through foramina in the skull.

Spinal cord

The **spinal cord** begins at the **foramen magnum**, which is the site in the base of the skull where the lower part of the brainstem (medulla) ends. The spinal cord terminates in the adult at the first lumbar vertebra, and gives rise to 30 pairs (or 31 if the coccygeal nerves are included) of spinal nerves, which exit the spinal cord between the vertebral bones of the spine. The first eight spinal nerves originate from the **cervical spinal cord** with the first pair exiting above the first cervical vertebra and the next 12 spinal nerves originate from **the thoracic or dorsal spinal cord**. The remaining 10 pairs of spinal nerves originate from the lower cord, five from the **lumbar** and five from the **sacral** regions.

The spinal nerves consist of an **anterior or ventral root** that innervates the skeletal muscles, while the **posterior or dorsal root** carries sensation to the spinal cord from the skin that shared a common embryological origin during development with that part of the spinal cord (see Chapter 2). In the case of the dorsal root fibres, they have their cell bodies in the **dorsal root ganglia** which lie just outside the spinal canal.

The spinal cord itself consists of **white matter**, which is that part of it containing the nerve fibres that form the **ascending and descending pathways of the spinal cord,** while the **grey matter** is located in the centre of the spinal cord and contains the cell bodies of the neurons (see Chapter 11).

Brainstem, cranial nerves and cerebellum

The spinal cord gives way to the **brainstem** that lies at the base of the brain and which is composed of the **medulla, pons and midbrain** (or mesencephalon) and contains discrete collections of neurons or nuclei for 10 of the 12 cranial nerves (see Chapter 13). The brainstem and the **cerebellum** constitute the structures of the posterior fossa. The cerebellum is connected to the brainstem via three cerebellar peduncles, and is involved in the coordination of movement (see Chapter 33).

Cerebral hemispheres

The **cerebral hemispheres** are composed of **four major lobes: occipital, parietal, temporal and frontal**. On the medial part of the temporal lobe are a series of structures, including the **hippocampus,** that form the limbic system (see Chapter 39).

The outer layer of the cerebral hemisphere is termed the **cerebral cortex**, and contains neurons that are organised both in horizontal layers and vertical columns (see Chapter 14). The cerebral cortex is interconnected over long distances via pathways that run subcortically. These pathways, together with those that connect the cerebral cortex to the spinal cord, brainstem and nuclei deep within the cerebral hemisphere, constitute **the white matter of the cerebral hemisphere**. These deep nuclei include structures such as the **basal ganglia** (see Chapter 34) and the **thalamus**.

Meninges

The CNS is enclosed within the skull and vertebral column and separating these structures are a series of membranes known as the **meninges**. The **pia mater** which is separated from the delicate **arachnoid membrane** by the subarachnoid space, which in turn is separated from the **dura mater** by the subdural space (see Chapter 15).

Autonomic nervous system (ANS)

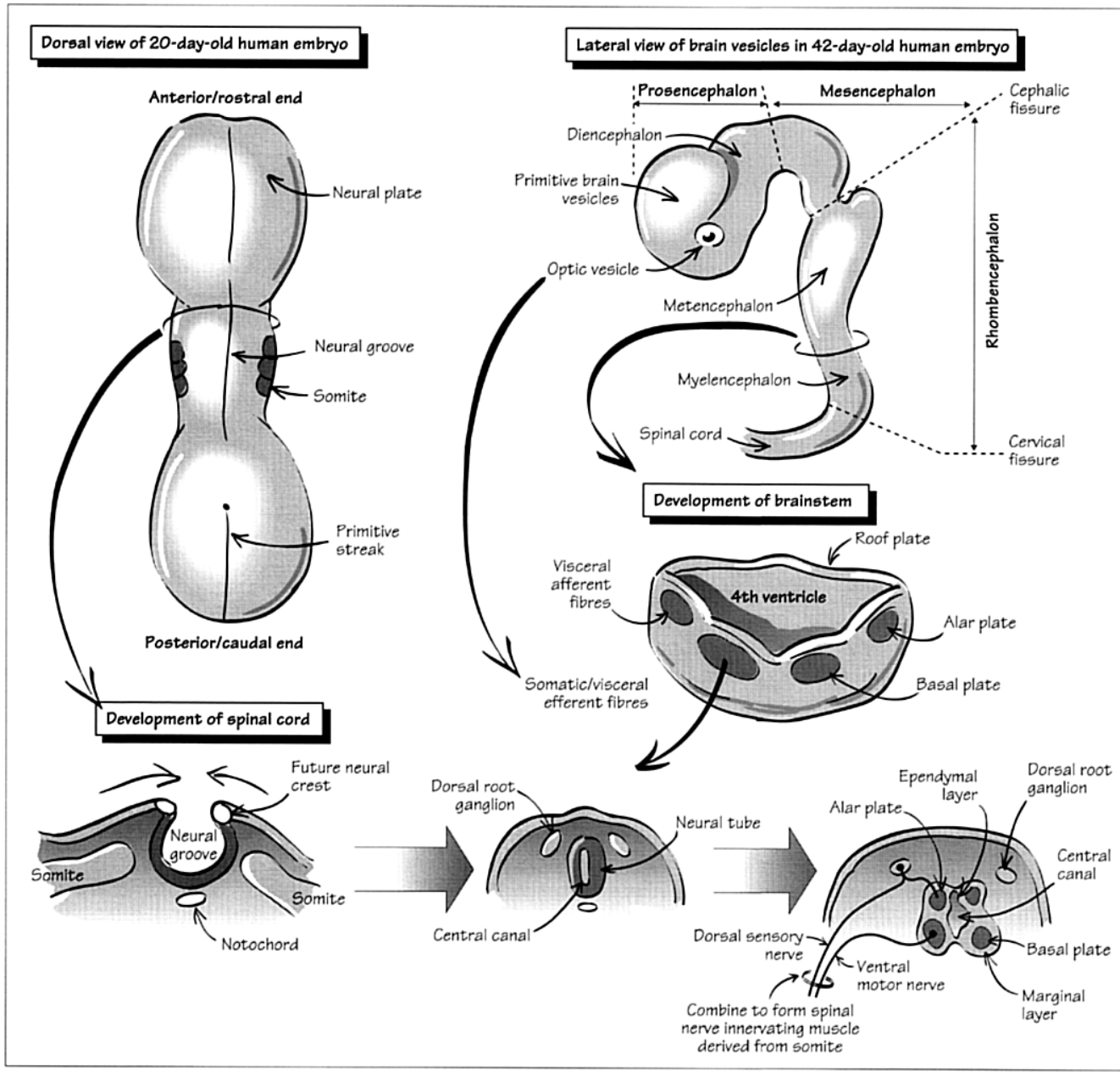
The **ANS** has both a central and peripheral component and is concerned with the innervation of internal and glandular organs (see Chapter 36): it has an important role in the control of the endocrine and homeostatic systems of the body (see Chapter 37). The peripheral component of the autonomic nervous system is defined in terms of the **enteric, sympathetic and parasympathetic systems** (see Chapter 36).

The efferent fibres of the ANS originate either from the **intermediate zone** (or **lateral column**) of the spinal cord or specific cranial nerve and sacral nuclei and synapse in a **ganglion**, the site of which is different for the sympathetic and parasympathetic systems. The afferent fibres from the organs innervated by the ANS pass via the dorsal root to the spinal cord.

Abbreviations

ANS	autonomic nervous system
CNS	central nervous system
PNS	peripheral nervous system

2 The development of the nervous system



The first signs of nervous system development occur in the third week of gestation, probably under the influence of the **notochord**, with the formation of a **neural plate** along the dorsal aspect of the embryo. This plate broadens, folds (forming the **neural groove**) and fuses to form the **neural tube** which ultimately gives rise to the brain at its rostral end and the spinal cord caudally. This fusion begins approximately halfway along the neural groove at the level of the fourth somite and continues caudally and rostrally with the closure of the posterior/caudal and anterior/rostral neuropore during the fourth week of gestation. Abnormalities in this process of neuropore closure results in ***anencephaly*** at the rostral end and to certain forms of ***spina bifida*** at the caudal end (see below).

The development of the spinal cord

The process of neural tube fusion isolates a group of cells termed the **neural crest**. This structure gives rise to most of

the cells of the PNS (including the **dorsal root ganglia**—DRG) and peripheral components of the ANS. The DRG contain the sensory cell bodies which send their developing axons into the evolving spinal cord and skin. These growing neuronal processes or neurites have an advancing **growth cone** that finds its appropriate target in the periphery and CNS, using a number of mechanisms including cell adhesion molecules and diffusable neurotrophic factors (see Chapter 43).

The neural tube surrounds the neural canal which forms the central canal of the fully developed spinal cord. The tube itself contains the neuroblasts with those adjacent to the canal (**ependymal layer**) dividing and migrating out to the **mantle layer** where they differentiate into neurons and by so doing form the grey matter of the spinal cord (see Chapter 1). The developing processes from the neuroblasts/neurons grow out into the **marginal layer** which therefore ultimately forms the white matter of the spinal cord. The dividing neuroblasts segregate into two discrete populations, the **alar** and **basal plates**, which in turn will form the dorsal and ventral horns of the spinal cord whilst a small lateral horn of visceral efferent neurons (i.e. part of the ANS) develops at their interface in the thoracic and upper lumbar cord (see Chapter 36).

The development of the brain

The rostral part of the neural tube enlarges before closure with the formation of three **primary brain vesicles (**the **prosencephalon, mesencephalon** and **rhombencephalon)** and two **flexures (cervical and cephalic)**. The primary brain vesicles develop into the cerebral hemispheres, brainstem and cerebellum whilst the neural canal will ultimately form the ventricular system of the brain (see Chapter 15).

The **prosencephalon** consists of the telencephalon which forms the cerebral hemispheres and part of the basal ganglia whilst the **diencephalon** forms the thalamus, hypothalamus, posterior pituitary and optic nerve and retina.

The neuroblasts again originate adjacent to the neural canal (the ventricular zone) but in this case they migrate not only locally to form the deep subcortical nuclei of the brain but also out along developing radial glial fibres to form the cerebral cortex (see Chapter 14). This intervening area which is rich in glial fibres will ultimately form the white matter of the cerebral hemisphere.

The **mesencephalon** gives rise to the midbrain with the neural canal forming the central aqueduct of Sylvius whilst the **rhombencephalon** consists of the **metencephalon** that gives rise to the pons and cerebellum and the **myelencephalon** that forms the medulla (see Chapter 12). The brainstem develops in a similar fashion to the spinal cord except the development is more in a mediolateral than anteroposterior direction. Thus the developing motor nuclei lie medial to the sensory nuclei with a parasympathetic component interposed between the two. This anterolateral expansion therefore explains the organisation of the cranial nerve nuclei within the brainstem (see Chapters 12 and 13).

The cerebellum develops from the rhombic lip and adjacent alar layer.

Disorders of CNS embryogenesis

- ***Anencephaly*** occurs when there is failure of fusion of the anterior rostral neuropore. The cerebral vesicles fail to develop and thus there is no brain development. The vast majority of fetuses with this abnormality are spontaneously aborted.
- ***Spina bifida*** refers to any defect at the lower end of the vertebral column and/or spinal cord. The commonest form of spina bifida refers to a failure of fusion of the dorsal parts of the lower vertebrae (***spina bifida occulta***). This can be associated with defects in the meninges and neural tissue which may herniate through the defect to form a ***meningocoele*** and ***meningomyelocoele***, respectively. The most serious form of spina bifida is when nervous tissue is directly exposed as a result of a failure in the posterior/caudal neuropore to properly fuse. Spina bifida is often associated with hydrocephalus (see Chapter 15).

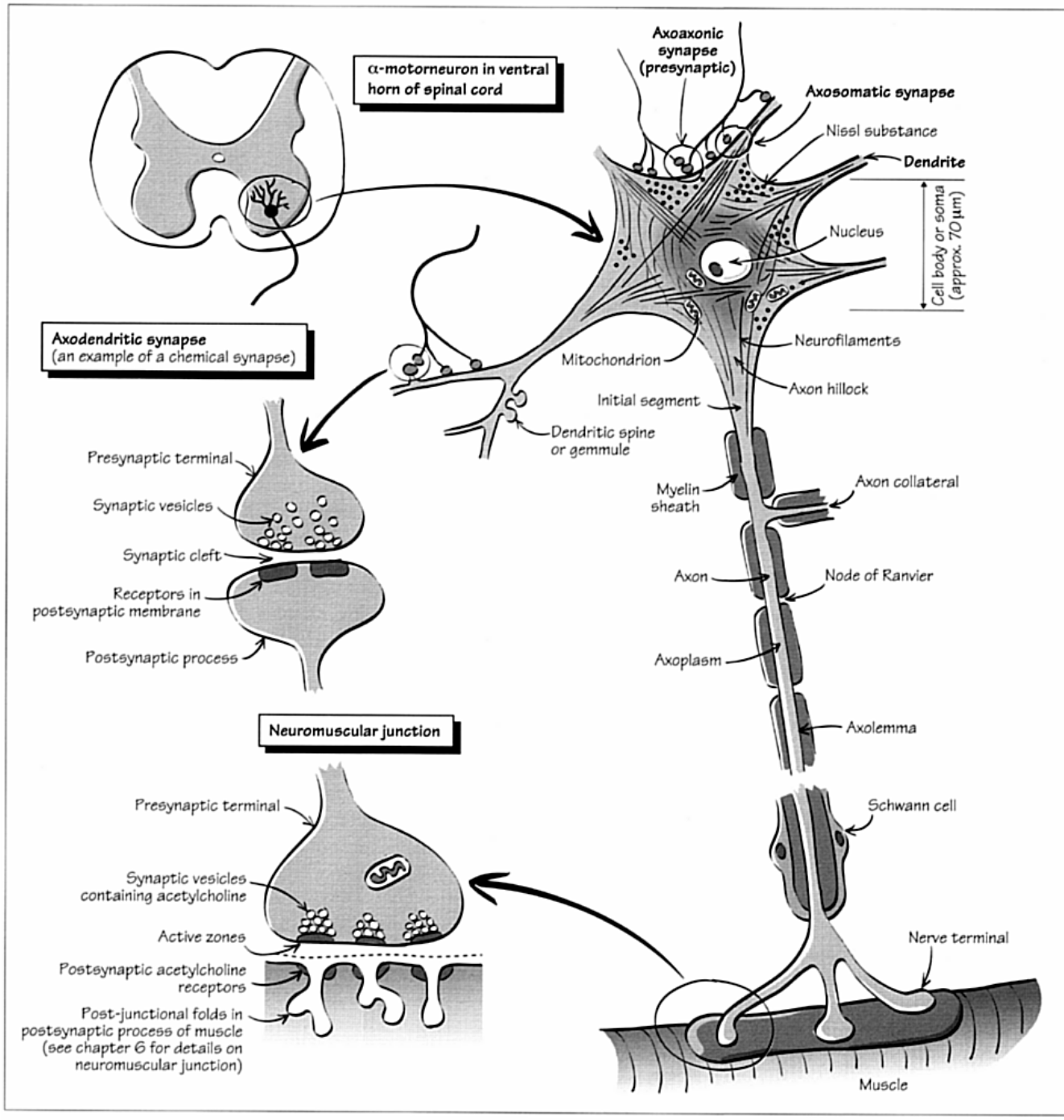
Occasionally bony defects are found at the base of the skull with the formation of a ***meningocoele***. However, unlike the situation at the lower spinal cord, these can often be repaired without any neurological deficit being accrued.

- ***Cortical dysplasia*** refers to a spectrum of defects which are the result of the abnormal migration of developing cortical neurons. These defects are becoming increasing recognised with improved imaging of the human CNS, and are now known to be an important cause of ***epilepsy*** (see Chapter 45).
- Many intrauterine infections (such as rubella), as well as some environmental agents (e.g. radiation), cause major problems in the development of the nervous system. In addition a large number of rare genetic conditions are associated with defects of CNS development but these lie beyond the scope of this book.

Abbreviations

ANS	autonomic nervous system
DRG	dorsal root ganglia
PNS	peripheral nervous system

3 The cells of the nervous system I: Neurons



There are two major classes of cells in the nervous system, the neuroglial cells and neurons, with the latter making up only 10–20% of the whole population. The neurons are specialised for excitation and nerve impulse conduction (see Chapters 5, 6 and 8), and communicate with each other by means of the synapse (see Chapter 7) and so act as the structural and functional unit of the nervous system.

Neurons

The **cell body (soma)** is that part of the neuron containing the nucleus and surrounding cytoplasm. It is the focus of cellular metabolism, and houses most of the neuron's intracellular organelles (**mitochondria**, Golgi apparatus and peroxisomes) and is associated typically with two types of neuronal process; the **dendrites** and **axon**. Most neurons also contain the granular basophilic staining, **Nissl substance**, which is composed of granular endoplasmic reticulum and ribosomes and is responsible for protein synthesis. This is located within the cell body and dendritic processes but is absent from the **axon hillock** and axon itself, for reasons that are not clear. In addition, throughout the cell body and processes are **neurofilaments** which are important in maintaining the architecture or cytoskeleton of the neuron. Furthermore, two other fibrillary structures within the neuron are important in this respect, microtubules and microfilaments, structures which are also important for axoplasmic flow (see below) and axonal growth.

The **dendrites** are neuronal cell processes that taper from the soma outwards, branch profusely and are responsible for conveying information towards the soma from **synapses** on the dendritic tree (**axodendritic synapses**; see also Chapter 8). Most neurons have many dendrites (so-called **multipolar neurons**) and while some inputs synapse directly on the dendrite, some do so via small **dendritic spines or gemmules**. Thus the primary role of dendrites is to increase the surface area for synapse formation allowing integration of a large number of inputs which are relayed to the cell body. In contrast the **axon**, of which there is only one per neuron, originates at the axon hillock and conducts information away from the soma towards the **nerve terminal** and synapses (see Chapter 8). Although there is only one axon per neuron, it can branch to give several processes. This branching occurs close to the soma in the case of sensory neurons (so-called **pseudo-unipolar** neurons; see Chapter 19), but more typically occurs close to the synaptic target of the axon. The axon originates from the soma at the **axon hillock** where the **initial segment** of the axon emerges. This is the most excitable part of a neuron because of its high density of sodium channels, and so is the site of initiation of the action potential (see Chapter 6).

All neurons are bounded by a lipid bilayer (**cell membrane**) within which proteins are located, some of which form ion channels (see Chapter 5), others form receptors to specific chemicals that are released by neurons (see Chapters 7 and 9) and others act as ion pumps moving ions across the membrane against their electrochemical gradient, e.g. Na^+–K^+ exchange pump (see Chapter 6). The axonal surface membrane is known as the **axolemma** and the cytoplasm contained within it, the **axoplasm**. The ion channels within the axolemma imbue the axon with its ability to conduct action potentials while the axoplasm contains neurofilaments, microtubules and mitochondria. These latter organelles are not only responsible for maintaining the ionic gradients necessary for action potential production but also allow for the transport and recycling of proteins away from (and to a lesser extent towards) the soma to the nerve terminal. This **axoplasmic flow or axonal transport** is either slow (~1 mm/day) or fast (~100–400 mm/day) and is not only important in permitting normal neuronal/synaptic activity but may also be important for neuronal survival and development.

Many axons are surrounded by a layer of lipid, or **myelin sheath**, that acts as an electrical insulator. This myelin sheath alters the conducting properties of the axon, and allows for rapid action potential propagation without a loss of signal integrity (see Chapter 6). This is achieved by means of gaps, or **nodes (of Ranvier)**, in the myelin sheath where the axolemma contains many ion channels (typically Na^+ channels) which are directly exposed to the tissue fluid. The nodes of Ranvier are also those sites from which axonal branches originate, and these branches are termed **axon collaterals**. The myelin sheath encompasses the axon just beyond the initial segment and finishes just prior to its terminal arborisation. The myelin sheath is formed by **Schwann cells** in the peripheral nervous system (PNS) and by **oligodendrocytes** in the central nervous system (CNS) (see Chapter 4), with many CNS axons being ensheathed by a single oligodendrocyte while in the PNS one Schwann cell provides myelin for one internode.

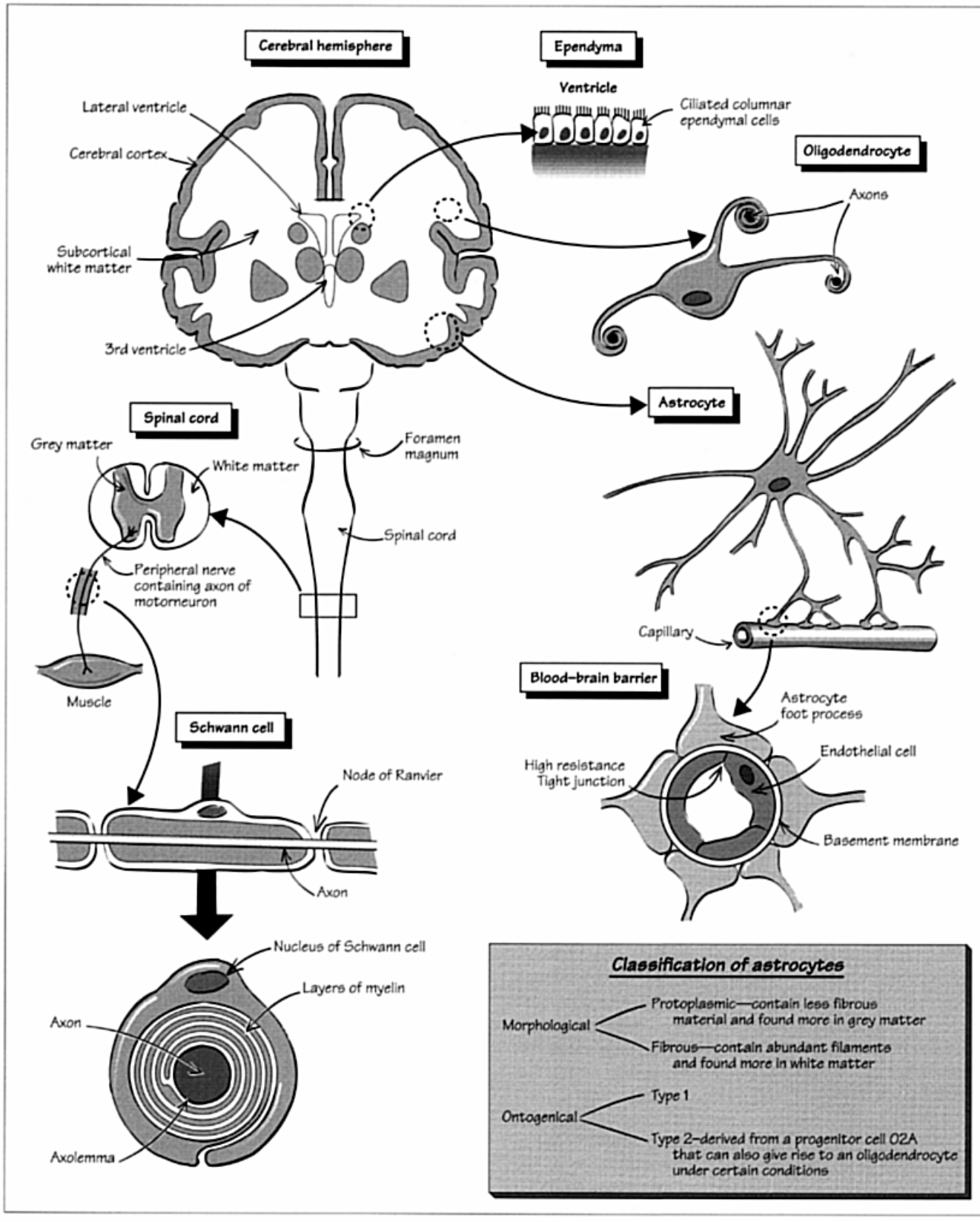
The **synapse** is the junction where a neuron meets another cell, which in the case of the CNS is another neuron. In the PNS the target can be muscle, glandular cells or other organs. The typical synapse in the nervous system is a **chemical** one which is composed of a **presynaptic nerve terminal (bouton or end-bulb)** and a **synaptic cleft** which physically separates the nerve terminal from the **postsynaptic membrane** and across which the chemical or neurotransmitter from the presynaptic terminal must diffuse (see Chapter 7). This synapse is typically between an axon of one neuron and the dendrite of another (**axodendritic synapse**) although synapses are found where the point of contact between the axon and the postsynaptic cell is either at the level of the cell body (**axosomatic synapses**) or, less frequently, the presynaptic nerve terminal (**axoaxonic synapse**; see Chapter 8). A few synapses within the CNS do not possess these features but are low-resistance junctions (gap junctions) and are termed **electrical synapses**. However, their existence in the human CNS is questioned.

Neuronal death is a feature of a number of neurological disorders, and those diseases in which this is the primary event are discussed in Chapter 42.

Abbreviation

PNS peripheral nervous system

4 The cells of the nervous system II: Neuroglial cells



There are four main classes of neuroglial cells within the CNS; astrocytes; oligodendrocytes, ependymal cells and microglia and they all subserve different functions. In contrast, in the PNS, Schwann cells are the only example of neuroglia and are involved in myelination and facilitating axonal regeneration.

Astrocytes are small stellate cells that are found throughout the CNS and classified either morphologically or ontogenetically (see figure). They subserve many important functions within the CNS and are not simply passive support elements.

- They form a structural and supporting framework for neuronal cells and capillaries by virtue of their cytoplasmic processes, which end in close apposition not only to neurons but also capillaries. In this respect they form the glia limitans—where the astrocytic foot processes cover the basal laminae around blood vessels and at the pia mater.
- They maintain the integrity of the **blood–brain barrier (BBB),** by promoting the formation of high-resistance junctions between brain capillary endothelial cells (see also Chapter 15).
- They are capable of taking up, storing and releasing some neurotransmitters (e.g. glutamate, γ-aminobutyric acid (GABA)) and thus may be an important adjunct in chemical neurotransmission within the CNS.
- They can take up and disperse excessive ion concentration in the extracellular fluid, especially K^+.
- They participate in neuronal guidance during development (see Chapter 14), and may also be important in the response to injury (see Chapter 44).
- They may have a role in presenting antigen to the immune system in situations where the CNS and BBB are damaged (see Chapter 46).

The commonest clinical disorder of astrocytes is their abnormal proliferation in tumours called ***astrocytomas***. These tumours produce effects by compressing adjacent CNS tissue and this presents as an evolving neurological deficit (with or without epileptic seizures) depending on its site of origin within the CNS. In adults the tumours most commonly arise in white matter of the cerebral hemispheres.

Oligodendrocytes are responsible for the myelination of CNS neurons, and are therefore found in large numbers in the white matter. Each oligodendrocyte forms internodal myelin for 3–50 fibres and also surrounds many other fibres without forming myelin sheaths. In addition they have a number of molecules associated with them that are inhibitory to axonal growth, and thus contribute to the failure of damaged adult CNS neurons to regenerate (see Chapter 44).

Clinical disorders of oligodendrocyte function cause central demyelination which is seen in a number of conditions including ***multiple sclerosis*** (see Chapter 46), while abnormal proliferation of oligodendrocytes produces a slow-growing tumour (an ***oligodendroglioma***) which tends to present with epileptic seizures (see Chapter 45).

Ependymal cells are important in facilitating the movement of cerebrospinal fluid (CSF) as well as interacting with astrocytes to form a barrier separating the ventricles and the CSF from the neuronal environment. They also line the central canal in the spinal cord (see Chapter 11). These ependymal cells are termed ependymocytes to distinguish them from those ependymal cells that are involved in the formation of CSF (the choroid plexus) and those that transport substances from the CSF to blood (tanycytes). Tumours of the ependyma (***ependymomas or choroid plexus papillomas***) occur either in the ventricles where they tend to produce ***hydrocephalus*** (see Chapter 15) or spinal cord where they cause local destruction of the neural structures.

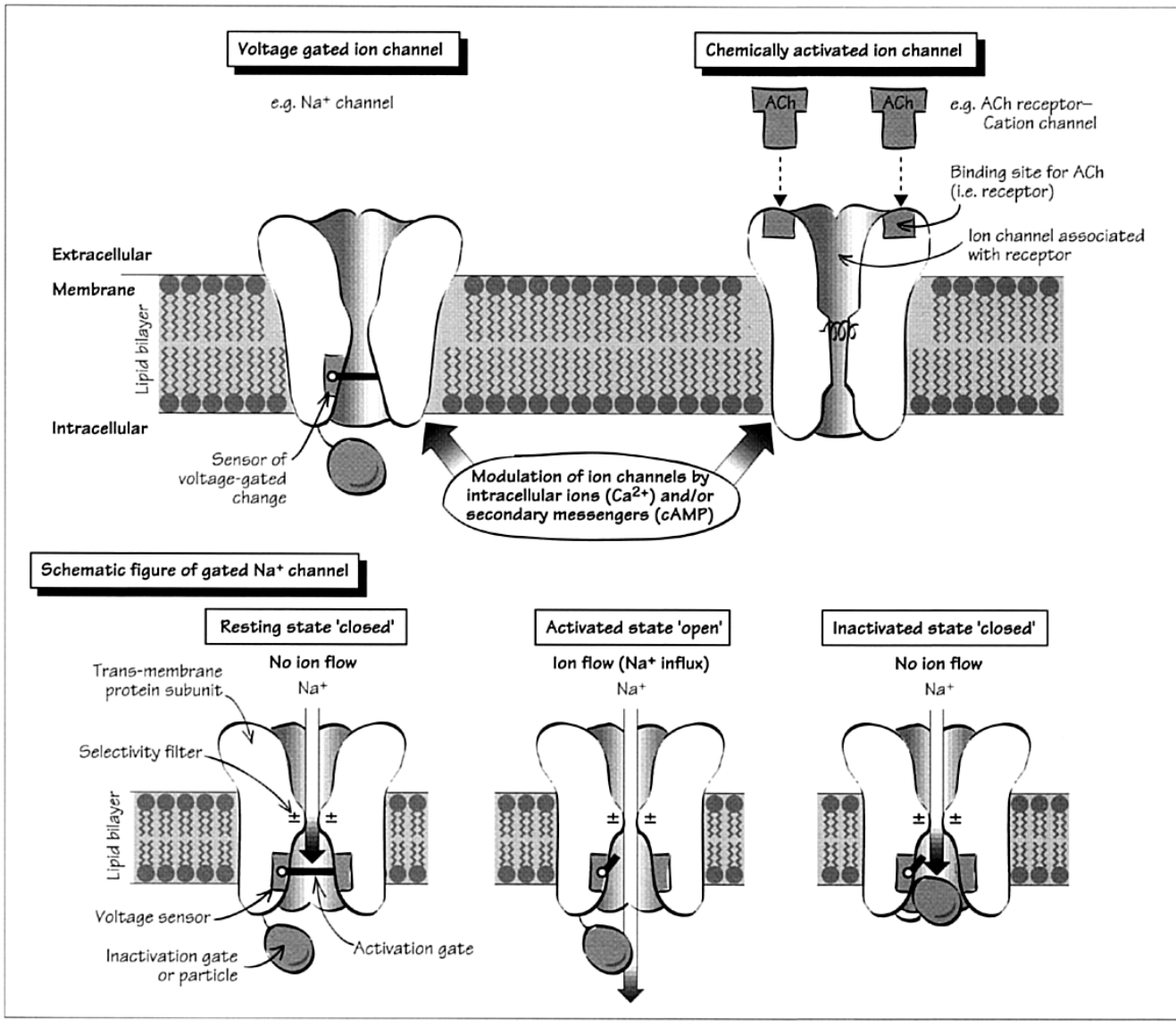
Microglial cells (not shown on figure) take their origin from the reticulo-endothelial system, and are found throughout the white and grey matter of the CNS. They are phagocytic in nature and are important in mediating immune responses within the CNS (see Chapter 46).

Schwann cells are found only in the PNS and are responsible for the myelination of peripheral nerves by a process that involves the wrapping of the cell around the axon. Thus the final myelin sheath is composed of multiple layers of Schwann cell membrane in which the cytoplasm has been extruded. Unlike oligodendrocytes, one Schwann cell envelops one axon and provides myelin for one internode. In addition Schwann cells are important in the regeneration of damaged peripheral axons, in contrast to the largely inhibitory functions of the central neuroglial cells (see Chapters 43 and 44). A number of genetic and inflammatory neuropathies are associated with the loss of peripheral myelin (as opposed to the loss of axons), which results in peripheral nerve dysfunction (so-called ***demyelinating neuropathies***; see Chapters 6 and 47). In addition, benign tumours of Schwann cells can occur (***schwannomas***), especially in certain genetic conditions such as ***neurofibromatosis type I***, where there is the loss of the tumour suppressor gene, neurofibromin. These tumours are typically asymptomatic but if they arise in areas of limited space they can produce symptoms by compression of the neighbouring neural structures; for example, at the cerebellopontine angle in the brainstem or spinal root (see Chapters 11–13 and 25).

Abbreviations

BBB	blood–brain barrier
CSF	cerebrospinal fluid
GABA	γ-aminobutyric acid
PNS	peripheral nervous system

5 Ion channels



An **ion channel** is a protein macromolecule which spans a biological membrane and allows ions to pass from one side of the membrane to the other. The ions move in a direction determined by the electrochemical gradient across the membrane. In general, ions will tend to flow from an area of high concentration to one of low concentration, but in the presence of a voltage gradient it is possible for there to be no ion flow even with unequal concentrations. The ion channel itself can be open or closed. Opening can be achieved either by changing the voltage across the membrane (for example, a depolarisation or the arrival of an action potential) or by the binding of a chemical substance to a receptor in or near the channel. The two types of channel are called **voltage gated** (or **voltage sensitive**) and **chemically activated** (or **ligand gated**) channels, respectively. However, this distinction is somewhat artificial as a number of voltage sensitive channels can be modulated by neurotransmitters as well as by Ca^{2+}. Furthermore, some ion channels are not opened by voltage changes or chemical messengers but are directly opened by mechanical stretch or pressure (e.g. the somatosensory and auditory receptors; see Chapters 18, 19 and 24).

The most important property of ion channels is that they imbue the neuron with electrical excitability (see Chapter

6) and, while they are found in all parts of the neuron, and to a lesser extent in neuroglial cells, they are also seen in a host of non-neural cells.

All biological membranes, including the neuronal membrane, are composed of a lipid bilayer which has a high electrical resistance, i.e. ions will not readily flow through it. Therefore in order for ions to move across a membrane it is necessary to have either 'pores' (ion channels) in the lipid bilayer or 'carriers' that will collect the ions from one side of the membrane and carry them across to the other side where they are released. In neurons the rate of ion transfer necessary for signal transmission is too fast for any carrier system and so ion channels (or 'pores') are employed by neurons for the transfer of ions across the membrane.

The fundamental properties of an ion channel are as follows:

- It is composed of a number of protein subunits that traverse the membrane and which allow ions to cross from one side to the other, i.e. a **transmembrane pore**.
- The channel so formed must be able to move from a **closed** to an **open** state and back, although intermediate steps may be required.
- It must be able to open in response to specific stimuli. Most channels possess a sensor of voltage change and so open in response to a depolarising voltage, i.e. one that moves the resting membrane potential from its resting value of ~–70 to –80 mV to a less negative value.

In contrast some channels, especially those found at synapses, are not opened by a voltage change but by a chemical, e.g. acetylcholine (ACh). These channels have a **receptor** for that chemical and the binding of the chemical to this receptor leads to channel opening. However, many channels possess both voltage and chemical sensors and the presence of an intracellular ion or secondary messenger molecule (e.g. cyclic adenosine monophosphate (cAMP)) leads to a **modulation** of the ion flow across the membrane which the voltage-dependent process has produced.

Activation of the voltage sensor or chemical receptor leads to the opening of a **'gate'** within the channel which allows ions to flow through the channel. The channel is then closed by either a process of **deactivation** (which is simply the reversal of the opening of the gate) or **inactivation** which involves a **second gate** moving into the channel more slowly than the activation gate moves out, so that there is a time when there is no gate in the channel and ions can flow through it.

The flow of ions through the channel can be either **selective or non-selective**. If the channel is selective then it only allows certain ions through and it achieves this by means of a **'filter'**. The selectivity filter is based on energetic considerations (thermodynamically) and gives the channel its name, e.g. the sodium channel. Certain channels are, however, non-selective in that they allow many different types of similarly charged ions through, e.g. the ACh cation channel.

The overall description of an ion channel is in terms of a number of different physical measures. The net flow of ions through a channel is termed the **current**; while the **conductance** is defined as the reciprocal of resistance (current/voltage) and represents the ease with which the ions can pass through the membrane. **Permeability**, on the other hand, is defined as the rate of transport of a substance or ion through the membrane for a given concentration difference.

There are many different types of ion channels and even within a single family of ion-specific channels there are multiple subtypes, e.g. there are at least five different types of potassium channels.

The number and type of ion channels governs the response characteristics of the cell. In the case of neurons, this is expressed in terms of the rate of action potential generation and its response to synaptic inputs (see Chapters 6–8, 39 and 43).

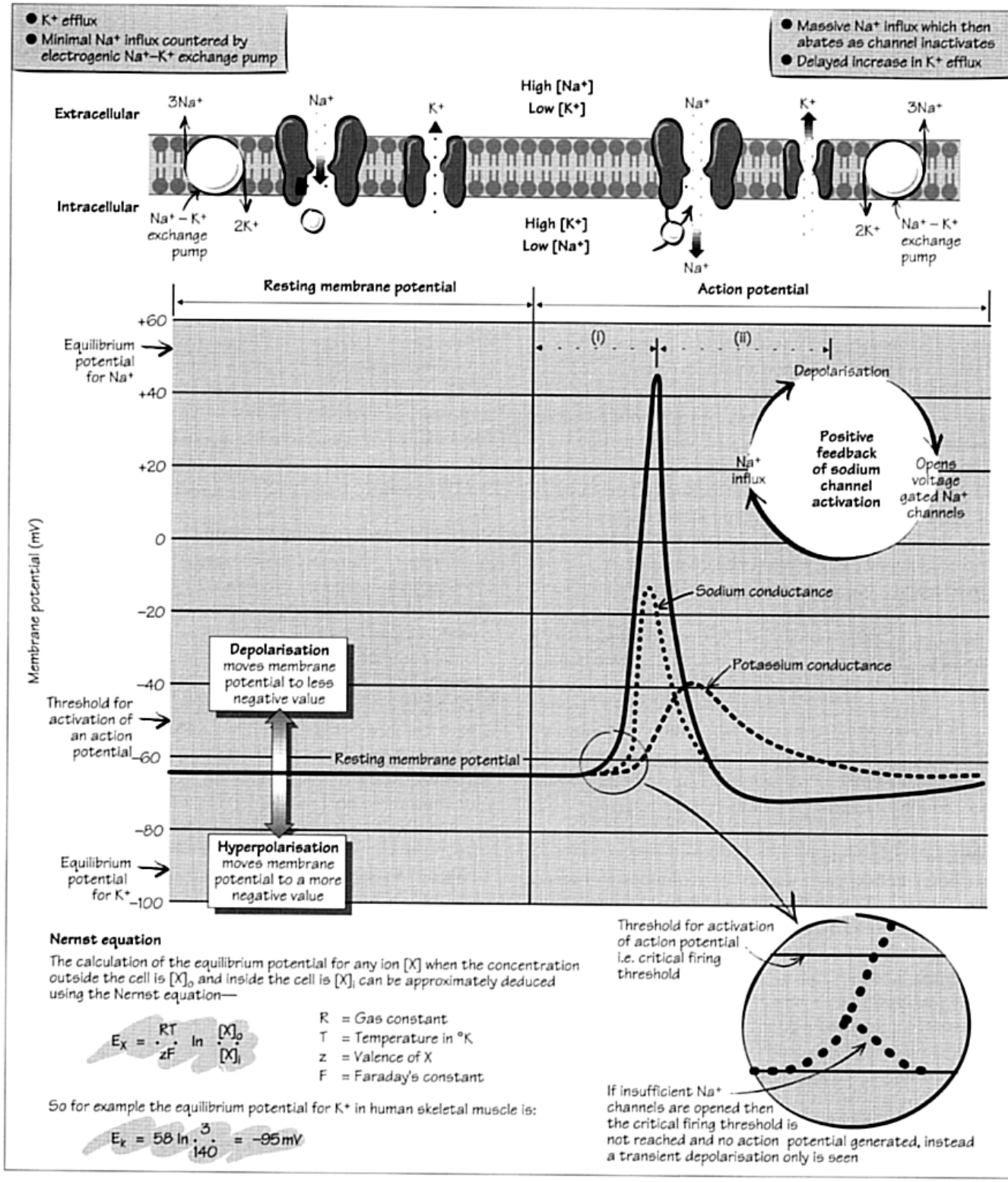
Clinical disorders of ion channels

A number of pharmacological agents work at the level of ion channels, including local anaesthetics and some anti-epileptic drugs. However, in recent years a number of neurological disorders, primarily involving muscle, have been found to be caused by mutations in the sodium and chloride ion channels. These conditions include various forms of ***myotonia*** (delayed relaxation of skeletal muscle following voluntary contraction, i.e. an inability to let go of objects easily) and various forms of ***periodic paralyses*** in which patients develop a transient flaccid weakness which can be either partial or generalised. Furthermore, certain forms of familial hemiplegic ***migraine*** are associated with abnormalities in the Ca^{2+} channel, and some forms of ***epilepsy*** (see Chapter 45) may be caused by a disorder of specific ion channels. In other disorders there is a redistribution or exposing of normally non-functioning ion channels. This commonly occurs at the node of Ranvier as a result of central demyelination in ***multiple sclerosis*** and peripheral demyelination in the ***Guillain–Barré syndrome***, and results in an impairment in action potential propagation (see Chapters 6 and 46).

Abbreviations

ACh acetylcholine
cAMP cyclic adenosine monophosphate

6 The resting membrane and action potential



Nernst equation

The calculation of the equilibrium potential for any ion [X] when the concentration outside the cell is $[X]_o$ and inside the cell is $[X]_i$ can be approximately deduced using the Nernst equation—

$$E_X = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i}$$

R = Gas constant
T = Temperature in °K
z = Valence of X
F = Faraday's constant

So for example the equilibrium potential for K^+ in human skeletal muscle is:

$$E_k = 58 \ln \frac{3}{140} = -95\,mV$$

Resting membrane potential

In the resting state the neuronal cell membrane is relatively impermeable to ions. This is important in the generation of the **resting membrane potential**. The major intracellular ion is potassium compared to sodium in the extracellular fluid and so the natural flow of ions according to their concentration gradients is for K^+ to leave the cell (or efflux) and for Na^+ to enter (or influx). The movement of positive ions out of the cell leads to the generation of a negative membrane potential or **hyperpolarisation**, while the converse is true for positive ion influx (a process of **depolarisation**). However, the resting membrane is relatively impermeable to Na^+ ions while being relatively permeable to K^+ ions. At rest therefore, K^+ will tend to efflux from the cell down its concentration gradient leaving excess negative charge behind and this will continue until the chemical concentration gradient driving K^+ out of the cell is exactly offset by the electrical potential difference generated by this efflux (the membrane potential) drawing K^+ back into the cell. The membrane potential at which this steady state is achieved is the **equilibrium potential** for K^+ (E_{K+}) and can be derived using the **Nernst equation** (see figure for details). In fact the measured resting membrane potential in axons is slightly more positive than expected because there is some small permeability to Na^+ of the membrane in the resting state. The small Na^+ influx is countered by an adenosine triphosphate (ATP) dependent **Na^+–K^+ exchange pump** which is itself slightly electrogenic. This pump is essential in maintaining the ionic gradients, and is electrogenic by virtue of the fact that it pumps out three Na^+ ions for every two K^+ ions brought in. It makes only a small contribution to the level of the resting membrane potential.

Action potential generation

One of the fundamental features of the nervous system is its ability to generate and conduct electrical impulses (see Chapters 8 and 17). These can take the form of generator potentials, synaptic potentials and action potentials—the latter being defined as a single electrical impulse passing down an axon. **This action potential (nerve impulse or spike)** is an **all or nothing phenomenon**, that is to say once the threshold stimulus intensity is reached an action potential will be generated. Therefore information in the nervous system is coded by frequency of firing rather than size of the action potential (see Chapter 17). The threshold stimulus intensity is defined as that value at which the net inward current (which is largely determined by Na^+ ions) is just greater than the net outward current (which is largely carried by K^+ ions), and is typically around –55 mV (**critical firing threshold**). This occurs most readily in the region of the axon hillock where there is the highest density of Na^+ channels, and is thus the site of action potential initiation in the neuron. If, however, the threshold is not reached the graded depolarisation will not generate an action potential and the signal will not be propagated along the axon.

The sequence of events in the generation of an action potential are as follows:

1 The depolarising voltage activates the voltage sensitive Na^+ channels in the neuronal membrane which allows some Na^+ ions to flow down their electrochemical gradient (increased Na^+ conductance). This depolarises the membrane still further opening more Na^+ channels in a **positive feedback loop**. When sufficient Na^+ channels are opened to produce an inward current greater than that generated by the K^+ efflux, there is rapid opening of all the Na^+ channels producing a large influx of Na^+ which depolarises the membrane towards the **equilibrium potential for Na^+** (namely ~ +55 mV). The spike of the action potential is therefore generated, but fails to reach the equilibrium potential for Na^+ because of the persistent and increasing K^+ efflux.

2 The falling phase of the action potential then follows as the voltage sensitive Na^+ channels become inactivated (see Chapter 5). This inactivation is voltage dependent, in that it is in response to the depolarising stimulus, but has slower kinetics than the activation process and so occurs later (see also Chapter 5). During this falling phase a voltage dependent K^+ current becomes important as its activation by the depolarisation of the membrane has even slower kinetics than sodium channel inactivation. This voltage activated K^+ channel leads to a brief period of membrane hyperpolarisation before it deactivates and the membrane potential is returned to the resting state.

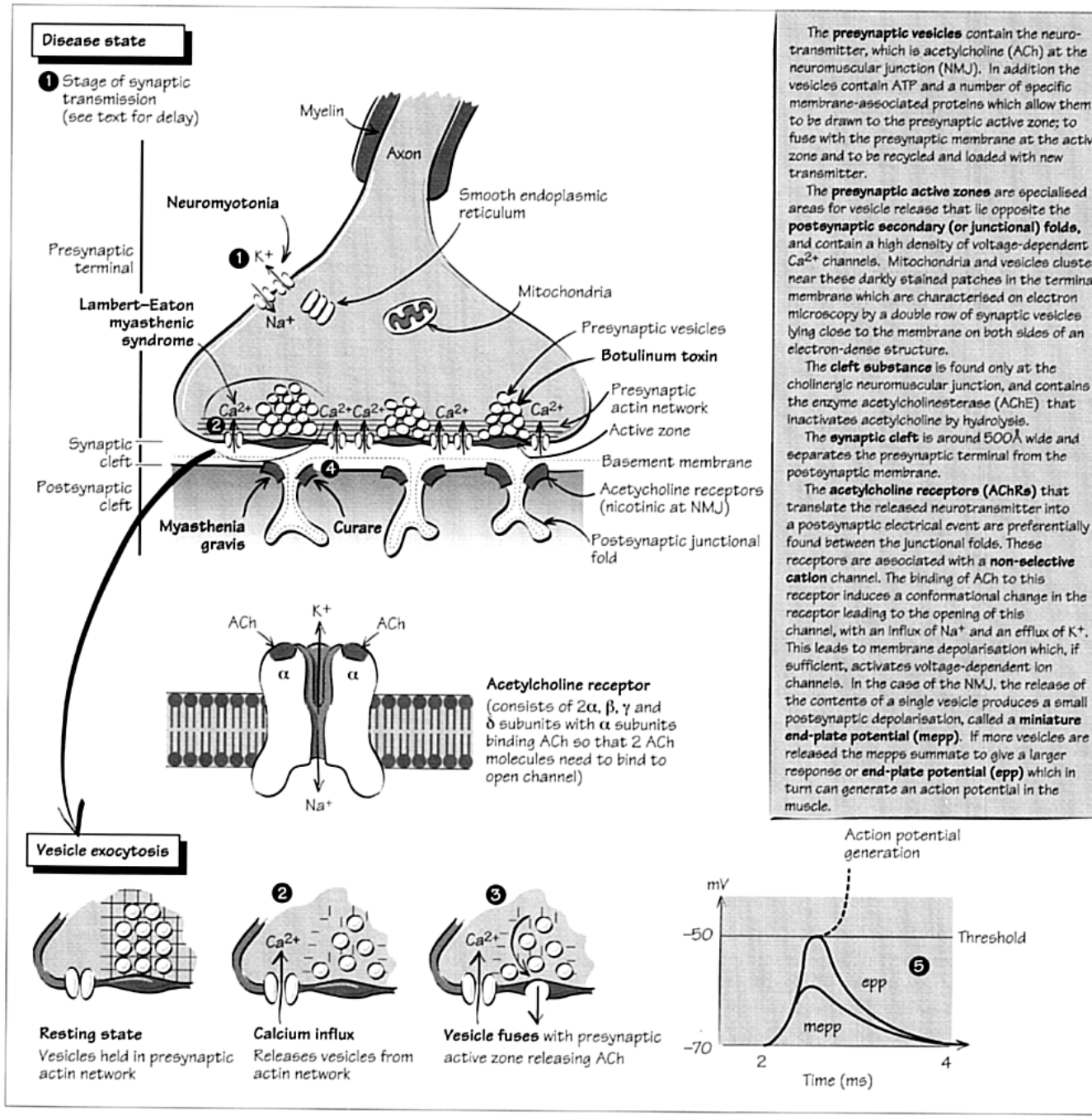
Immediately after the spike of the action potential there is a **refractory period** when the neuron is either inexcitable (**absolute refractory period**) or only activated to submaximal responses by suprathreshold stimuli (**relative refractory period**). The absolute refractory period occurs at the time of maximal Na^+ channel inactivation while the relative refractory period occurs at a later time when most of the Na^+ channels have returned to their resting state but the voltage activated K^+ current is well developed. The refractory period has two important implications for action potential generation and conduction. First, action potentials can be conducted only in one direction, away from the site of its generation, and secondly, they can be generated only up to certain limiting frequencies (see Chapter 17).

The original description of the mechanism of generation of the action potential was by Hodgkin and Huxley in the squid giant axon in the 1950s but subsequently has been confirmed in many other cells and neurons. This, together with the discovery of a large number of ion channels, has meant that many modifications relating to the generation and characteristics of action potentials in neurons and other cells have been described.

Abbreviation

ATP adenosine triphosphate

7 The neuromuscular junction and synapses



The **presynaptic vesicles** contain the neurotransmitter, which is acetylcholine (ACh) at the neuromuscular junction (NMJ). In addition the vesicles contain ATP and a number of specific membrane-associated proteins which allow them to be drawn to the presynaptic active zone; to fuse with the presynaptic membrane at the active zone and to be recycled and loaded with new transmitter.

The **presynaptic active zones** are specialised areas for vesicle release that lie opposite the **postsynaptic secondary (or junctional) folds**, and contain a high density of voltage-dependent Ca^{2+} channels. Mitochondria and vesicles cluster near these darkly stained patches in the terminal membrane which are characterised on electron microscopy by a double row of synaptic vesicles lying close to the membrane on both sides of an electron-dense structure.

The **cleft substance** is found only at the cholinergic neuromuscular junction, and contains the enzyme acetylcholinesterase (AChE) that inactivates acetylcholine by hydrolysis.

The **synaptic cleft** is around 500Å wide and separates the presynaptic terminal from the postsynaptic membrane.

The **acetylcholine receptors (AChRs)** that translate the released neurotransmitter into a postsynaptic electrical event are preferentially found between the junctional folds. These receptors are associated with a **non-selective cation** channel. The binding of ACh to this receptor induces a conformational change in the receptor leading to the opening of this channel, with an influx of Na^+ and an efflux of K^+. This leads to membrane depolarisation which, if sufficient, activates voltage-dependent ion channels. In the case of the NMJ, the release of the contents of a single vesicle produces a small postsynaptic depolarisation, called a **miniature end-plate potential (mepp)**. If more vesicles are released the mepps summate to give a larger response or **end-plate potential (epp)** which in turn can generate an action potential in the muscle.

Sherrington in 1897 coined the term '**synapse**' to mean the junction of two neurons. Much of the work on the synapse has been done with the cholinergic **neuromuscular junction (NMJ)**, although it appears that this chemical synapse is similar in its mode of action to those found in the CNS. The chemical synapse is the predominant synapse type found in the nervous system, but electrical synapses are found in certain sites, e.g. cardiac muscle and glial cells.

Synaptic transmission

The sequence of events at a chemical synapse is as follows:

- The arrival of the action potential leads to the depolarisa-

tion of the presynaptic terminal (labelled **(1)** on figure) with the opening of **voltage-dependent Ca^{2+} channels** in the **active zones** of the presynaptic terminal and subsequent Ca^{2+} influx **(2)** (this is the stage that represents the major delay in synaptic transmission);

- The influx of Ca^{2+} leads to the phosphorylation and alteration of a number of presynaptic calcium binding proteins (some of which are found in the vesicle membrane) which liberates the **vesicle** from its **presynaptic actin network** allowing it to bind to the **presynaptic membrane (3)**;
- The fusion of the two hemichannels (presynaptic vesicle and presynaptic membrane) leads to the formation of a small pore that rapidly expands with the release of vesicular contents into the **synaptic cleft**. The vesicle membrane can then be recycled by **endocytosis** into the presynaptic terminal, either by a rapid non-selective or slower more selective process;
- most of the released neurotransmitter then diffuses across the synaptic cleft and binds to the **postsynaptic receptor (4)**. Some transmitter molecules diffuse out of the synaptic cleft and are lost, while others are inactivated before they have time to bind to the postsynaptic membrane receptor. This **inactivation** is essential for the synapse to function normally and, although enzymatic degradation of acetylcholine (ACh) is employed at the neuromuscular junction, other synapses employ uptake mechanisms with the recycling of the transmitter into the presynaptic neuron (see Chapter 9).
- The activation of the postsynaptic receptor leads to a change in the postsynaptic membrane potential. Each vesicle contains a certain amount or quantum of neurotransmitter, whose release generates a small postsynaptic potential change of a fixed size—the **miniature end-plate potential or mepp**. The release of transmitter from several vesicles leads to mepp summation and the generation of a larger depolarisation or **end-plate potential (epp)** which, if sufficiently large, will reach threshold for action potential generation in the postsynaptic muscle fibre **(5)**.

This **vesicle hypothesis** has been criticised, because not all synapses contain their neurotransmitters in vesicles and because electrical synapses are found in some neural networks. Alternative theories have therefore been put forward that invoke either molecules to carry the neurotransmitter across the presynaptic membrane or pores that open in the presynaptic membrane in response to a calcium influx. There is little evidence in favour of either of these theories.

Disorders of neuromuscular transmission

There are a number of naturally occurring toxins that can affect the neuromuscular junction.

- **Curare** binds to the acetylcholine receptor (AChR) and prevents ACh from acting on it and so induces paralysis. This is exploited clinically in the use of curare derivatives for muscle paralysis in certain forms of surgery.
- **Botulinum toxin** prevents the release of ACh presynaptically. In this case an exotoxin from the bacterium *Clostridium botulinum* binds to the presynaptic membrane of the ACh synapse and prevents the quantal release of ACh. The accidental ingestion of this toxin in cases of food poisoning produces paralysis and autonomic failure (see Chapter 36). However, the toxin can be used therapeutically in small quantities by injecting it into muscles that are abnormally overactive in certain forms of focal ***dystonia***—a condition in which a part of the body is held in a fixed abnormal posture by overactive muscular activity (see Chapter 34).

A number of neurological conditions affect the NMJ selectively. These include ***myasthenia gravis***, ***the Lambert–Eaton myasthenic syndrome (LEMS)*** and ***neuromyotonia or Isaac's syndrome***. In ***neuromyotonia*** the patient complains of muscle cramps and stiffness as a result of continuous motor activity in the muscle. This is often caused by an antibody directed against the presynaptic voltage-gated K^+ channel, so the nerve terminal is always in a state of depolarisation with transmitter release. In contrast in ***LEMS*** there is an antibody directed against the presynaptic Ca^{2+} channel, so that on repeated activation of the synapse there is a steady increase in Ca^{2+} influx as the blocking antibody is competitively overcome by exogenous Ca^{2+}. The patient complains of weakness, especially of the proximal muscles, which transiently improves on exercise. In contrast ***myasthenia gravis*** is caused by an antibody against the AChR, and patients complain of weakness that increases with exercise, so-called fatiguability. This is because the number of AChR are reduced and the presynaptic release of ACh competes for the few available receptors.

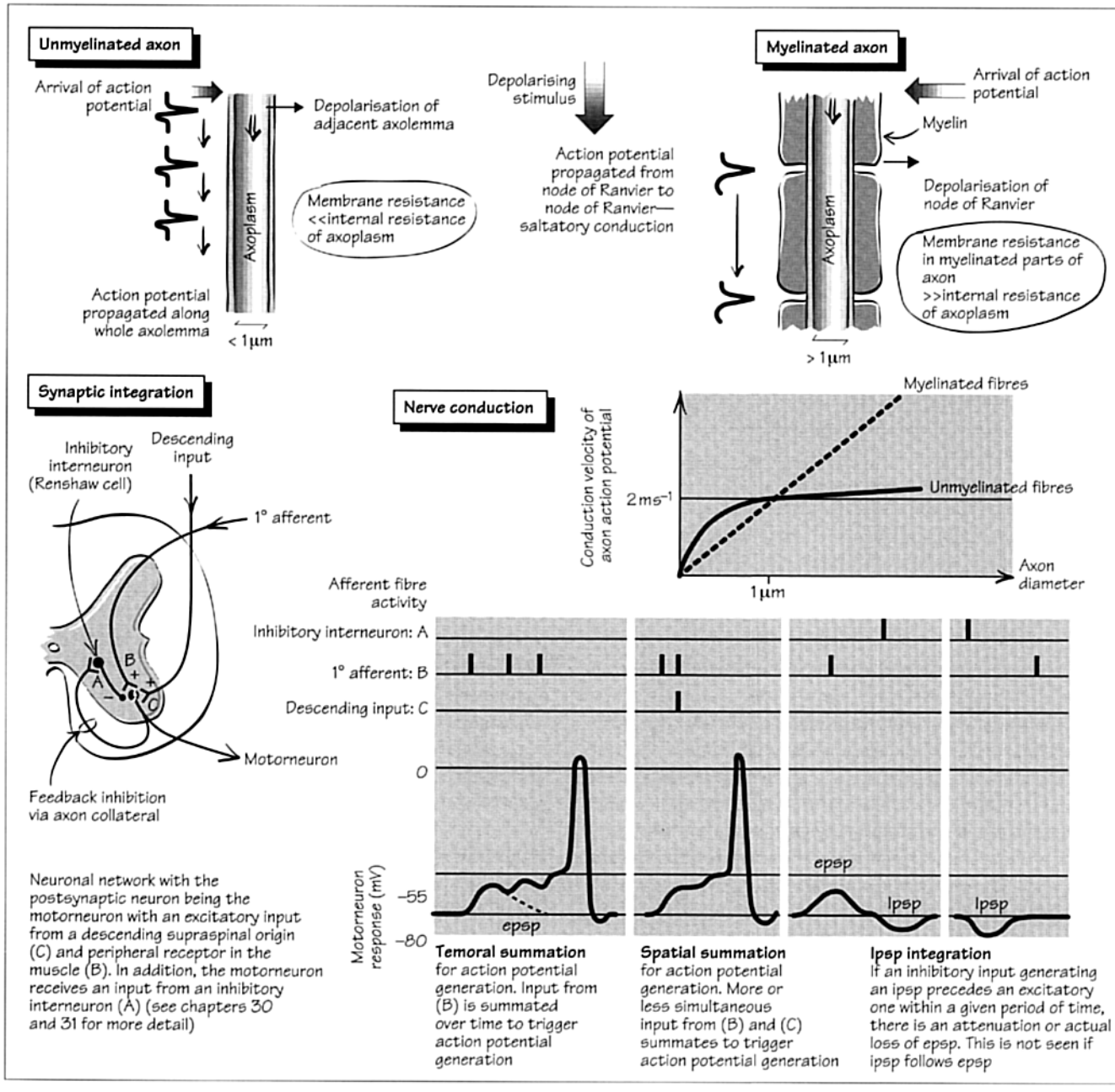
Electrical synapses

These are rarely found in the human CNS, because they allow minimal synaptic integration (see Chapter 8). However, such synapses do exist in certain syncytial tissues such as astrocytes and cardiac muscle cells. In these cases the presence of the fast conducting gap junctions, that make up the electrical synapse, allow for the rapid and widespread propagation of depolarising inputs.

Abbreviations

ACh	acetylcholine
AChE	acetylcholinesterase
AChR	acetylcholine receptor
ATP	adenosine triphosphate
epp	end-plate potential
LEMS	Lambert–Eaton myasthenic syndrome
mepp	miniature end-plate potential
NMJ	neuromuscular junction

8 Nerve conduction and synaptic integration



Neuronal network with the postsynaptic neuron being the motorneuron with an excitatory input from a descending supraspinal origin (C) and peripheral receptor in the muscle (B). In addition, the motorneuron receives an input from an inhibitory interneuron (A) (see chapters 30 and 31 for more detail)

Nerve conduction

Action potential propagation is achieved by local current spread and is made possible by the large safety factor in the generation of an action potential as a consequence of the positive feedback of Na^+ channel activation in the rising phase of the nerve impulse (see Chapter 6). The use of local current spread does, however, set constraints not only on the velocity of nerve conduction but also influences the fidelity of the signal being conducted. The nervous system overcomes these difficulties by insulating nerve fibres above a given diameter with myelin which is periodically interrupted by the nodes of Ranvier.

In **unmyelinated axons** an action potential at one site leads to depolarisation of the membrane immediately in front and theoretically behind it, although the membrane at

this site is in its refractory state and so the action potential is only conducted in one direction (see Chapter 6). The current preferentially passes across the membrane (because of the high internal resistance of the axoplasm) and is greatest at the site closest to the action potential.

However, while nerve impulse conduction is feasible and accurate in unmyelinated axons, especially in the very small diameter fibres where the internal axoplasmic resistance is very high, it is nevertheless slow. Conduction velocity can therefore be increased by either increasing the axon diameter (of which the best example is the squid giant axon with a diameter of ~1 mm) or insulating the axon using a high resistance substance such as the lipid-rich myelin.

Conduction in **myelinated fibres** follows exactly the same sequence of events as in unmyelinated fibres, but with a crucial difference: the advancing action potential encounters a high-resistance, low-capacitance structure in the form of a nerve fibre wrapped in myelin. The depolarising current therefore passes along the axoplasm until it reaches a low-resistance **node of Ranvier** with its high density of Na^+ channels and an action potential is generated at this site. The action potential therefore appears to be conducted down the fibre, from node to node—a process termed **saltatory conduction**. The advantage of myelination is that it allows for rapid conduction whilst minimising the metabolic demands on the cell. It also increases the packing capacity of the nervous system, so that many fast conducting fibres can be packed into a small nerve. As a result most axons over a certain diameter (~1 μm) are myelinated.

Disturbances in nerve conduction are clinically seen when there is a disruption of the myelin sheath, for example in the PNS in inflammatory demyelinating neuropathies such as the ***Guillain–Barré syndrome*** and in the CNS with ***multiple sclerosis*** (see Chapter 46). In both conditions there is a loss of the myelin sheath, especially in the area adjacent to the node of Ranvier, which exposes other ion channels, as well as reducing the length of insulation along the axon. The result is that the propagated action potential has to depolarise a greater area of axolemma, part of which is not as excitable as the normal node of Ranvier because it contains fewer Na^+ channels. This leads to slowing of the action potential propagation, and if the demyelination is severe enough actually leads to an attenuation of the propagated action potential to the point that it can no longer be conducted—so-called conduction block.

Synaptic integration

Each central neuron receives many hundreds of synapses and each input is integrated into a response by that neuron, a process that involves the summation of inputs from many different sites at any one time **(spatial summation)** as well as the summation of one or several inputs over time **(temporal summation)**.

The presynaptic nerve terminal usually contains one neurotransmitter, although recently the release of two or more transmitters at a single presynaptic terminal has been described—a process termed **cotransmission** (see Chapter 9). The amount of neurotransmitter released is dependent not only on the degree to which the presynaptic terminal is depolarised but the rate of neurotransmitter synthesis, the presence of inhibitory presynaptic autoreceptors and presynaptic inputs from other neurons in the form of axoaxonic synapses (see Chapter 3). These synapses are usually inhibitory (i.e. presynaptic inhibition) and are more common in sensory pathways (see, for example, Chapter 20).

The released neurotransmitter acts on a specific protein or **receptor** in the postsynaptic membrane and in certain synapses on **presynaptic autoreceptors** (see Chapter 9). When this binding leads to an opening of ion channels with a cation influx in the postsynaptic process with depolarisation, then the synapse is said to be **excitatory**, while those ion channels that allow postsynaptic anion influx with hyperpolarisation are termed **inhibitory**.

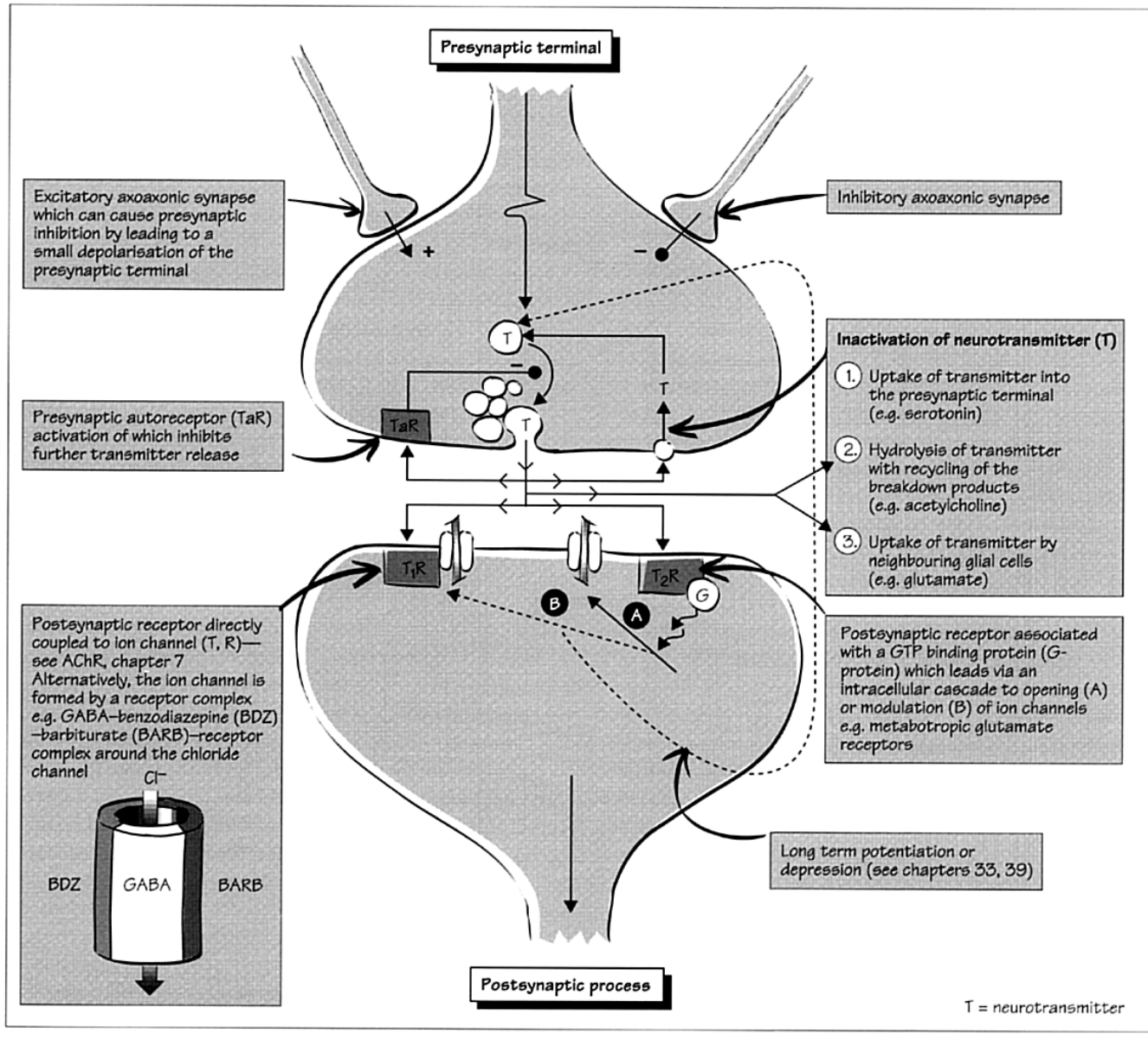
Excitatory postsynaptic potentials (EPSPs) are the depolarisations recorded in the postsynaptic cell to a given excitatory synaptic input. The depolarisations associated with the EPSPs can go on to induce action potentials if they are summated either in time or space. **Spatial summation** involves the integration by the postsynaptic cell of several EPSPs at different synapses with the summed depolarisation being sufficient to induce an action potential. **Temporal summation**, on the other hand, involves the summation of inputs in time such that each successive EPSP depolarises the membrane still further until the threshold for action potential generation is reached. In contrast **inhibitory postsynaptic potentials (IPSPs)** are hyperpolarisations of the postsynaptic membrane, usually as a result of an influx of Cl^- and an efflux of K^+ through their respective ion channels. IPSPs are very important in modulating the neuron's response to excitatory synaptic inputs (see figure). Therefore inhibitory synapses tend to be found in strategically important sites on the neuron—the proximal dendrite and soma—so that they can have profound effects on the input from large parts of the dendritic tree. In addition some neurons can inhibit their own output by the use of axon collaterals and a local inhibitory interneuron (**feedback inhibition**) e.g. motorneurons and Renshaw cells of the spinal cord (see Chapter 31).

More **long-term modulations of synaptic transmission** are discussed in Chapters 33, 39 and 44.

Abbreviations

EPSP excitatory postsynaptic potential
IPSP inhibitory postsynaptic potential

9 Neurotransmitters, receptors and their pathways



Neurotransmitters and synaptic function

The neurotransmitter released at a synapse interacts with a specific protein in the postsynaptic membrane, known as a **receptor**. At some synapses the neurotransmitter also binds to a **presynaptic autoreceptor** that regulates the amount of transmitter that is released. Receptors are usually specific for a given neurotransmitter, although several different types of that receptor may exist. In some cases co-released neurotransmitters can either modulate the binding of another neurotransmitter to its receptor or act synergistically on a common single ion channel (e.g. the **γ-aminobutyric acid (GABA)–benzodiazepine–barbiturate receptor**).

Receptors for specific neurotransmitters are either **coupled directly to ion channels** (T_1R on figure, e.g. acetylcholine receptors (AChR); see Chapter 7) or **to a membrane enzyme (T_2R)**. In these latter instances the binding of the neurotransmitter to the receptor either opens an ion channel via an intracellular enzyme cascade (e.g. cyclic adenosine monophosphate (cAMP) and G proteins) or indirectly modulates the probability of other ion channels opening in response to voltage changes

(so-called **neuromodulation**). These receptors therefore mediate slower synaptic events, unlike those receptors directly coupled to ion channels that relay fast synaptic information.

The activated receptor can only return to its resting state once the neurotransmitter has been removed either by a process of enzymatic **hydrolysis** or **uptake** into the presynaptic nerve terminal or neighbouring glial cells. Even then there are often intermediate steps in the process of returning the receptor and its associated ion channel to the resting state. At some synapses the affinity and ultimately the number of receptors is dependent on the previous activity of the synapse. For example, at catecholaminergic synapses the receptors become less sensitive to the released transmitter when the synapse is very active—a process of **desensitisation and down regulation**. This process involves a decrease in the affinity of the receptor for the transmitter in the short term, which goes on in the long term to an actual decrease in the number of receptors.

The converse is true with synapses that are rarely activated (so-called **supersensitivity and upregulation**), and in this way synaptic activity is modulated by its ongoing activity. In addition, at some synapses the activation of the postsynaptic receptor–ion channel complex can modulate the long-term activity of the synapse, either by affecting the presynaptic release of neurotransmitter or the postsynaptic receptor response—a process known as either **long-term potentiation (LTP) or long-term depression (LTD)** depending on the actual change in synaptic efficacy over time (see Chapters 33 and 44). Therefore the state, number and types of receptors for a specific neurotransmitter as well as the presence of receptors to other neurotransmitters are all important in determining the extent of synaptic activity at any given synapse.

Diversity and anatomy of neurotransmitter pathways

The nervous system employs a large number of neurotransmitters, but these can be seen to form families (see Appendix 1, p. 122).

Excitatory amino acids

These represent the main excitatory neurotransmitters in the CNS, and are important at most synapses in maintaining ongoing synaptic activity. The main excitatory amino acid is **glutamate** which acts at a number of receptors, that are defined by the agonists that activate them. The **ionotropic** receptors consist of the ***N*-methyl-D-aspartate (NMDA)** and **non-NMDA receptors**, the former receptor with its associated calcium channel may be important in the generation of LTP (Chapter 39), excitotoxic cell death (Chapter 42) and possibly ***epilepsy*** (Chapter 45).

A separate group of G-protein associated glutamate receptors, the **metabotropic receptors**, respond on activation by initiating a number of intracellular biochemical events which modulate synaptic transmission and neuronal activity. These receptors may underlie long-term depression in the hippocampus.

Inhibitory amino acids

The major CNS inhibitory neurotransmitters are the amino acids **GABA**, which is present throughout the CNS, and **glycine** which is predominantly found in the spinal cord. Abnormalities of GABA neurons may underlie some forms of movement disorders as well as anxiety states and epilepsy (see Chapters 30 and 43) while mutations in the glycine receptor have now been linked to some forms of ***hyperekplexia***—a condition in which there is an excessive startle response, such that any stimulus induces a stiffening of the body with collapse to the ground without any impairment of consciousness.

Monoamines

The monoaminergic systems of the CNS originate from small groups of neurons in the brainstem, which then project widely to all areas of the CNS. They are found at many other sites within the body, including the autonomic nervous system (see Chapter 36). In all locations they bind to a host of different receptors and thus can have complex actions (see Chapters 20, 34 and 38).

Acetylcholine

This neurotransmitter is widely distributed throughout the nervous system, including the neuromuscular junction (see Chapter 7) and autonomic nervous system (see Chapter 36). Therefore many agents have been developed which target the different cholinergic synapses in the periphery and which are used routinely in surgical anesthesia. Several disease processes can affect the peripherally located cholinergic synapses (see Chapter 7), while abnormalities in the central cholinergic pathways may be important in ***Parkinson's disease and dementia of the Alzheimer type*** (see Chapter 42).

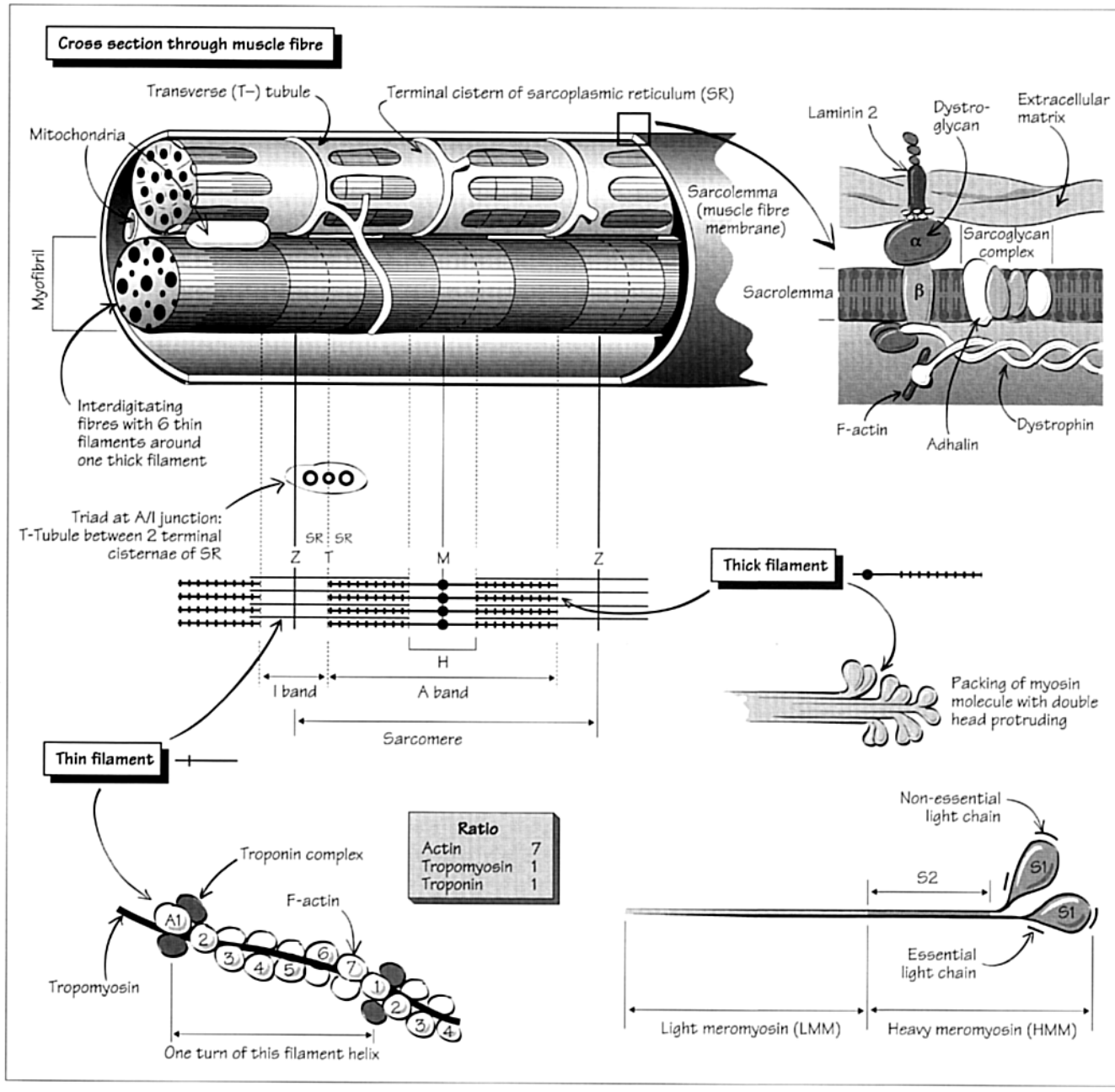
Neuropeptides

These neurotransmitters, of which there are many different types, are found in all areas of the nervous system and are often co-released with other neurotransmitters. They can act as conventional neurotransmitters as well as having a role in neuromodulation (e.g. pain pathways, see Chapter 20).

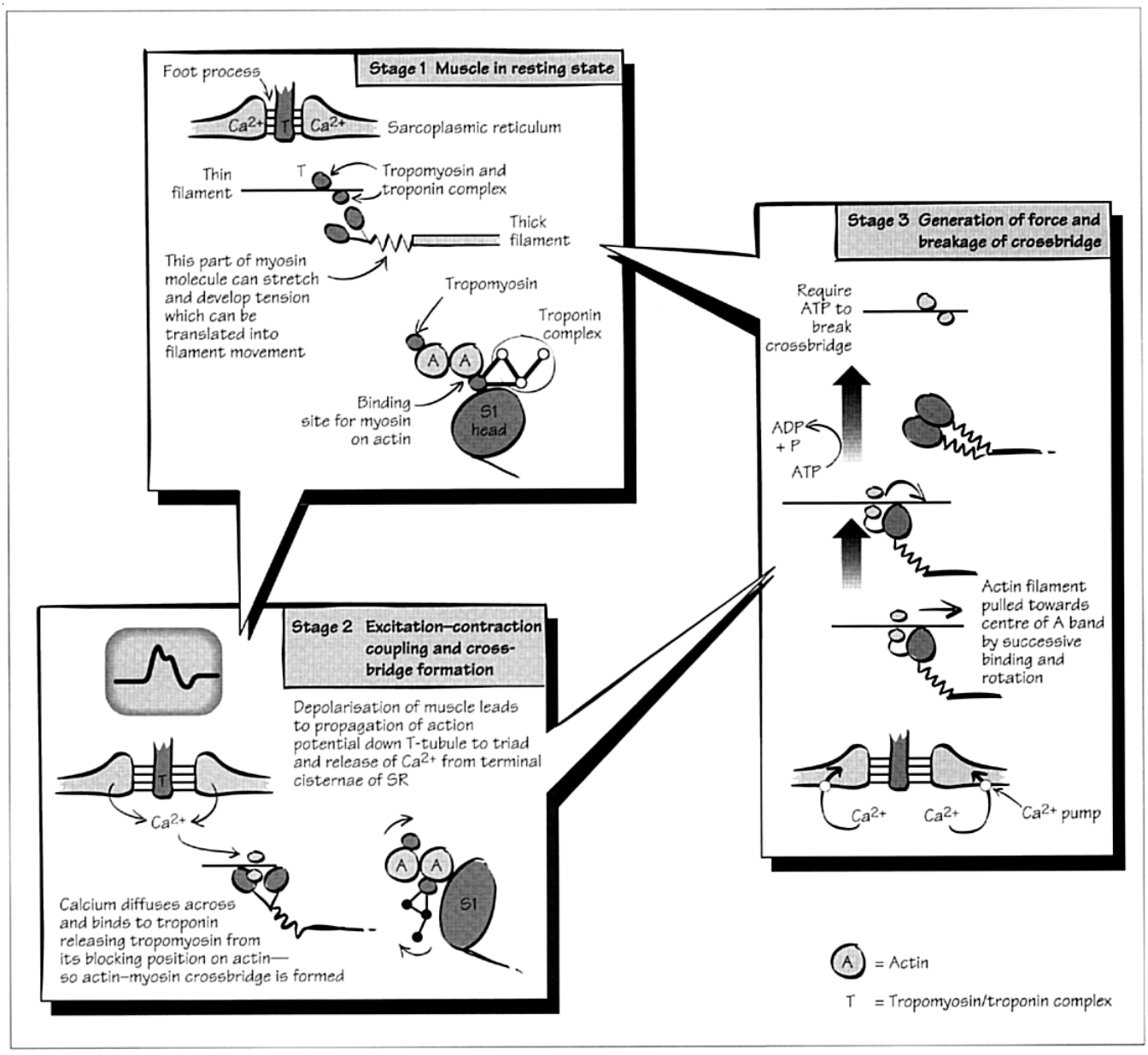
Abbreviations

AChR	acetylcholine receptor
cAMP	cyclic adenosine monophosphate
GABA	γ-aminobutyric acid
G-protein	guanosine triphosphate (GTP)-binding protein
LTD	long-term depression
LTP	long-term potentiation

10 Skeletal muscle structure and contraction



Skeletal muscle is responsible for converting the electrical impulse from a lower motorneuron that arrives at the neuromuscular junction (NMJ) into a mechanical force by means of contraction. The arrival of the action potential leads to the release of acetylcholine (ACh) that activates the nicotinic ACh receptor (AChR) in the postsynaptic muscle, which in turn leads to the depolarisation of the muscle fibre (see Chapter 7). This produces a calcium influx into the muscle fibre which leads to the removal of the blocking calcium-binding protein complex of **tropomyosin** and **troponin** from **actin**, the main component of the **thin filament**. The removal of this stearic block allows **myosin**, the major component of the **thick filaments**, to bind to actin via a **crossbridge**. The fibres are then pulled past each other; the crossbridge between the two fibres is broken at the end of this power stroke by the **hydrolysis of adenosine tripho-**



sphate (ATP). The cycle of crossbridge formation and breakage can then be repeated and the muscle contracts in a ratchet-like fashion. The whole process is termed the **sliding filament hypothesis** of muscle contraction.

Structure of skeletal muscle

Skeletal muscle is composed of groups of muscle fibres which are long multinucleated cells. These fibres contain **myofibrils**, which in turn are made up of thick and thin filaments which overlap to some extent giving this type of muscle its striated appearance. The myofibrils are bounded by the **sarcolemma** which invaginates amongst the myofibrils in the form of **transverse or T-tubules**. This structure is separate from the **sarcoplasmic reticulum (SR)** which envelops the myofibrils and is important as an intracellular store of Ca^{2+}. The sarcolemma is a complex structure and abnormalities in some of its membrane components have recently been found to underlie some forms of inherited muscular dystrophies.

The **thick filament** is composed of myosin and lies at the centre of the **sarcomere**. Myosin is composed of two heavy chains that form the **light and heavy meromyosin proteins** (LMM and HMM, respectively). The HMM portion contains **S2 and S1 subfragments**. The S1 fragment consists of two heads and associated with each head are two light chains. The light chain found at the tip of the S1 head is termed **non-essential** and is responsible for breaking down ATP at the end of the power stroke of crossbridge forma-

tion. The remaining **essential** light chain is attached at the point where the S1 head swings out towards the actin and is important in the process of myosin head movement. By virtue of the properties of LMM, myosin filaments spontaneously pack together so that the S1 heads are on the outside towards the actin filaments. The S1 heads therefore form the major part of the crossbridge with the actin.

Thin filaments are composed of **F-actin, tropomyosin and troponin,** which is itself composed of three subunits (troponin-I, -C and -T). These three components of the troponin complex all subserve different functions but as a whole they regulate muscle contraction by holding the tropomyosin in position so that it physically blocks the S1 head of the myosin from binding to the actin. The depolarisation of the muscle leads to a calcium influx, which then binds to troponin producing a conformational change in the thin filament such that the tropomyosin shifts off the binding site for myosin on actin. Thus tropomyosin and troponin regulate muscle contraction by a process of **stearic block**. In some muscles in other animals the regulation of the interaction between actin and myosin lies with the myosin-associated light chains.

At the point of overlap of these two sets of filaments the **triad** structure of a T-tubule linked to two terminal cisternae of SR by foot processes is to be found.

Muscle contraction

The sequence of events in the contraction of muscle is as follows.

- Stage 1: In the resting state the troponin complex holds the tropomyosin in such a position that it blocks myosin from binding to actin (stearic block).
- Stage 2: The arrival of an action potential at the NMJ causes a postsynaptic action potential to be initiated, which is propagated down the specialised invagination of the muscle membrane known as the **T-tubule**. This T-tubule conducts the action potential down into the muscle, so that all the muscle fibres can be activated. It lies adjacent to the terminal cisternae of the SR in a structure known as a **triad**, i.e. a T-tubule lies between two terminal cisternae of the SR (muscle equivalent of smooth endoplasmic reticulum) which contain high concentrations of Ca^{2+}. The T-tubules are linked to the SR by foot processes, which are part of a calcium ion channel. The arrival of the action potential at the triad leads to the release of Ca^{2+} from the terminal cisternae, by a process of mechanical coupling. The action potential opens a common Ca^{2+} ion channel between the T-tubule and SR, which then allows Ca^{2+} to influx down its electrochemical gradient towards the myofibrils.

The Ca^{2+} then binds to the troponin complex and this leads to a rearrangement of the tropomyosin so that the myosin head can now bind to the actin, forming a crosslink or crossbridge.

- Stage 3: Once the myosin has bound to the actin there is a delay before tension develops in the crossbridge. The tension pulls and rotates the actin past the myosin and this causes the muscle to contract. The crossbridge at the end of this power stroke detaches the myosin from actin with hydrolysis of ATP, a process that is also calcium dependent. The whole cycle can then be repeated. The process of crossbridge formation with filament movement is called the **sliding filament hypothesis** of muscle contraction, as the two filaments slide past each other in a ratchet-like fashion as the cycle repeats. The Ca^{2+} released by the terminal cisternae of the SR, allowing the process of crossbridge formation and breakage, is actively taken back up into this structure by a specific Ca^{2+} pump.

Disorders of skeletal muscle

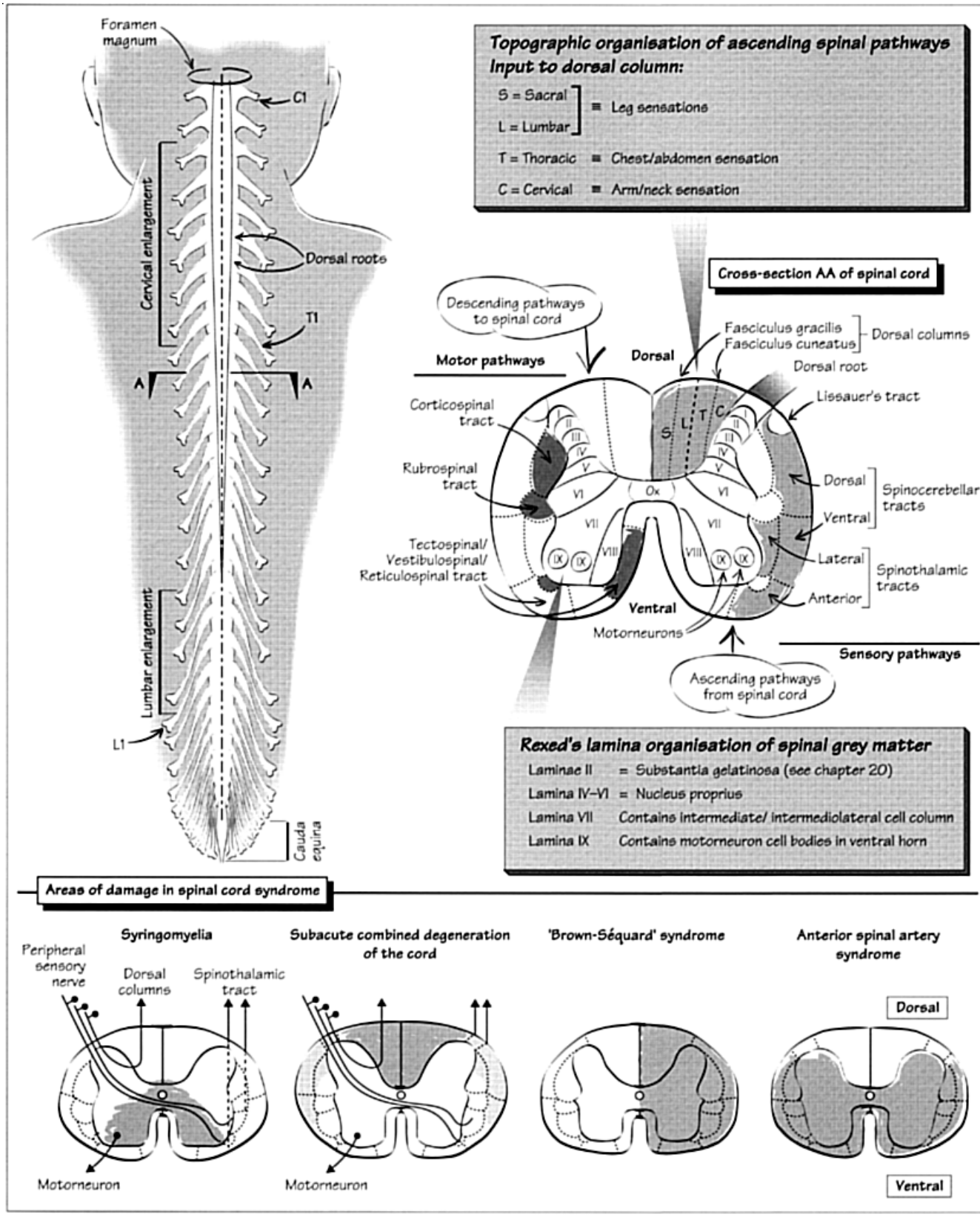
There are many disorders of the muscle, which include disorders of excitability through mutations in the ion channels (see Chapter 5) as well as inflammation (see Chapter 46) and abnormalities in the structural proteins of the muscle itself. These latter conditions underlie many of the inherited muscular dystrophies of which the best characterised are Duchenne's and the limb girdle muscular dystrophies. ***Duchenne's muscular dystrophy (DMD)*** is an X-linked disorder in which there is a deletion of the gene coding for the structural protein dystrophin, with the milder form of the disease ***(Becker's muscular dystrophy)*** having a reduced amount of this same protein. Patients with DMD typically present early in life with clumsiness and difficulty in walking, with an associated wasting of the proximal limb muscles and pseudohypertrophy of the calf muscles. As the disease progresses the patient becomes increasingly disabled with the development of cardiac and other abnormalities which lead to death, typically in the third decade. Characteristically the patients have a raised creatine kinase (a marker of muscle damage) as the muscles in these patients are prone to necrosis as a result of the absence of dystrophin. This protein lies beneath the sarcolemma of skeletal (as well as smooth and cardiac) muscle and provides stability and flexibility to the muscle membrane, such that when absent the membrane can be easily disrupted. This allows entry of large quantities of Ca^{2+} which precipitates necrosis by excessive activation of proteases.

The ***limb girdle muscular dystrophies (LGMD)***, in contrast, can present at any age with progressive weakness of the proximal limb muscles and a raised creatine kinase. The condition can be inherited in a number of different ways, and recently the autosomal recessive forms of this condition have been found to contain abnormalities in the dystrophin associated glycoproteins, adhalin and the sarcoglycan complex. These proteins link the intracellular dystrophin with components of the extracellular matrix and so are important in maintaining the integrity of the sarcolemma.

Abbreviations

ACh	acetylcholine
AChR	acetylcholine receptor
ATP	adenosine triphosphate
DMD	Duchenne's muscular dystrophy
HMM	heavy meromyosin
LGMD	limb girdle muscular dystrophy
LMM	light meromyosin
NMJ	neuromuscular junction
SR	sarcoplasmic reticulum
T-tubule	transverse tubule

11 Organisation of the spinal cord



Overall structure

The spinal cord lies within the vertebral canal and extends from the foramen magnum to the lower border of the first lumbar vertebra and is enlarged at two sites (cervical and lumbar regions) corresponding to the innervations of the upper and lower limbs (see Chapter 1). The lower part of the vertebral canal (i.e. below L1) contains the lower lumbar and sacral nerves and is known as the **cauda equina**.

Sensory nerve fibres enter the spinal cord via the **dorsal (posterior) roots** and their accompanying cell bodies are located in the dorsal root ganglia, while the motor and preganglionic autonomic fibres exit via the **ventral (or anterior) root,** together with some mostly unmyelinated afferent fibres. The **motor cell bodies (or motorneurons)** are found in the ventral horn of the spinal cord, while the preganglionic cell bodies of the sympathetic nervous system are found in the **intermedio-lateral column** of the spinal cord.

The neuronal cell bodies that make up the central grey matter of the cord are organised into a series of **laminae (of Rexed)**. The white matter surrounding this is composed of myelinated and unmyelinated axons constituting the ascending and descending spinal tracts.

Organisation of sensory afferent fibres entering the spinal cord

Sensory information from the peripheral receptors is relayed by primary afferent nerve fibres which terminate in layers I–V of the dorsal horn, the site for termination being different for different receptors. In reality, however, many afferent fibres divide (into an ascending and a descending branch) as they enter the spinal cord so that synaptic contact can be made both with many interneurons in the dorsal horn, as well as up and down the cord through Lissauer's tract.

Sensory processing in the dorsal horn

Typically, a number of primary afferents make synaptic contact with a single dorsal horn neuron. This **convergence** of input has the effect of reducing the acuity (accuracy) of stimulus location. However, the process of **lateral inhibition** helps minimise this loss of acuity by promoting the inhibition of submaximally activated fibre inputs and thus increasing spatial contrast in the sensory input. The dorsal horn receives a number of descending inputs from supraspinal structures that are important in modulating the processing of sensory information through the spinal cord (see Chapter 20).

Ascending sensory pathways in spinal cord

The spinothalamic (STT), spinocerebellar and dorsal columns (DC) are the major ascending pathways of the spinal cord (see Table 11.1). Each tract relays specific information in a topographic fashion, i.e. the sensory information from different parts of the body is conserved in

Table 11.1 Ascending sensory pathways in spinal cord.

Tract	Spinothalamic tract (STT)	Dorsal column-medial lemniscal pathway	Spinocerebellar tract (SCT)
Relevant chapter	20	19	33
Site of origin	Dorsal horn (Laminae I, III, IV and V) Crosses midline in spinal cord	Primary afferents from mechanoreceptors, muscle and joint receptors	Spinal cord interneurons and proprioceptive information from muscle and joint
Termination	Somatotopic organisation with more caudal fibres added laterally Projects to brainstem and contralateral thalamus	Somatotopic organisation with fibres terminating in dorsal column nuclei of medulla Decussate at this level to form medial lemniscus that synapses in ventroposterior nucleus of the thalamus	Two tracts: Dorsal SCT relays information from spinal cord interneurons via inferior cerebellar peduncle to cerebellum Ventral SCT relays information from muscle and joint receptors via superior cerebellar peduncle to cerebellum
Function	Conveys pain and temperature	Conveys proprioception, light touch and vibration	Conveys proprioceptive information as well as information of on-going activity in spinal cord interneurons

the organisation of the ascending pathways. Inputs from the more rostral parts of the body (arm as opposed to leg) supply fibres that lie more laterally in the ascending pathway. Both the DC and STT are **decussate** (fibres cross the midline) and therefore the sensory information they relay is ultimately processed in the **contralateral** cerebral hemisphere. However, the site at which this decussation occurs is different for the two pathways (see Chapters 19 and 20).

Spinal motorneurons

α- and γ-motorneurons (MNs) are both found in the ventral (anterior) horn. The α-MN is one of the largest neurons found in the nervous system and innervates skeletal muscle fibres while the γ-MN innervates the intrafusal muscle fibres of the muscle spindle (see Chapter 30). The cervical cord MNs innervate the arm muscles while the lumbar and sacral MNs innervate the leg musculature. The MNs are arranged **somatotopically** across the ventral horn such that the more medially placed MNs innervate proximal muscles while those located more laterally innervate distal muscles (see Chapter 31).

Descending motor tracts

There are a number of descending motor pathways that are defined by their site of origin within the brain (see Table 11.2). The corticospinal (CoST) or pyramidal tract originates in the cerebral cortex and with the rubrospinal tract innervates the laterally placed MNs that supply the distal musculature. In contrast, the remainder of the extrapyramidal tracts (vestibulo-, reticulo- and tectospinal) tracts innervate the more ventromedially placed MNs that control the axial musculature (see Chapters 29–32).

Clinical features of spinal cord damage

A knowledge of the organisational anatomy of the spinal cord indicates that damage to it produces a predictable series of deficits, which is of great value in clinical neurology. Examples of specific spinal cord lesions and syndromes illustrating this point include the following.

Syringomyelia

Syringomyelia is the development, for a number of reasons, of a cyst or cavity around or near to the central canal, usually in the cervical region. The lesion typically disrupts the STT fibres as they cross just ventral to the central canal, resulting in a dissociated sensory loss, i.e. reduced temperature and pain sensation at the level of the lesion but normal light touch, vibration perception and joint position sense (see also Chapter 20). In addition there may be motor involvement because of expansion of the cyst into the ventral horn or laterally into the descending motor tracts.

Subacute combined degeneration of the spinal cord

This is usually associated with pernicious anaemia and a

Table 11.2 Descending motor tracts.

Tract	Corticospinal or pyramidal tract (CoST)	Rubrospinal tract (RuST)	Vestibulospinal tract (VeST)	Reticulospinal tract (ReST)
Relevant chapter	19,31,32	31,32	26,31,32	31,32
Site of origin	Primary motor cortex (40%) Premotor cortex (30%) Somatosensory cortex (30%)	Magnocellular part of red nucleus in midbrain	Deiter's nucleus in the medulla (i.e. part of the vestibular nuclear complex)	Caudal reticular formation in pons and medulla
Major actions	Important in independent fractionated finger movements A role in sensory processing (see Ch.19)	Projects to a similar population of MNs as CoST, namely those concerned with distal motor control Experimentally lesions of this tract produce little deficit unless combined with lesions of the CoST Its existence and significance in humans is debated	Innervates predominantly the extensor and axial muscles, and as such is important in the control of posture and balance	The ReST has both an excitatory and inhibitory input to the spinal cord interneurons and to a lesser extent MNs This pathway is important in damping down activity within the spinal cord such that a loss of this pathway produces profound extensor tone

The tectospinal tract is a relatively minor tract originating from the tectum in the midbrain. It is briefly discussed in Chapter 35.

lack of vitamin B_{12}. It is characterised by demyelination and eventually degeneration of the DCs, the spinocerebellar tracts and the CoST and in addition there is damage to peripheral nerves ***(peripheral neuropathy)***. Patients therefore develop a combination of paraesthesiae and sensory loss (especially light touch, vibration perception and joint position sense) with weakness and incoordination (see also Chapter 19).

Brown-Séquard syndrome

This describes a lesion involving one half of the cord such that there is an ipsilateral loss of position and tactile senses (DC sensory information), a contralateral loss of temperature sensation originating from several segments below the lesion (STT sensory information), and ipsilateral spasticity and weakness because of involvement of the CoST pathway (see also Chapters 19 and 20).

Anterior spinal artery syndrome

This syndrome describes the situation when there is occlusion of the artery providing blood to the anterior two-thirds of the cord. The patient has weakness and sensory loss to temperature and pain with preservation of DC sensory modalities such as joint position sense and vibration perception (see also Chapter 16).

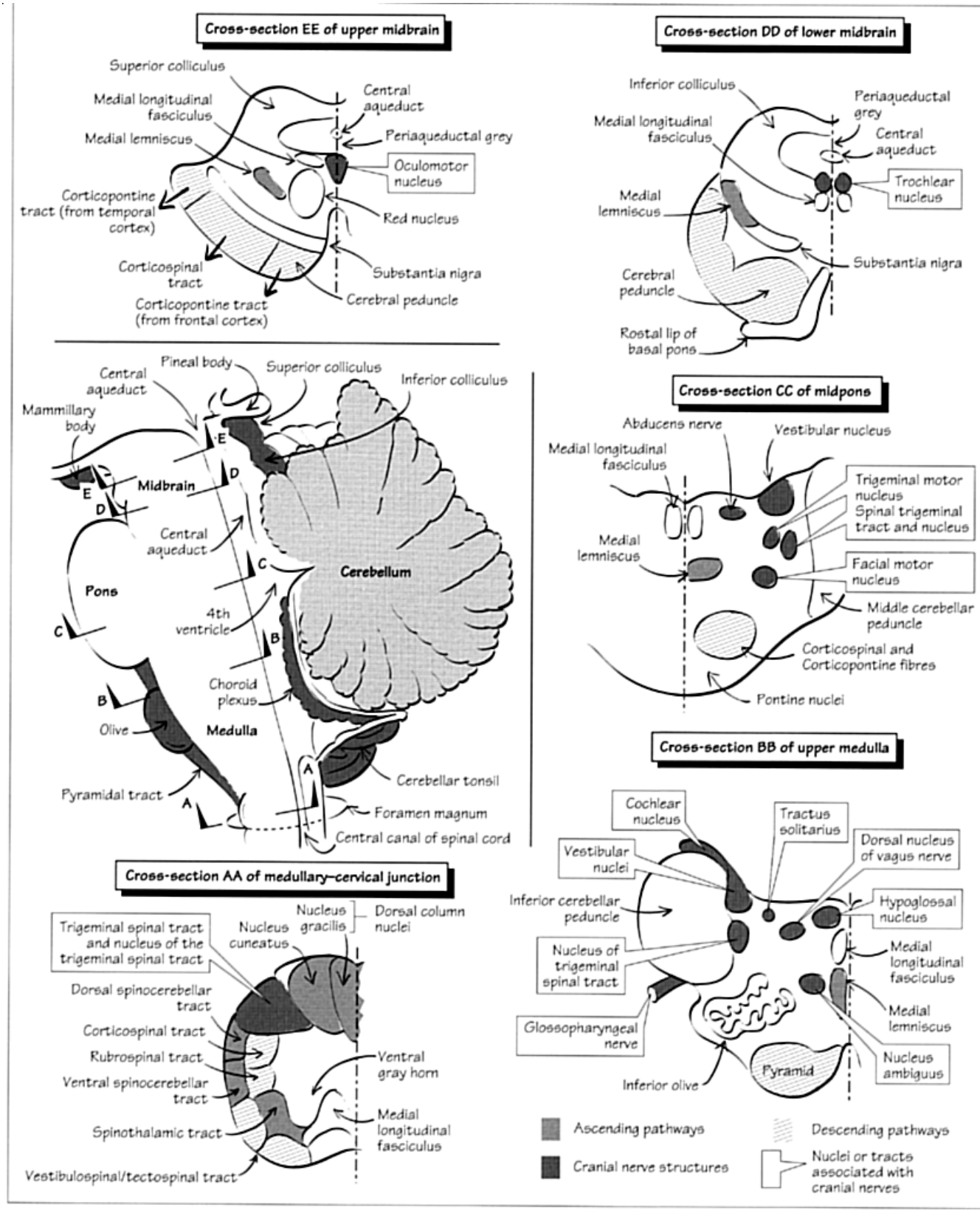
Transverse myelitis

Transverse myelitis (not shown in figure) describes a complete lesion of the whole spinal cord at one level which produces a complete sensory loss with weakness from that level down. The weakness characteristically being caused by a disruption of both the descending motor pathways and the spinal motorneurons.

Abbreviations

CoST	corticospinal tract
DC	dorsal column
MN	motorneuron
STT	spinothalamic tract

12 Anatomy of the brainstem



The brainstem consists of that part of the brain that begins at the **foramen magnum** and extends to the cerebral peduncles and thalamus. It consists of the **medulla, pons** and **midbrain** and is located anterior to the cerebellum to which it is connected by three cerebellar peduncles. It contains the following:

- The nuclei for 10 of the 12 pairs of **cranial nerves** (see Chapter 13), the exceptions being the olfactory and optic nerves.
- The apparatus for controlling eye movements which includes the third, fourth and sixth cranial nerves (see Chapter 35).
- The monoaminergic nuclei that project widely throughout the CNS (see Chapters 9, 20 and 38).
- Areas that are vital in the control of respiration and the cardiovascular system, as well as the autonomic nervous system (see Chapter 36).
- Areas important in the control of consciousness, which include some of the monoaminergic nuclei (see Chapter 38).
- A number of ascending and descending pathways linking the spinal cord to supraspinal structures, such as the cerebral cortex and cerebellum, some of which take their origin from the brainstem (see Chapters 11, 17, 19, 20, 29, 31, 32 and 33).

A number of structures found within the brainstem are worthy of special comment.

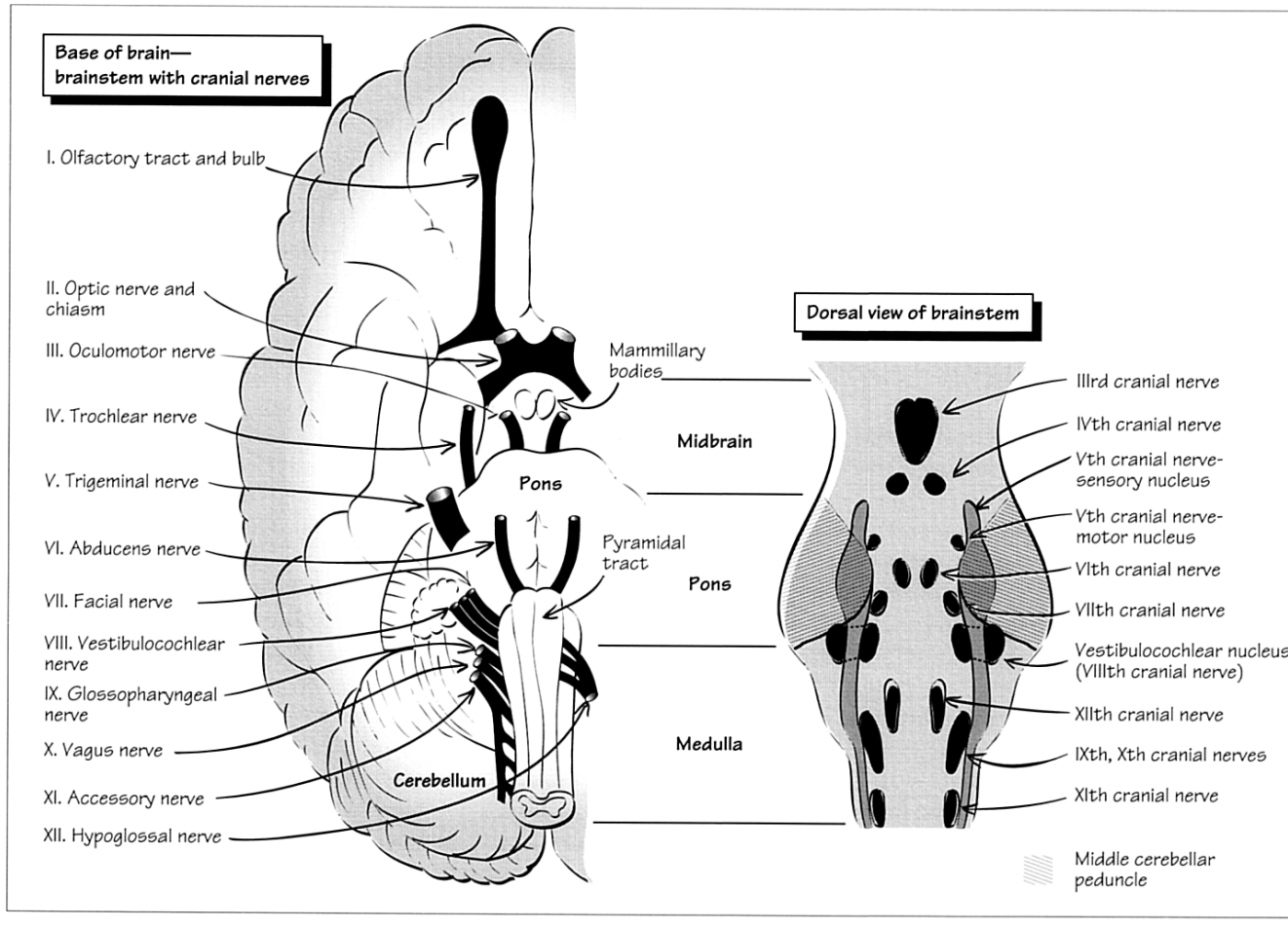
- The **dorsal column nuclei** represent the primary site of termination of the fibres conveyed in the dorsal columns (DCs), responsible for light touch, vibration perception and joint position sense. The relay neurons in this structure send axons that decussate in the lower medulla to form the **medial lemniscus** that synapses within the thalamus (see Chapters 11 and 19).
- The **pyramid** which represents the descending corticospinal tract (CoST) in the medulla, a pathway that decussates at the lower border of this structure.
- The **tractus solitarius** and **nucleus ambiguus** are intimately associated with taste and the motor innervation of the pharynx by the glossopharyngeal and vagus nerves (see Chapter 13).
- The **inferior olive** in the medulla receives inputs from a number of sources and provides the climbing fibre input to the cerebellum (see Chapters 33 and 44).
- The **cerebellar peduncles** convey information to and from the cerebellum (see Chapter 33).
- The **medial longitudinal fasciculus** originates in the vestibular nucleus and projects rostrally connecting the oculomotor nuclei (third, fourth and sixth cranial nerves) as well as caudally as part of the vestibulospinal tract.
- The **vestibular nucleus** has important connections from the ear and projects to the spinal cord and cerebellum as well as other brainstem structures (see Chapters 26, 31 and 33).
- The **substantia nigra** in the midbrain contains both dopamine and γ-aminobutyric acid (GABA) neurons and forms part of the basal ganglia and is involved in the control of movements (see Chapters 34 and 35). The loss of its dopaminergic neurons is the major pathological event in Parkinson's disease.
- The **red nucleus** in the midbrain is intimately associated with the cerebellum, and is the site of origin for the rubrospinal tract which, with the CoST, forms the lateral descending pathway of motor control (see Chapters 11, 31 and 33).
- The **periaqueductal grey matter** of the mesencephalon is an area rich in endogenous opioids and thus is important in the supraspinal modulation of nociception (see Chapter 20).
- The **central aqueduct of Sylvius** running through the midbrain connects the third to the fourth ventricle, and narrowing of it (stenosis) can cause hydrocephalus (see Chapter 15).
- The **cerebral peduncles** contain the descending motor pathways from the cerebral cortex to the spinal cord and brainstem, especially the pons (see Chapter 29).
- The **inferior colliculus** in the midbrain is intimately involved with the auditory system (see Chapter 25) while the **superior colliculus** is more involved with visual processing and eye movement control (see Chapters 22 and 35).

Thus damage to the brainstem can have devastating consequences, although small lesions can often be localised with great accuracy because of the number of structures located within this small area of the brain. The commonest causes of lesions in this part of the brain are either inflammatory (e.g. ***multiple sclerosis***; see Chapter 46) or vascular in nature (see Chapter 16). However, disorders of the brainstem can also be seen with tumours (see Chapter 4) and a host of other conditions.

Abbreviations

CoST	corticospinal tract
DC	dorsal column
GABA	γ-aminobutyric acid

13 Cranial nerves



Cranial nerves

I Olfactory nerve

The receptors for olfaction are found within the nasal mucosa, and their axons project through the cribriform plate to the olfactory bulb on the undersurface of the frontal lobe (see Chapter 27). This cranial nerve therefore does not originate or pass through the brainstem, but is a CNS structure.

II Optic nerve

The photoreceptors in the eye project via ganglion cells to the CNS via the optic nerve. The nerve passes through the optic canal into the brain to form the optic chiasm, whence the fibres pass back as the optic tract and radiation (see Chapter 22). This cranial nerve therefore does not originate or pass through the brainstem, but is a CNS structure. There is, however, a projection from the optic tract to the midbrain which is important in controlling the **pupillary response to light** (see Chapter 22).

III The oculomotor nerve

This originates in the midbrain at the level of the superior colliculus and supplies all the extraocular muscles apart from the lateral rectus which is supplied by the abducens (sixth cranial) nerve and superior oblique that is supplied by the trochlear (fourth cranial) nerve. The oculomotor nerve also carries the parasympathetic innervation to the eye as well as providing the major innervation of levator palpebrae superioris. A complete third nerve palsy causes the eye to lie 'down and out' with a fixed, dilated, unresponsive pupil and **ptosis**.

IV The trochlear nerve

This nerve originates in the midbrain at the level of the inferior colliculus, and passes out of the brainstem dorsally. It supplies the superior oblique muscle and damage to this nerve causes double vision (diplopia) on looking down.

V The fifth cranial or trigeminal nerve

The trigeminal nerve has both a motor and sensory function. The motor nucleus is situated at the midpontine level, medial to the main sensory nucleus of the trigeminal nerve, and receives an input from the motor cortex (see Chapter 32). It supplies the muscles of mastication. Sensation from the whole face (including the cornea) passes to the brainstem in the trigeminal nerve, and synapses in three major nuclear complexes: the nucleus of the spinal tract of the trigeminal nerve; the main sensory nucleus of the trigeminal nerve; and the mesencephalic nucleus. Sensation from the face is relayed via the three branches of the trigeminal nerve: the ophthalmic division that supplies the forehead; the maxillary division that supplies the cheek; and the mandibular branch that supplies the jaw—with the more rostral fibres (ophthalmic branch fibres) passing to the lowest part of the nucleus of the spinal tract in the upper cervical cord. These brainstem trigeminal nuclei in turn project to the thalamus as part of the somatosensory and pain systems (see Chapters 19 and 20). Damage to the trigeminal nerve results in weak jaw opening and chewing, coupled to facial sensory loss and an absent corneal reflex.

VI The sixth cranial or abducens nerve

This originates from the dorsal lower portion of the pons and supplies the lateral rectus muscle. Damage to it causes horizontal diplopia when looking to the lesioned side.

VII The seventh cranial or facial nerve

This is predominantly a motor nerve, although it does carry parasympathetic fibres to the lacrimal and salivary glands (via the greater superficial petrosal nerve and chorda tympani) as well as sensation from the anterior two-thirds of the tongue (via the chorda tympani). The motor nucleus for the facial nerve originates in the pons, and supplies all the muscles of the face except for those involved in mastication.

Damage to this nerve is not uncommon and can occur at any site along its long course, as it passes out of the brainstem through the internal auditory meatus, middle ear and mastoid and through the stylomastoid foramen and into the soft tissue structures of the face. A lesion of this nerve at any of these sites produces a lower facial nerve palsy with weakness of all the facial muscles ipsilateral to the side of the lesion. In addition, there is a loss of taste on the anterior two-thirds of the tongue if the lesion occurs proximal to the departure of the chorda tympani. This is most commonly seen in ***Bell's palsy***. In contrast, damage to the descending motor input to the facial nucleus from the cortex (an upper motorneuron facial palsy) causes weakness of the lower part of the face only, as the musculature of the upper part of the face has an upper motorneuron innervation from the motor cortex of both hemispheres (see Chapters 29–32).

VIII The eighth cranial or vestibulocochlear nerve

This conveys information from the cochlea (the auditory or cochlear nerve; see Chapters 24 and 25) as well as the semicircular canals and otolith organs (the vestibular nerve; see Chapter 26). Damage to this nerve (e.g. in ***acoustic neuromas***), causes disturbances in balance with deafness and tinnitus (a ringing noise).

IX The ninth cranial or glossopharyngeal nerve

The glossopharyngeal nerve contains motor, sensory and parasympathetic fibres. The motor fibres originate from the rostral nucleus ambiguus and supply the stylopharyngeus muscle, while the sensory fibres synapse in the tractus solitarius (or nucleus of the solitary tract) and provide taste and sensation from the posterior tongue and pharynx. The parasympathetic fibres originate in the inferior salivatory nucleus and provide an input to the parotid gland. Damage to this nerve is usually in conjunction with the vagus nerve (see below).

X The tenth cranial or vagus nerve

This nerve provides a motor input to the soft palate, pharynx and larynx which originates in the dorsal motor nucleus of the vagus and nucleus ambiguus. It also has a minor sensory role, conveying taste from the epiglottis and sensation from the pinna, but has a significant parasympathetic role (see Chapter 36). Damage to the vagus nerve causes dysphagia and articulation disturbances and, as with glossopharyngeal nerve lesions, there may be a loss of the gag reflex. This reflex involves tongue retraction and elevation of the pharyngeal musculature in response to a sensory stimulus on the posterior pharynx.

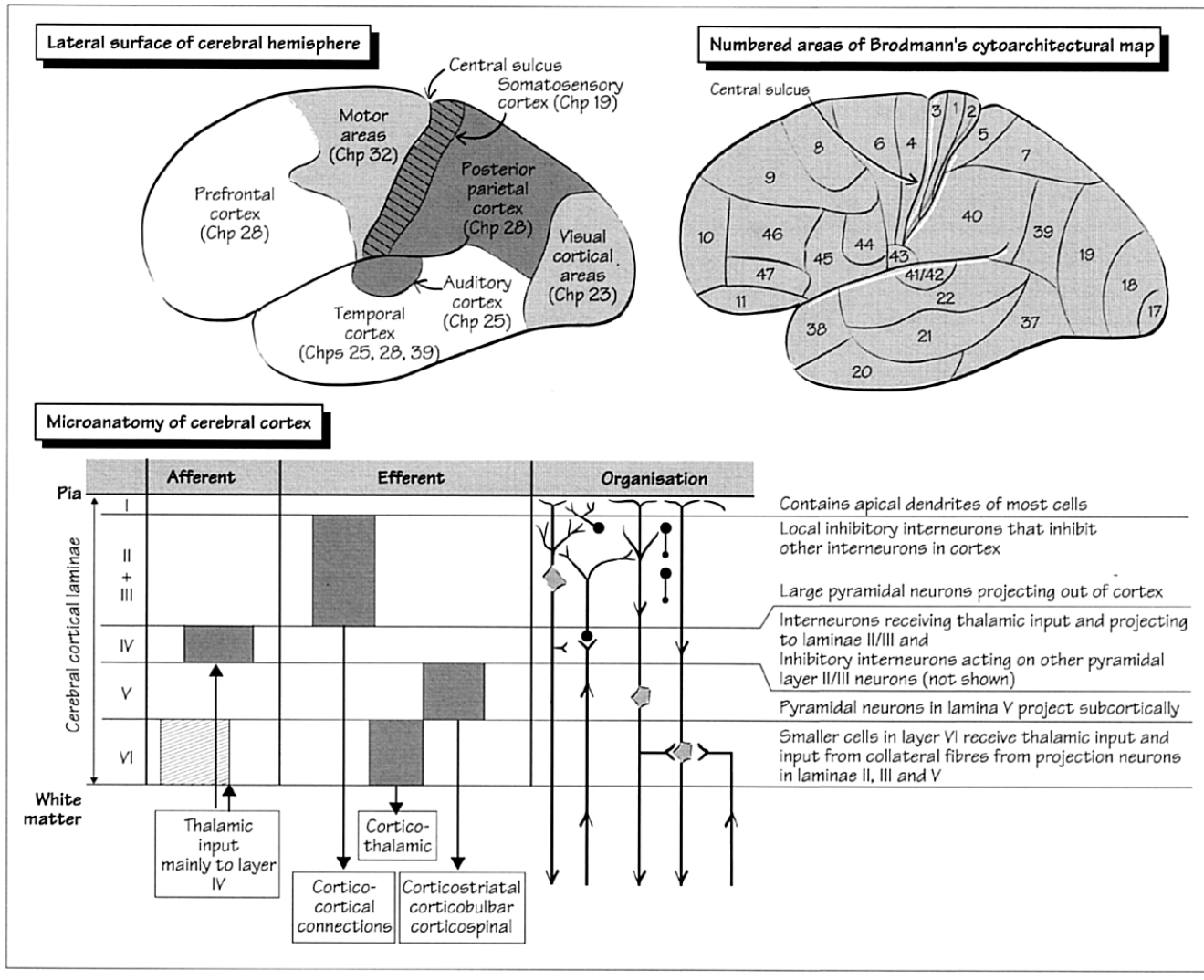
XI The eleventh cranial or spinal accessory nerve

This is purely motor in nature and originates from the nucleus ambiguus in the medulla and the accessory nucleus in the upper cervical spinal cord and supplies the sternocleidomastoid and trapezius muscles. Damage to it causes weakness in these muscles, although in practice this nerve is often damaged in conjunction with other lower cranial nerves.

XII The twelfth cranial or hypoglossal nerve

The hypoglossal nerve provides the motor innervation of the tongue. Its fibres originate from the hypoglossal nucleus in the posterior part of the medulla. Damage to this nerve causes wasting and weakness in the tongue which leads on to problems of swallowing and speech. This nerve is commonly affected with other lower cranial nerves (e.g. IX, X, XI cranial nerves with motorneuron disease) and in such cases the patient may present with a ***bulbar palsy***. A ***pseudobulbar palsy***, in contrast, refers to a loss of the descending cortical input to these cranial nerve nuclei.

14 The organisation of the cerebral cortex



The organisation of the outer layer of the cerebral hemisphere or **cerebral cortex** (neocortex) can be considered in various ways. Some of the earliest ways of doing this with cytoarchitectural maps are still used (e.g. **Brodmann's map** of the human brain from 1909). This way of mapping the cortex equates to some extent with the functional organisation of this structure into motor, sensory and association areas, as evidenced by the **laminar organisation** of the cortex. An area of cortex that is predominantly sensory in character has a prominent layer IV within it as this is the site of termination for thalamic afferent fibres, while cortical motor areas have a prominent layer V. An alternative approach is to view the cortex as being organised vertically. This vertical organisation has become known as the **columnar hypothesis** and proposes that the 'column' of cortex is the basic unit of cortical processing and that the phylogenetic development of the cortex has involved an increase in the number of these columns. This explains why the enlargement of the neocortex in primates has been accomplished by a great expansion of its surface area, without striking changes in the number of neurons in a vertical penetration across the thickness of the cortex.

Anatomical organisation of the cerebral cortex

The neocortex is classically described as consisting of six layers, although in certain areas of the cerebral cortex further subdivisions are used, e.g. the primary visual cortex (see Chapter 23). The thalamic afferent fibres, relaying sensory information, project to layer IV often with a smaller input to layer VI, and terminate in discrete patches

thus ensuring that sensory information from a specific location and/or receptor type is relayed to a specific area of cortex. This input then synapses on interneurons within the cortex which in turn project vertically to neurons in layers II, III and V which in turn project to other cortical and subcortical sites, respectively. Thus the weight of synaptic relations within the cerebral cortex is in the vertical direction, although corticocortical connections linking columns of similar characteristics are found. This arrangement of synaptic connections is well seen in the somatosensory and visual cortices (see Chapters 19 and 23), and it means that a given sensory input from the thalamus will be analysed by a vertical column of cortical neurons. In cortical areas with a motor function, the motor output from that cortical area is such that it is directed back at the motorneurons (MNs) controlling the muscles that move the sensory receptors which ultimately project to that same area of cortex—so-called input–output coupling (see Chapter 32 for more details).

The anatomical evidence thus supports the notion of a vertical columnar organisation to the neocortex, but further evidence comes from developmental and neurophysiological studies.

Developmental organisation of the cerebral cortex

In the mammalian CNS the entire population of cortical neurons is produced by a process of migration from the proliferative zones that are situated around the cavities of the cerebral ventricles. The **radial glial fibres** that guide the migrating neurons and which span the fetal cerebral wall disappear or become transformed into astrocytes towards the end of gestation (see Chapter 4). On closure of the neural tube the **ventricular and subventricular zones** display cell division, and some of these cells are destined to become cortical neurons and thus migrate out along the radial glial fibres through an **intermediate zone** which will later become the subcortical white matter. The cells eventually reach the developing **cortical plate**. Thus developmentally, the cortex forms in a vertical fashion.

Neurophysiological organisation of the cerebral cortex

Neurophysiologically, if a recording electrode is passed at right angles through the cortex, it encounters cells with similar properties. However, if the electrode is passed tangentially then cells shift their response characteristics. This has been shown in all the primary sensory cortices, as well as the primary motor cortex (see Chapters 19, 23 and 32).

This columnar organisation of the cortex means that topography can be maintained and that the reorganisation of the cortex in the event of a change in the peripheral input is relatively straightforward (see Chapter 44).

Functional organisation of the cerebral cortex

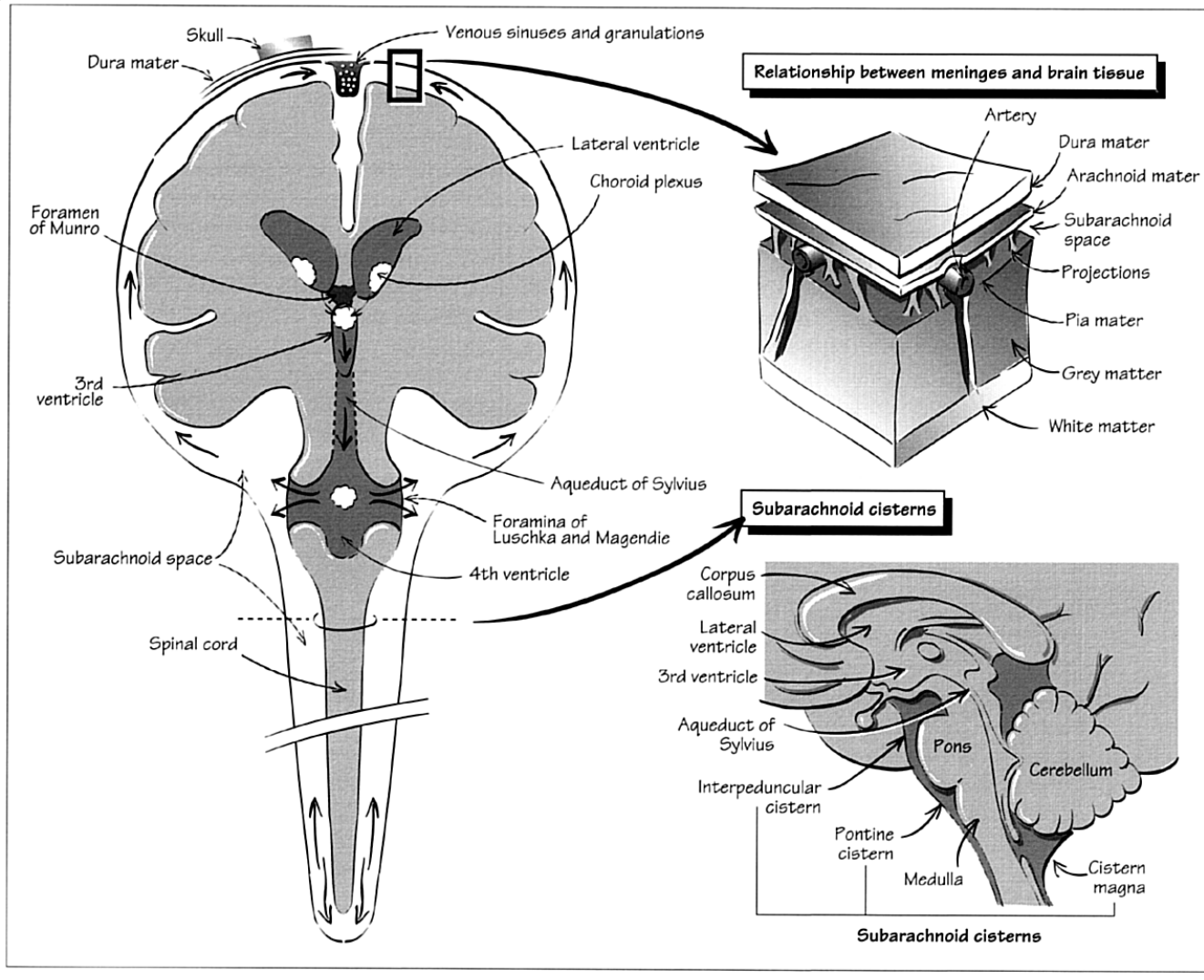
The relationship of cortical columns to one another raises many interesting questions as to the mode of function employed by the cerebral cortex. The original models on information processing in the cortex proposed that it was performed in a serial fashion, such that the cortical cells form a series of levels in a **hierarchy**. Thus one set of cells perform a relatively straightforward analysis which then converges on another population of neurons that perform a more complex analysis (see, for example, Chapter 23). The ultimate prediction of these hierarchical models is that one neuron at the top of the hierarchy will register the percept—the so-called **'grandmother' cell**. However, the discovery of the X, Y and W classes of ganglion cells in the retina (see Chapter 21) led on to the development of a competing theory that proposed that information is analysed by a series of **parallel pathways**, with each pathway analysing one specific aspect of the sensory stimulus (e.g. colour or motion with visual stimuli; see Chapter 23). This theory does not exclude hierarchical processing but relegates it to the mode of analysis within separate parallel pathways. In practice, however, the cortex employs both modes of analysis.

It should be stressed that cortical columns are not to be viewed as a static mosaic structure, as one column may be a member of a number of different pathways of analysis. This organisation has been termed the **distributed system theory** and describes the brain as a complex of widely and reciprocally interconnected systems, with the dynamic interplay of neural activity within and between these systems as the very essence of brain function. Consequently one column may be a member of many distributed systems, because each distributed system is specific for one feature of a stimulus and one column may code for several features of the stimulus. An analogy for viewing this is to imagine the London underground system where each station is defined by the connections it has with other stations. Thus one station may be part of many different lines and providing to each a unique quality. This analogy also helps explain the plasticity within the CNS, as damage to a station can be compensated for, up to a point, by the remaining networks as there is a degree of redundancy to the representation. However, if there is severe damage, especially of important centres or the peripheral terminals, then the system cannot compensate and lasting deficits ensue.

Abbreviation

MN motorneuron

15 Meninges and cerebrospinal fluid



Within the cranium the brain is enclosed by three protective layers which also extend down the spinal cord. The **dura mater** is a thick tough membrane lying close to the cranium and vertebrae and innervated by afferent fibres of the trigeminal nerve and upper cervical nerves. Headache can be associated with disturbance or inflammation of the dura. Adjacent to this is the **arachnoid mater**, a thin membrane with thread-like processes which project into the subarachnoid space and make contact with the delicate **pia mater** which envelopes the contours of the brain surface and dips into the sulci.

The **subarachnoid space** is filled with cerebrospinal fluid (CSF) and also accommodates major arteries, branches of which project down through the pia into the brain. At specific sites the size of the subarachnoid space increases to form **cisterns**. These are particularly prevalent in the region of the brainstem and the largest is the **cisterna magna** found between the cerebellum and medulla.

The meninges extend caudally enclosing the spinal cord. Here the dura is attached to the foramen magnum at its upper limit and projects down to the second sacral vertebrae.

CSF production and circulation

CSF is largely secreted by the **choroid plexuses** found primarily in the lateral ventricles. The rate of production varies

between about 300 and 500 ml/24 h and the ventricular volume is about 75 ml. CSF is similar to blood plasma although it has considerably less albumin, potassium, bicarbonate, calcium and glucose. After production, CSF flows from the lateral ventricles into the third ventricle via the intraventricular foramina of Munro. Subsequently it passes into the fourth ventricle via the central aqueduct of Sylvius and into the subarachnoid space via the foramina of Luschka and Magendie. Within the spinal cord most of the CSF descends in the **subarachnoid space**, with very little flowing in the central spinal canal. From the subarachnoid space at the base of the brain CSF flows rostrally over the cerebral hemispheres.

CSF reabsorption occurs within the superior sagittal and related venous sinuses. Arachnoid **granulations** are minute pouches of the arachnoid membrane projecting through the dura into the venous sinuses. The exact mechanism by which CSF is reabsorbed is not clear but does involve the movement of all CSF constituents into the venous blood.

Apart from playing an important part in maintaining a constant intracerebral chemical environment (see below), the CSF also helps to protect the brain from mechanical damage by reducing the effect of impact damage experienced by the head.

Blood–brain barrier (BBB)

The BBB used to be thought of as a single physical barrier preventing the passage of molecules and cells into the brain. More recently, however, it has been shown to be made up of a series of different transport systems for facilitating or restricting the movement of molecules across the blood–CSF interface. A characteristic of cerebral capillary endothelial cells is the presence of tight junctions between such cells, which are induced and maintained by astrocytic foot processes (see Chapter 4). These unusually tight junctions reduce opportunities for the movement of molecules, and thus require the existence of specific transport systems for the passage of certain critical molecules into the brain.

Small molecules such as glucose pass readily into the CSF despite not being lipid soluble. Larger protein molecules do not enter the brain but there are a number of carrier mechanisms which enable the transport of other sugars and some amino acids to occur. The effect of the barrier is to maintain a constant intracerebral chemical environment and protect against osmotic challenges, while granting the CNS relative immunological privilege (see Chapter 46). However, from a therapeutic point of view the barrier reduces or prevents the delivery of many therapeutic drugs (e.g. antibiotics) into the brain.

Clinical disorders

Hydrocephalus is defined as dilatation of the ventricular system. This is usually as a result of increased pressure within the ventricular system, secondary to an obstruction in the flow of CSF. This typically occurs at the outlets from the fourth ventricle into the subarachnoid space, where the obstruction may be linked to the presence of a tumour, congenital malformation or the sequelae of a previous infection (see below). Alternatively the flow of CSF from the third to the fourth ventricle may be impaired as a result of the development of ***central aqueduct stenosis***. Hydrocephalus is seen in conditions of oversecretion of CSF (e.g. tumours of the choroid plexus) as well as reduced absorption as occurs in ***spina bifida***.

The symptomatology of hydrocephalus is varied but classically the patient presents with features of raised intracranial pressure (early morning headache, nausea, vomiting) and, in acute rises of pressure, altered levels of consciousness with brief periods of visual loss. However, the commonest cause of raised intracranial pressure is a glial tumour (see Chapter 4) producing an effect by virtue of its mass, although such tumours in the posterior fossa can cause hydrocephalus.

In hydrocephalus the treatment focuses on draining excess CSF using a variety of shunts linking the ventricles to either the heart (atrium) or the peritoneal cavity.

Meningitis

Meningitis or inflammation within the meningeal membrane can be caused by a number of different organisms. The more common acute disease is characterised by the rapid spread of inflammation throughout the entire subarachnoid space of the brain and spinal cord, which produces the symptoms of headache, pyrexia, vomiting, neck stiffness (meningism) and, in severe forms of the disease, reduced levels of consciousness. The early administration of antibiotics is essential although the type of antibiotic employed will depend on the nature of the organism responsible for the inflammation.

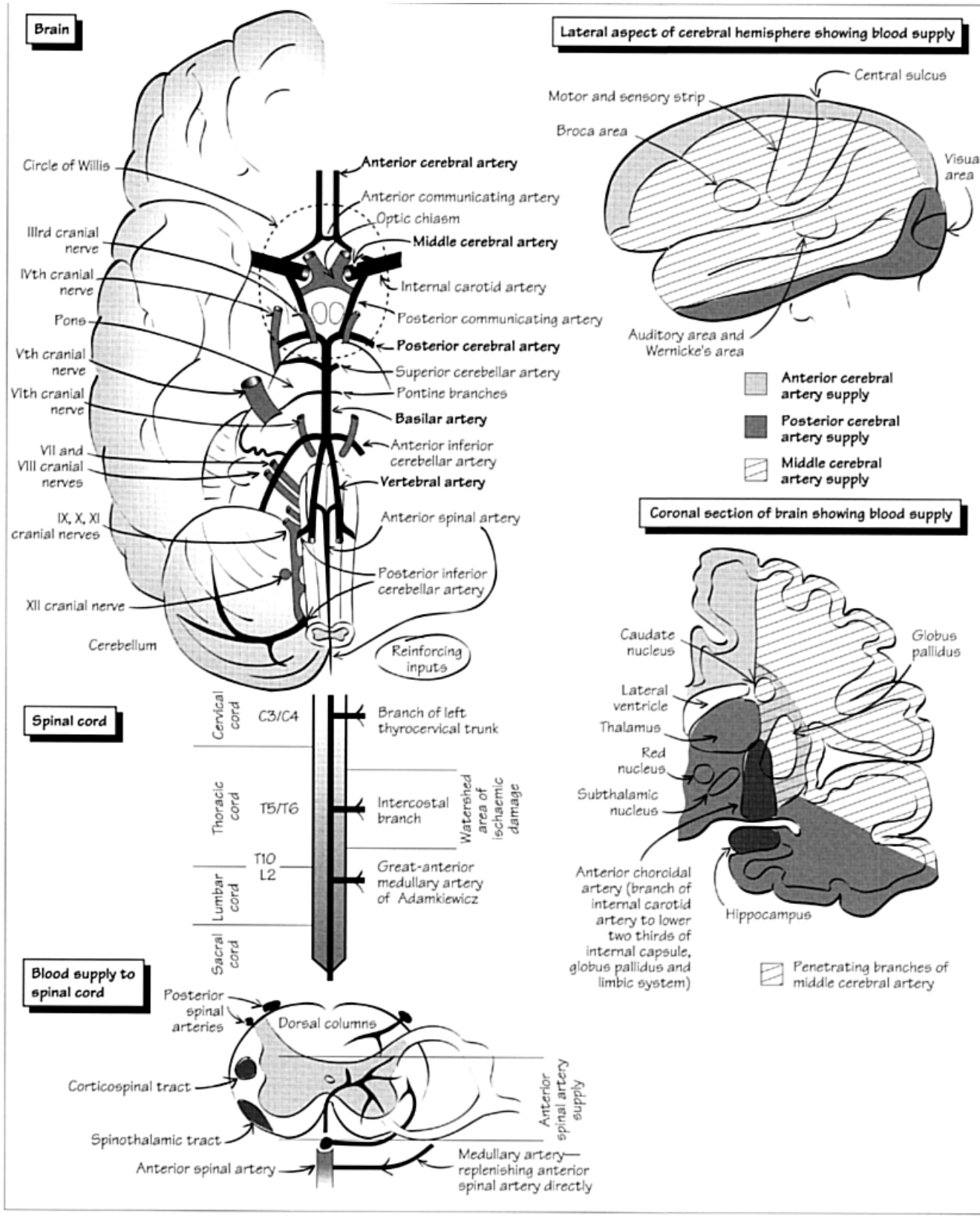
In other cases the infection may follow a more subacute course, such as tuberculous meninigitis. In cases such as this, secondary hydrocephalus may ensue as a result of meningeal thickening at the base of the brain obstructing CSF flow.

Rarely, tumours can spread up the meninges giving a ***malignant meningitis***. This characteristically presents as an evolving cranial nerve or nerve root syndrome with pain. This is to be distinguished from primary tumours of the meninges—***meningiomas***—which are slow growing and benign and typically present with epileptic seizures or deficits secondary to compression of neighbouring CNS structures.

Abbreviations

BBB blood–brain barrier
CSF cerebrospinal fluid

16 Blood supply of the central nervous system



Blood supply to the brain

The arterial blood supply to the brain comes from four vessels: the right and left internal carotid and vertebral arteries. The **vertebral arteries** enter the skull through the foramen magnum and unite to supply blood to the brainstem **(basilar artery)** and posterior parts of the cerebral hemisphere **(posterior cerebral arteries)**—the whole network constituting the so-called posterior circulation. The **internal carotid arteries (ICAs)** traverse the skull in the carotid canal and the cavernous sinus before piercing the dura and entering the middle cranial fossa just lateral to the optic chiasm. They then divide and supply blood to the anterior and middle parts of the cerebral hemispheres **(anterior and middle cerebral arteries; ACAs and MCAs, respectively)**. In addition, the posterior and anterior cerebral circulations anastomose at the base of the brain in the **circle of Willis**, with the anterior and posterior communicating arteries offering the potential to maintain cerebral circulation in the event of a major arterial occlusion. Such a situation is not uncommonly seen in atherosclerotic disease where a slowly progressive stenosis of the ICA allows the collateral system to develop prior to the final occlusion of the vessel. These patients remain asymptomatic or may experience transient neurological disturbances as microthrombi are thrown off from the stenosing vessel (so-called ***transient ischaemic attacks or TIAs***) which stop without a significant deficit once the vessel is completely occluded.

The **ICA** prior to its terminal bifurcation supplies branches to the pituitary (hypophysial arteries), the eye (ophthalmic artery), parts of the basal ganglia (globus pallidus) and limbic system (anterior choroidal artery) as well as providing the posterior communicating artery. The **MCA** forms one of the two terminal branches of the ICA and supplies the sensorimotor strip surrounding the central sulcus (with the exception of its medial extension which is supplied by the ACA) as well as the auditory and language cortical areas in the dominant (usually left) hemisphere. Therefore occlusion of the MCA causes a contralateral paralysis that affects the lower part of the face and arm especially, with contralateral sensory loss or inattention and a loss of language if the dominant hemisphere is involved (see Chapters 19, 25, 28 and 32). In addition, there are a number of small penetrating branches of the MCA that supply subcortical structures such as the basal ganglia and internal capsule (see below).

The two **ACAs**, which form the other major terminal vessel of the ICA, are connected via the anterior communicating artery and supply blood to the medial portions of the frontal and parietal lobes as well as the corpus callosum. There is an inconstant branch of the ACA, the recurrent artery of Heubner, which supplies part of the basal ganglia (neostriatum) and descending motor pathways in the internal capsule. Occlusion of the ACA characteristically gives paresis of the contralateral leg with sensory loss, and on occasions deficits in gait and micturition with mental impairment and ***dyspraxia*** (see Chapters 19, 28 and 32).

The **vertebral arteries** which arise from the subclavian artery ascend to the brainstem via foramina in the transverse processes of the upper cervical vertebrae. At the level of the lower part of the pons the vertebral arteries unite to form the basilar artery which then ascends before dividing into the two **posterior cerebral arteries (PCAs)** at the superior border of the pons. Each vertebral artery *en route* to forming the basilar artery has a number of branches including the posterior spinal artery, the posterior inferior cerebellar artery (PICA) and the anterior spinal artery. These spinal arteries supply the upper cervical cord (see below), whereas the PICA supplies the lateral part of the medulla and cerebellum. Occlusion of this vessel gives rise to the ***lateral medullary syndrome of Wallenberg***.

The **basilar artery** has a number of branches: the anterior inferior cerebellar artery (AICA); the artery to the labyrinth; pontine branches; and the superior cerebellar artery. Occlusion of these branches gives a characteristic clinical picture that can be predicted from the anatomy of the brainstem (see Chapter 12).

The **PCAs** supply blood to the posterior parietal cortex, the occipital lobe and inferior parts of the temporal lobe. Occlusion of these vessels causes a visual field defect (usually a homonymous hemianopia with macular sparing, as this cortical area receives some supply from the MCA; see Chapter 22), amnesic syndromes (see Chapter 39), disorders of language (see Chapter 25) and occasionally complex visual perceptual abnormalities (see Chapter 23). The PCA has a number of central perforating or penetrating branches which supply the midbrain, thalamus, subthalamus, posterior internal capsule, optic radiation and cerebral peduncle. Occlusion of these vessels produces midbrain syndromes with a combination of cranial nerve palsies and motor abnormalities; in the case of thalamic involvement, they may also produce a syndrome of pain and dysaesthesia which is hard to treat (see Chapter 20). The small perforating arteries that arise from both the PCA and MCA are commonly affected in hypertension when their occlusion produces small **lacunar infarcts**.

Apart from occlusion, **haemorrhage** from cerebral vessels can occur which may be into the brain substance (intracerebral), the subarachnoid space or both. Such haemorrhages usually occur either in the context of trauma, hypertension or rupture of congenital aneurysms on the circle of Willis (so-called ***berry aneurysms***).

Venous drainage of the brain

Venous drainage of the brainstem and cerebellum is directly into the dural venous sinuses adjacent to the posterior cranial fossa. The cerebral hemispheres in

contrast have internal and external veins—the external cerebral veins drain the cortex and empty into the superior sagittal sinus (see Chapter 15). This sinus in turn drains into the transverse sinus, then the lateral sinus, before emptying into the internal jugular vein. The internal cerebral veins drain the deep structures of the cerebral hemisphere to the great vein of Galen and thence into the straight sinus. Occlusion of either of these venous systems can occur, causing raised intracranial pressure with or without focal deficits.

Blood supply to the spinal cord

The **blood supply to the spinal cord** comes in the form of a single anterior spinal artery and paired posterior spinal arteries. The anterior spinal artery arises from the vertebral arteries and extends from the level of the lower brainstem to the tip of the conus medullaris. It supplies the ventral surface of the medulla and the anterior two-thirds of the spinal cord. The posterior spinal arteries supply the dorsal third of the spinal cord, and also take their origin from the vertebral arteries. At certain sites along the spinal cord there are a number of reinforcing inputs from other arteries (see figure).

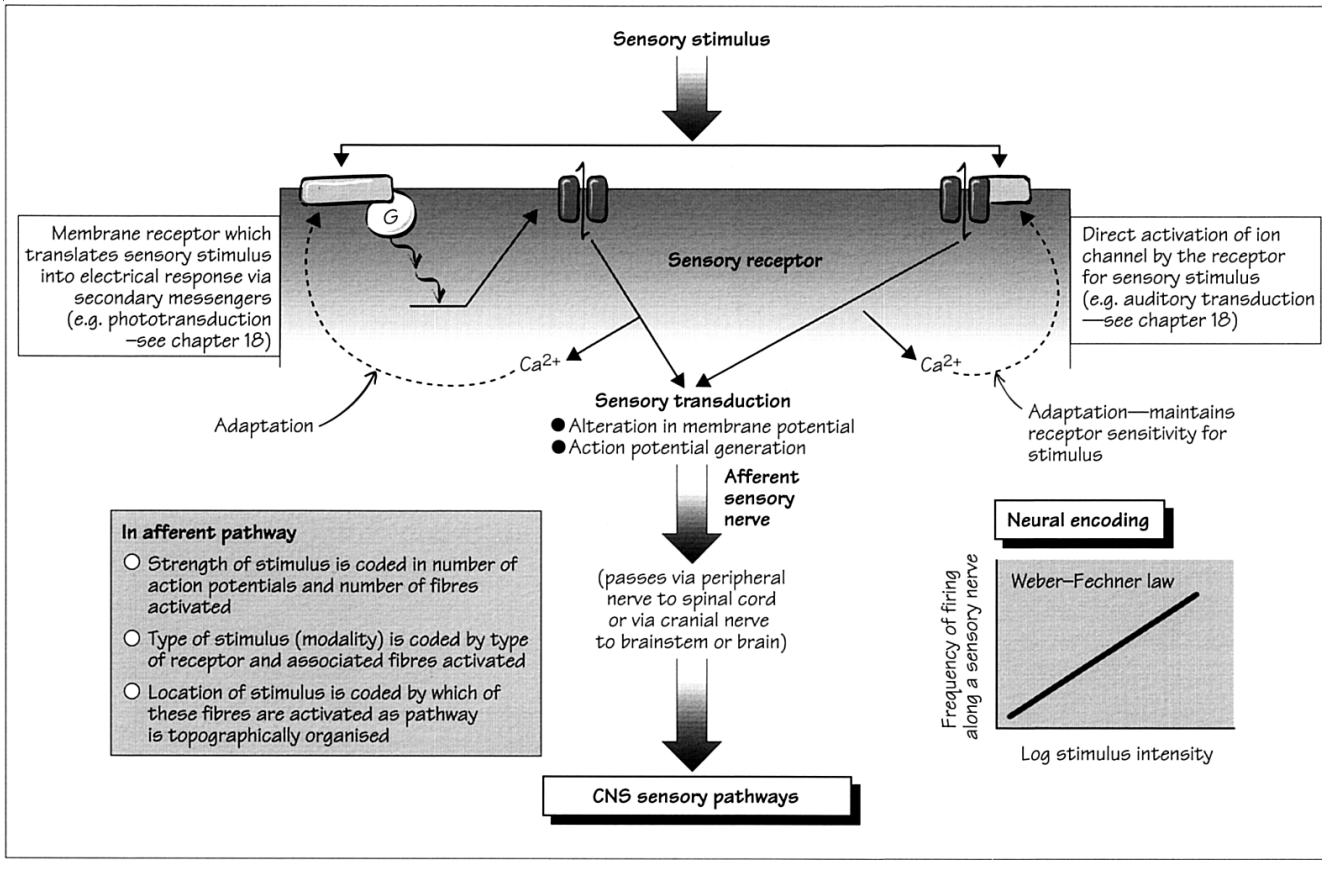
Vascular insults to the spinal cord occur most commonly at the watershed areas in the cord, namely the lower cervical and lower thoracic cord. Occlusion of the anterior spinal artery produces a loss of power and spinothalamic sensory deficit with preservation of the dorsal column sensory modalities (joint position sense and vibration perception; see Chapter 10). Posterior spinal artery occlusions are rare and produce a loss of dorsal column sensory modalities.

Abbreviations

ACA	anterior cerebral artery
AICA	anterior inferior cerebellar artery
ICA	internal carotid artery
MCA	middle cerebral artery
PCA	posterior cerebral artery
PICA	posterior inferior cerebellar artery
TIA	transient ischaemic attack

Part 2 **Sensory systems**

17 Sensory systems: an overview



A sensory system is one in which information is conveyed to the spinal cord and brain from peripheral sensory receptors, which in themselves are either specialised neurons or nerve endings. The specialised **sensory receptor**, **afferent axon** and **cell body** together with the synaptic contacts in the spinal cord, are known as the **primary afferent**, and the process by which stimuli from the external environment are converted into electrical signals for transmission through the nervous system is known as **sensory transduction** (see Chapter 18). The signal produced by the sensory receptor is relayed to the CNS via peripheral or cranial nerves and through a series of synapses eventually projects to a given area of cortex that is then capable of detailed analysis of that sensory input.

There are five main sensory systems in the mammalian nervous system: (i) touch/pressure, temperature and pain or the somatosensory system (see Chapters 19 and 20); (ii) vision (see Chapters 21–23); (iii) hearing and balance (see Chapters 24–26); (iv) taste (see Chapter 27); and (v) smell or olfaction (see Chapter 27). All but the somatosensory pathways are regarded as 'special' senses.

Sensory receptors

Sensory receptors transduce the sensory stimulus either by a process of **direct ion channel activation** (e.g. the auditory system) or **indirectly via a secondary intracellular messenger network** (e.g. the visual system). In both cases the sensory stimulus is converted into an electrical signal that can then be relayed to the CNS either in the form of graded depolarisations/hyperpolarisations leading on to action potentials (e.g. visual system) or the direct generation of action potentials at the level of the receptor (e.g. auditory system; see Chapter 18).

The **specificity or modality** of a sensory system relies on the activation of specialised nerve cells or fibres which are highly specific for different forms of afferent stimuli, e.g. receptors in the retina are highly specific for photons although they may be activated by other stimuli in non-physiological circumstances such as pressure with compression of the eye. The receptor will only respond to stimuli when they are applied within a given region around it (its **receptive field**); an area of skin in the somatosensory system or a part of the retina in the case of photoreceptors,

for example. This area or receptive field from which the receptor can be activated is recognised by the CNS as corresponding to a specific site or position in the body or outside world. However, the receptor will only transmit electrical information to the CNS when it receives a stimulus of sufficient intensity to reach the firing **threshold**. The incremental response to a change in stimulus intensity by the receptor gives the receptor its **sensitivity**. Many receptors have a high sensitivity to both the absolute level of stimulus detection and to changes in stimulus intensity because they are capable of both amplifying the original signal by the use of secondary messenger systems, and **adapting** to the presence of a continuous unchanging stimulus (see below and Chapter 18). Some receptors can change their sensitivity by altering the time and area over which they integrate incident stimuli, e.g. retinal rod photoreceptors in darkness. However, with very sensitive receptors the intrinsic instability of the transduction process is termed the **noise** and the challenge for the nervous system is to detect a sensory stimulus response or signal over this background noise (termed the **signal to noise ratio**).

The strength of a sensory stimulus can be coded for at the level of the receptor and its first synapse either in the form of action potentials or graded membrane potentials within the receptor which are subsequently converted into action potentials (see Chapter 18). The **afferent sensory nerve** can code (amongst other things) for the strength of the stimulus, first by increasing the number of afferent fibres activated **(recruitment or spatial coding)** and secondly by increasing the number of action potentials generated in each axon per unit time **(temporal or frequency coding)**. However, the relationship between the stimulus strength and the number of action potentials generated is often non-linear because of the limited number of action potentials an axon can conduct by virtue of its refractory period (see Chapter 6).

The receptor, while being able to detect and code for the intensity of a specific sensory stimulus at a specific site, must also be capable of adapting so that it can respond to changes in the sensory information it receives. **Adaptation** is therefore defined as the decrease in receptor sensitivity that occurs in the presence of a maintained stimulus, and intracellular Ca^{2+} is an important mediator of this process in most sensory systems (see Chapter 18). If such a mechanism did not exist then a continuously applied stimulus would greatly reduce the sensitivity or even inactivate the receptor to any other new sensory inputs (see, for example, the muscle spindle; see Chapter 30).

Sensory pathways

The coded information from the sensory receptors is relayed to the CNS via peripheral and cranial nerves, with each receptor having an associated axon. Each modality is associated with specific nerves or pathways; e.g. visual information is relayed via the optic nerve (see Chapter 22) while the somatosensory system relays information from a large number of peripheral nerves as well as the trigeminal nerve via the dorsal column–medial lemniscal system and spinothalamic tracts. Thus each sensory pathway has its own unique input to the CNS, although ultimately all the sensory pathways provide an input to the thalamus—the site of that projection being different for each sensory system. This in turn projects to the cortex, although the olfactory pathway primarily projects to limbic structures (see Chapter 27) and the muscle spindle to the cerebellum (see Chapter 33).

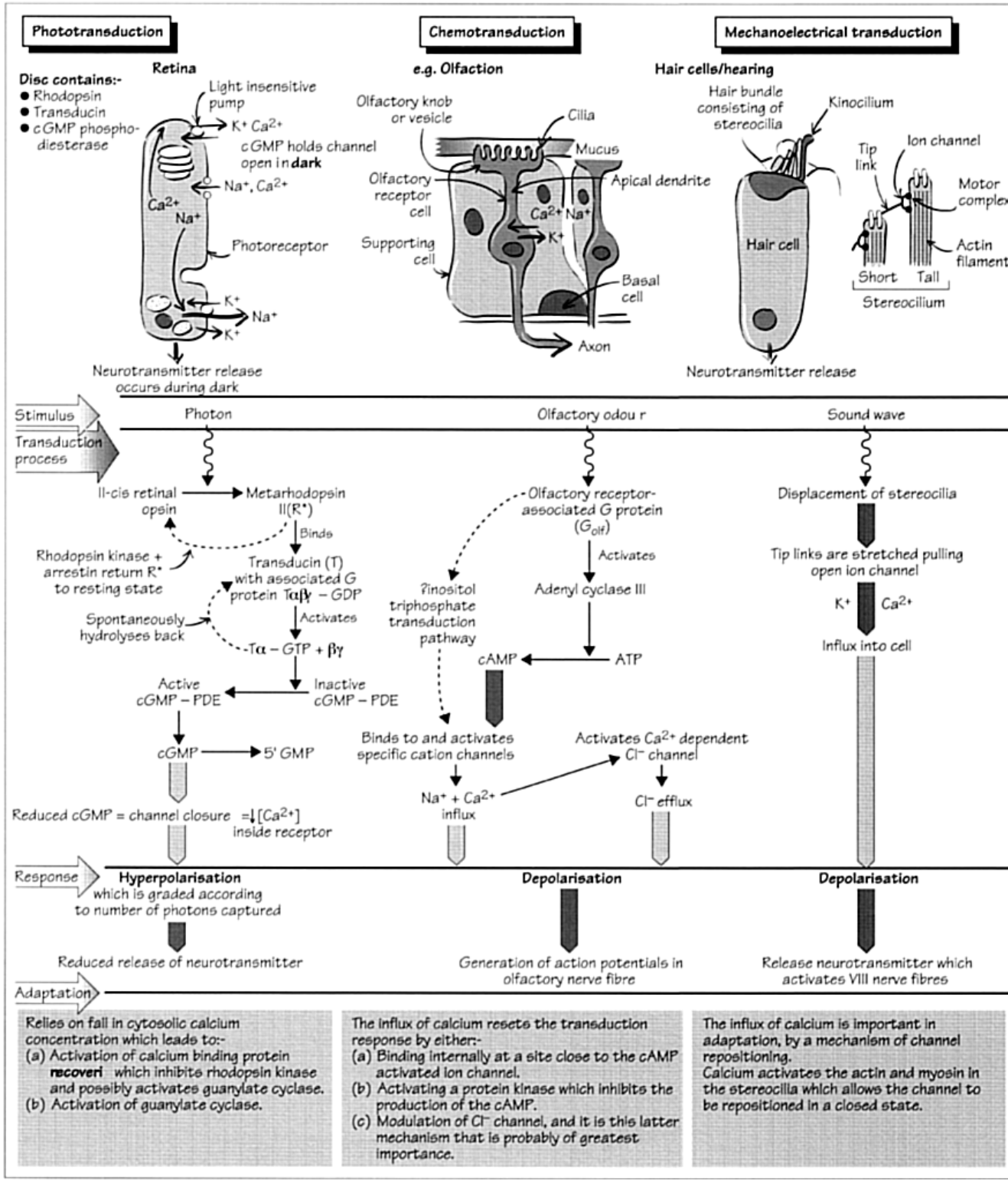
Each sensory system has its own area of cortex that is primarily concerned with analysing the sensory information and this area of cortex—the **primary sensory area**—is connected to adjacent cortical areas that perform more complex sensory processing **(secondary sensory areas)**. This in turn projects into the **association areas** (posterior parietal, prefrontal and temporal cortices; see Chapter 28) which then project to the limbic and motor systems (see Chapters 29 and 39). These latter areas are more involved in the processing of sensory information as a cue for moving and generating complex behavioural responses.

The primary sensory cortical areas not only project to secondary sensory areas but subcortically to their thalamic (and/or brainstem) projecting nuclei. This may be important in augmenting the detection of significant ascending sensory signals. This augmentation probably involves at least two major processes: **lateral inhibition** and **feature detection**. Lateral inhibition is a process by which those cells and axons with the greatest activity are highlighted by the inhibition of adjacent less active ones, which produces greater contrast in the afferent information. Feature detection, on the other hand, corresponds to the selective detection of given features of a sensory stimulus, which can occur at any level from the receptor to the cortex. Ultimately, though, the perception of any sensory stimulus relies on the synchronous activity of several areas of cerebral cortex (see Chapter 14).

Clinical disorders of the sensory pathways

Damage at different sites in a sensory pathway produces a deficit, the extent and nature of which is dependent on the anatomical location. In general the most devastating sensory losses are associated with damage to the receptors and their afferent pathways, while supraspinal lesions are often associated with more subtle deficits, which can be 'positive' in nature, e.g. paraesthesiae with focal ***epilepsy*** originating from the primary sensory cortex, or flashing lights with ischaemia of the visual cortex in ***migraine***.

18 Sensory transduction



Sensory transduction involves the conversion of a stimulus from the external or internal environment into an electrical signal for transmission through the nervous system. This process is performed by all sensory systems and in general involves either a **chemical process**, as occurs in the retina, tongue or olfactory epithelium, or a **mechanical process** as occurs in the cochlea and somatosensory systems. These contrasting modes of transduction are best characterised in some of the special senses.

Phototransduction

Phototransduction is the process by which light energy in the form of photons is translated into electrical energy in the form of potential changes in the outer segment of the photoreceptors (rods and cones) in the retina.

Photons are captured in pigments in the photoreceptor outer segment, which results in an amplification process using cyclic guanosine monophosphate (cGMP) as the secondary messenger. This results in reduced cGMP concentrations which leads to channel closure. The closure of these channels, which allow Na^+ and Ca^{2+} to enter the photoreceptor in the dark, leads to a hyperpolarisation response, the degree of which is graded according to the number of photons captured by the photoreceptor pigment. The hyperpolarisation response leads to reduced neurotransmitter release by the photoreceptor on to bipolar and horizontal cells (see Chapter 21).

The termination of the photoreceptor response to light is multifactorial, but changes in intracellular Ca^{2+} concentration are important. The light insensitive Ca^{2+} pump in the outer segment coupled to the closure of the cation channel leads to a significant reduction in intracellular Ca^{2+} concentrations which is important in terminating the photoreceptor response as well as mediating light (or background) adaptation.

A number of rare congenital forms of ***night blindness*** have now been associated with specific deficits within the phototransduction pathway.

Olfactory transduction

Olfactory transduction is similarly a chemically mediated process. The olfactory receptor cells are bipolar neurons consisting of a dendrite with a dendritic knob on which are found the cilia, and an axonal part that projects as the olfactory nerve to the olfactory bulb on the underside of the frontal lobe. The presence of cilia, which contain the olfactory receptors, greatly increase the surface area of the olfactory neuroepithelium and so increase the probability of trapping odorant molecules. The binding of the odorant molecule to the receptor leads to the activation of G_{olf} which activates adenylate cyclase type III which hydrolyses adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). cAMP then binds to and activates specific cation channels, thus allowing Na^+ and Ca^{2+} to influx down their concentration gradients. This not only partly depolarises the receptor, but also leads to the activation of a Ca^{2+} dependent Cl^- channel and the subsequent Cl^- efflux then further depolarises the olfactory receptor. There are probably additional transduction processes present in the olfactory receptor using inositol triphosphate as the secondary messenger. This can lead on to the generation of action potentials at the cell body which are then conducted down the olfactory nerve axons to the olfactory bulb.

The Ca^{2+} influx is also important in adaptation by resetting the transduction response.

Auditory transduction

In contrast to both phototransduction and olfactory transduction, the process of **auditory transduction** in the inner ear involves the mechanical displacement of stereocilia on the hair cells of the cochlea (see Chapter 24).

The sensory stimulus, a sound wave, causes displacement of the stapedial foot process in the oval window which generates waves in the perilymphatic filled scala vestibuli and tympani of the cochlea. This leads to displacement of the basilar membrane on which the hair cells are to be found in the organ of Corti. These cells transduce the sound waves into an electrical response by a process of mechanotransduction. The stereocilia at the apical end of the hair cell are linked at their tips by tip links, which are attached to ion channels.

The sound causes the stereocilia to be displaced in the direction of the largest stereocilia (or kinocilium) which creates tension within the tip links which then pull open an ion channel. This ion channel then allows K^+ (not Na^+, as the endolymph within the scala media is rich in K^+ and low in Na^+) and Ca^{2+} to flow into the hair cell and by so doing depolarise it. This depolarisation leads to the release of neurotransmitter at the base of the hair cell which activates the afferent fibres of the cochlear nerve.

The continued displacement of the stereocilia in response to a sound is countered by a process of adaptation with a repositioning of the ion channel such that it is now shut in response to that degree of tip link tension. This is achieved by the influx of Ca^{2+} through the ion transduction channels.

A number of syndromes with congenital deafness have now been identified as being caused by abnormalities in the myosin found in hair cells.

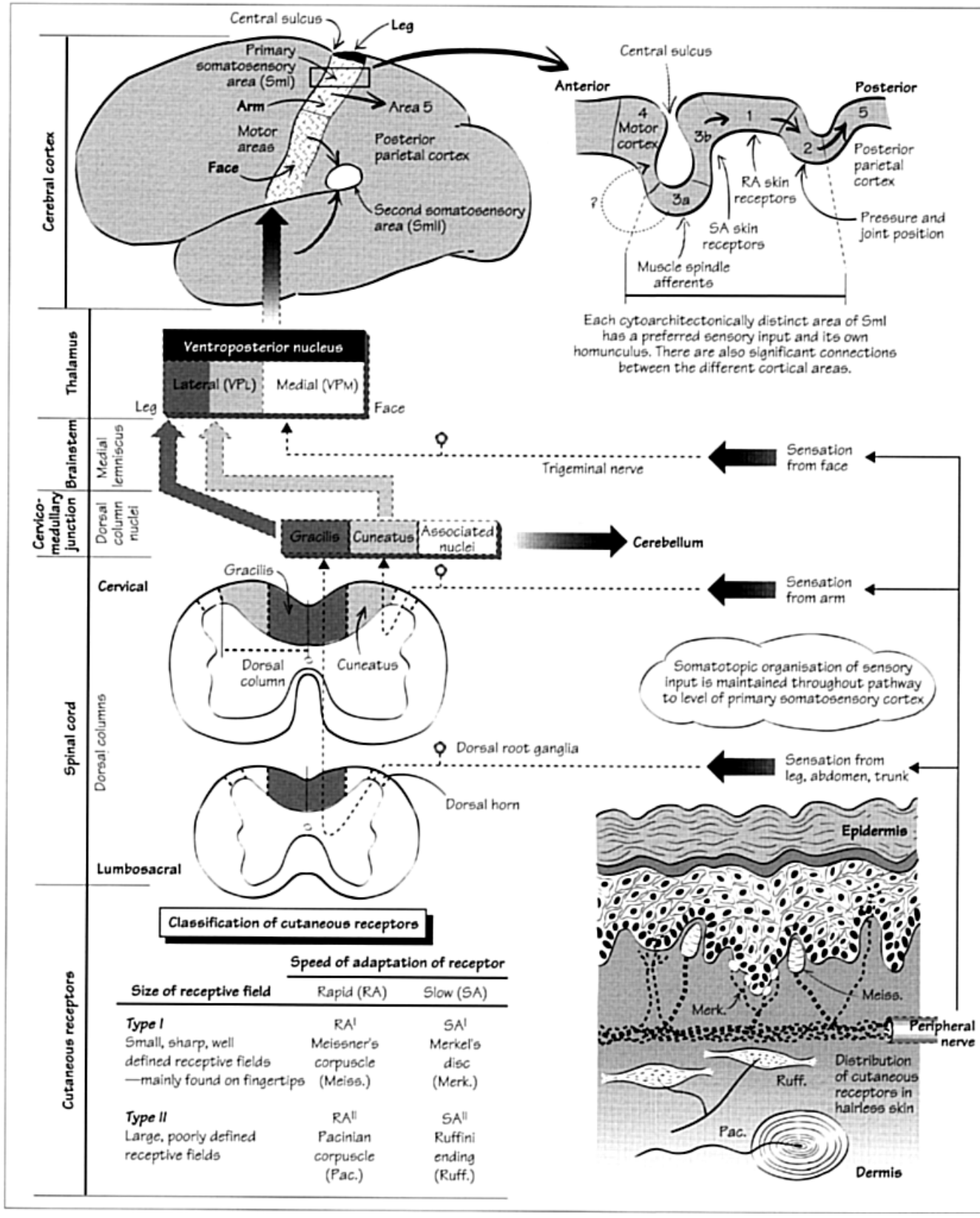
Other transduction processes

Transduction in the somatosensory receptors, nociceptors, thermoreceptors, taste receptors and muscle spindle are discussed in Chapters 19, 20, 27 and 30, respectively.

Abbreviations

cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
G_{olf}	G-protein associated with olfactory receptors

19 The somatosensory system



The somatosensory system is that part of the nervous system which is involved in the processes of touch, pressure, proprioception (or joint position sense—see Chapter 30), pain and temperature perception (see Chapter 20).

Sensory receptors

The **receptors for touch** are specialised nerve endings located in the skin, at particularly high density in the fingertips, while those for proprioception are found not only in the skin but also in the muscle and joints (see Chapter 30).

Skin receptors can best be characterised by their structure, location, receptive fields and speed of adaptation. Type I receptors (**Meissner's corpuscles** and **Merkel's discs**) are packed in high density at the fingertips and provide accurate information about the exact location of a felt stimulus. In contast, the rapidly adapting **Pacinian corpuscles** convey vibration perception while the more slowly adapting **Ruffini endings** sense the magnitude, direction and rate of change of tension in the skin and deeper tissues.

Dorsal column–medial lemniscal pathway

These receptors then project into the **dorsal horn** of the spinal cord via fast conducting, large diameter axons in the peripheral nerves, the cell bodies for which are found in the **dorsal root ganglia**. The **trigeminal sensory system** for the face has a similar organisation. Each class of receptor has a specific pattern of passage through the dorsal horn, but all ultimately end up in the **dorsal column**, where they are organised according to receptor type and body location (somatotopy; see Chapter 11). They then project ipsilaterally up to the dorsal column nuclei (consisting of the gracile and cuneate nuclei), where they make their first synapse, although it should be realised that many dorsal column axons synapse at other spinal sites.

The **dorsal column nuclei (DCN)** are a complex series of structures which lie at the cervicomedullary junction and which send axons that immediately decussate to form the **medial lemniscus** that projects to the thalamus. The DCN also project to other brainstem structures, as well as receiving an input from the primary somatosensory cortex (SmI).

The medial lemniscus projects to the **ventroposterior (VP) nucleus of the thalamus**, picking up the trigeminal system as it ascends. This latter projection synapses in the medial part of the VP nucleus (VPM) with the remainder of the tract terminating in the lateral nucleus (VPL). This medial lemniscal termination is in the form of an anteroposterior thalamic rod, where all the cells have a similar modality and peripheral location (e.g. index finger, rapidly adapting type I (RAI) receptors). The thalamic rod then projects to layer IV of the primary somatosensory cortex (SmI) and forms the basis of the cortical column (see also Chapter 14).

The **SmI** consists of four different areas (Brodmann's areas 3a, 3b, 1 and 2), each of which has a separate representation of the contralateral body surface, with the tongue being represented laterally and the feet medially. The cortical representation is proportional to the receptor density in the skin so, for example, the hand has a much greater representation than the trunk (the **sensory homunculus**).

Primary and secondary sensory cortices

Each cortical area within SmI has slightly different response properties with respect to the neurons found in these areas. As one moves posteriorly towards the posterior parietal cortex the response properties of the neurons become more complex, implying a higher level of cortical analysis. SmI projects not only back to the dorsal column nuclei but to **the posterior parietal cortex** and **second somatosensory area (SmII)**. This latter area is found in the lateral wall of the Sylvian sulcus and is important in tactile object recognition, while the posterior parietal cortex input from SmI is important in the attribution of significance to a sensory stimulus (see Chapter 28).

The primary somatosensory pathway has developed during evolution with the CoST, which has a selective role in the control of fine finger movements (see Chapter 32). These two systems act together in the process of 'active touch' by which we explore our environment. Both systems display a degree of plasticity even in adult life (Chapters 32 and 44). This is in part made possible by somatotopic organisation of the sensory pathway, i.e. adjacent areas of skin are represented in neighbouring parts of the sensory system, at least as far as SmI.

Clinical disorders of the somatosensory system

Damage to the receptors and their afferent fibres can occur in a large number of ***peripheral neuropathies***. Patients typically complain of both paraesthesiae and numbness, often in association with alterations in proprioception especially if the dorsal root ganglion is involved (Chapter 30).

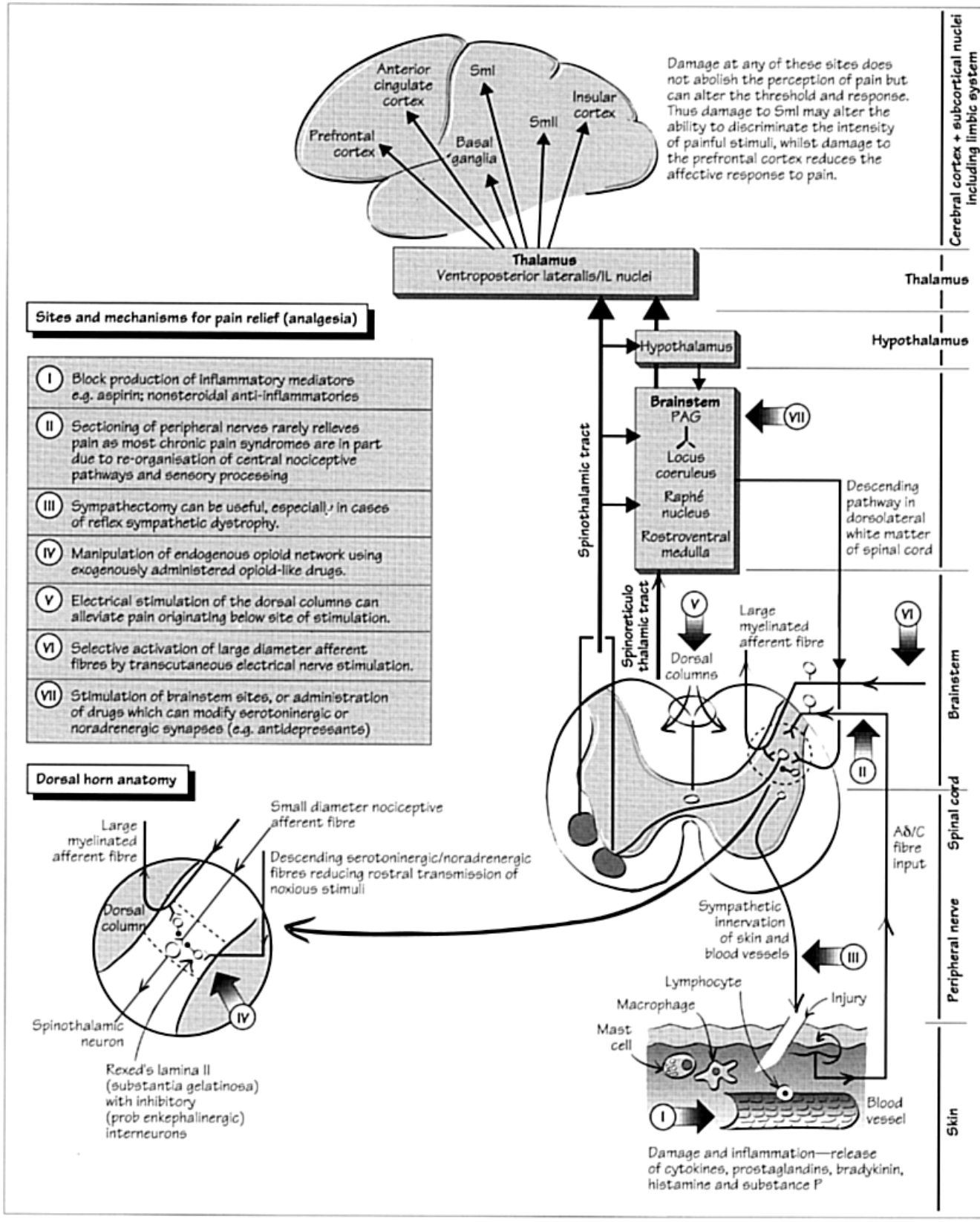
Lesions to the dorsal columns in the spinal cord are described in Chapter 11.

Damage to the somatosensory pathway above the level of the DCN produces a contralateral sensory loss that will involve the face if the lesion lies at or above the level of the upper brainstem.

Abbreviations

CoST	corticospinal tract
DCN	dorsal column nuclei
RA	rapidly adapting receptors
SA	slowly adapting receptors
SmI	primary somatosensory cortex
SmII	second somatosensory area
VP	ventroposterior nucleus of the thalamus
VPL	ventroposterior nucleus of the thalamus, lateral part
VPM	ventroposterior nucleus of the thalamus, medial part

20 Pain systems



Pain is defined as an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage. Much of what is known about pain mechanisms has derived from animal-based research where the affective component is unclear and for this reason neuroscientists prefer to use the term **nociception** which defines the processing of information about damaging stimuli by the nervous system up to the point where perception occurs, probably at the level of the cerebral cortex. This is an important distinction since tissue damage is not inevitably linked to pain and in man this can sometimes be seen with damaging injuries acquired in stressful situations such as in war.

Nociceptors

Nociceptors are found in the skin, visceral organs, skeletal and cardiac muscle and in association with blood vessels. They conduct information about noxious events to the dorsal horn of the spinal cord where the primary afferents synapse predominantly on interneurons as opposed to projection neurons.

There are basically two types of nociceptor distinguished by the diameter of the afferent fibre and the stimulus required to activate it. The **high threshold mechanoreceptor (HTM)** is activated by intense mechanical stimulation and innervated by **thinly myelinated Aδ fibres** conducting at 5–30 m/s. **Polymodal nociceptors (PMN)** respond to intense mechanical stimulation, temperatures in excess of about 42°C, and irritant chemicals. These receptors are innervated by **unmyelinated C fibres** conducting at 0.5–2 m/s. Sharply localised pain is thought to be conducted in the faster conducting fibres whereas poorly localised pain may be conducted in the C fibres.

Although nociceptors are histologically simple free nerve endings, the process of **transduction** at the receptor ending is complex but does appear to have a degree of reliance on some of the chemical mediators of inflammation. Thus bradykinin, histamine and prostaglandins all either activate or sensitise the receptor ending and indeed some of the transmitters in the nociceptive pathway are themselves released peripherally (e.g. substance P) to produce further sensitisation of the receptor ending. This receptor sensitisation helps to explain the perception of heightened pain **(primary hyperalgesia)** in areas of tissue damage, but it does not fully explain the perception of non-painful stimuli as painful **(allodynia or secondary hyperalgesia)** in cases of peripheral or central nerve damage. In this respect recent evidence suggests that both allodynia and some chronic pain syndromes (e.g. phantom limb pain) are caused by long-term changes in the processing of noxious information in the dorsal horn of the spinal cord. This includes the recruitment of normally silent nociceptors, enhanced synaptic transmission in the dorsal horn, as well as the sprouting of the large diameter sensory afferent fibres into the DH laminae normally receiving nociceptive inputs.

Visceral nociceptors project into the spinal cord via the small diameter myelinated and unmyelinated fibres of the autonomic nervous system, and synapse at the spinal level of their embryological origin. The development of pain in an internal organ can therefore produce the perception of a painful stimulus in the skin rather than the organ itself, at least in the early stages of inflammation—a phenomenon known as **referred pain**. For example, inflammation of the appendix initially leads to pain being perceived at the umbilicus.

Nociceptive pathways

The majority of nociceptors and thermoreceptors project into the spinal cord via the dorsal root, although some pass through the ventral horn. On reaching the spinal cord these sensory nerves synapse in a complex fashion in the dorsal horn. The postsynaptic cell then projects up the spinal cord as the **spinothalamic, spinoreticulothalamic** and **spinomesencephalic** tracts (latter not shown on figure), with the axons crossing at the spinal level by passing around the central canal of the cord. This crossing of fibres often occurs a few levels above where the nociceptive fibres enter the cord, and thus damage in the region of the central canal as occurs in ***syringomyelia*** leads to a loss of pain and temperature sensibility in a dermatomal distribution often several levels below the site of the lesion (see Chapter 11).

The postsynaptic cell and presynaptic nociceptive nerve terminal receive synapses from other peripherally projecting somato-sensory systems, descending projections from the brainstem and interneurons intrinsic to the dorsal horn. Many of these interneurons contain **endogenous opioid substances** known as enkephalins and endorphins which activate opioid receptors of which there are three main subtypes (μ κ δ). There is therefore enormous potential for modifying the transfer of nociceptive information at the level of the dorsal horn (see below).

The **ascending nociceptive pathways** synapse in a number of different CNS sites. Information concerning noxious events ascends in either the spinothalamic tract (providing acccurate localisation) or the spinoreticulothalamic system (transmitting information concerning the affective components of pain). However, some of the nuclei in the brainstem to which these pathways project (e.g. the raphé nucleus, periaqueductal grey matter (PAG) and locus coeruleus) in turn send axons back down the spinal cord to the dorsal horn, and can be exploited in the control of chronic pain syndromes (see below).

The thalamic termination of the spinothalamic pathway is in the intralaminar nuclei (IL) (including the posterior group), which in turn project to multiple cortical areas but especially the primary somatosensory cortex (SmI) and

second somatosensory area (SmII) and the anterior cingulate cortex. However, other areas receive an input from these nuclei including the prefrontal cortex, basal ganglia and insular cortex. Lesions to any of these sites alters the perception of pain but does not produce a true and complete loss of pain or analgesia, and indeed may even produce a chronic pain syndrome. Such syndromes are not uncommonly seen with small thalamic CVAs.

The thermoreceptors, and to a lesser extent the nociceptors, also project to the hypothalamus which has an important role in thermoregulation, and the autonomic response to a painful stimulus (see Chapters 36 and 37).

Management of pain

Pain relief or analgesia can be approached using a number of different strategies. Many analgesic therapies work by reducing the peripheral inflammatory response which is also responsible for receptor sensitisation (**Site I** on figure). The interruption of peripheral nerve conduction by the injection of local anaesthetics can be helpful in some pain states, but lesioning of the peripheral nerve is usually without effect in ameliorating neuropathic pain (**Site II**). However, in some cases nerve injury results in the formation of a neuroma which consists of scar tissue and aborted axonal regeneration (see also Chapter 43). This in turn leads to the generation of abnormal signals within the injured nerve that are perceived as painful. In such circumstances local excision of the neuroma may benefit the patient.

The organisation of the nociceptive input to the dorsal horn has been explored clinically in pain management. For example stimulation of non-nociceptive receptors can inhibit the transmission of nociceptive information in the dorsal horn, which means that painful stimuli can be 'gated' out by counter irritation using non-painful stimuli. This is the basis of the **gate theory** of Wall and Melzack and is exploited clinically by the use of transcutaneous nerve stimulation (TENS) in areas of pain (**Site VI**), as well as the stimulation of the dorsal columns themselves in some cases of chronic pain (**Site V**). Similarly the supraspinal input can also gate out noxious stimuli when activated (**Site VII**), as occurs in stressful situations when attending to a painful stimulus would not necessarily be useful (e.g. war injuries). These supraspinal nuclei can also be manipulated pharmacologically, with the administration of drugs that are normally used in the treatment of depression (see Chapter 40). These antidepressant drugs with a presumed action at the noradrenergic and serotoninergic synapse have been used to treat pain states, irrespective of any antidepressant action they might have (**Site VII**). The most commonly used agents are amine uptake inhibitors, such as imipramine and amitryptyline (so-called tricyclic antidepressants). These agents appear to alter the pain threshold but are not without side effects because they have blocking actions on muscarinic receptors (dry mouth, constipation, blurred vision), α-adrenoceptors (postural hypotension) and histamine H_1-receptors (sedation).

Furthermore, the recognition that one of the major transmitters in the nociceptive pathway is substance P (SP), has led to the development of other analgesic medications. For example, capsaicin (the active ingredient of red chilli) which initially releases SP from nociceptors and subsequently inactivates the SP-containing C fibres, can be used topically in some pain syndromes such as ***post-herpetic neuralgia***. Perhaps though, the commonest exploitation of this system medically is the manipulation of the enkephalinergic interneuron and opioid receptors by the exogenous administration of morphine and its analogues to control pain (**Site IV**).

Opioid analgesics are drugs that mimic endogenous opioid peptides by causing a prolonged activation of opioid receptors (usually μ-receptors). This reduces pain transmission at synapses in the dorsal horn of the spinal cord by an inhibitory action on the relay neurons. Opioids also stimulate noradrenergic and serotinergic neurons in the brainstem that descend in the spinal cord and further inhibit the relay neurons of the spinothalamic tract. Opioid analgesics are widely used to relieve dull poorly localised (visceral) pain. Repeated doses may cause dependence. In drug addicts, the dose necessary to cause euphoria may rapidly increase (tolerance) but in patients the necessity for higher dosage usually reflects progressively increasing pain.

Morphine is the most widely used analgesic in severe pain but, like all strong opioids, may cause nausea and vomiting. Other effects of morphine-type drugs include euphoria, respiratory depression, constipation and pin point pupils caused by stimulation of the third nerve nucleus. Other opioids used in severe pain include diamorphine (heroin), pethidine and methadone. Codeine and dextropropoxyphene are weaker drugs used in mild-to-moderate pain. **Naloxone** is an antagonist at opioid receptors and is used to reverse the effects of opioid overdoses.

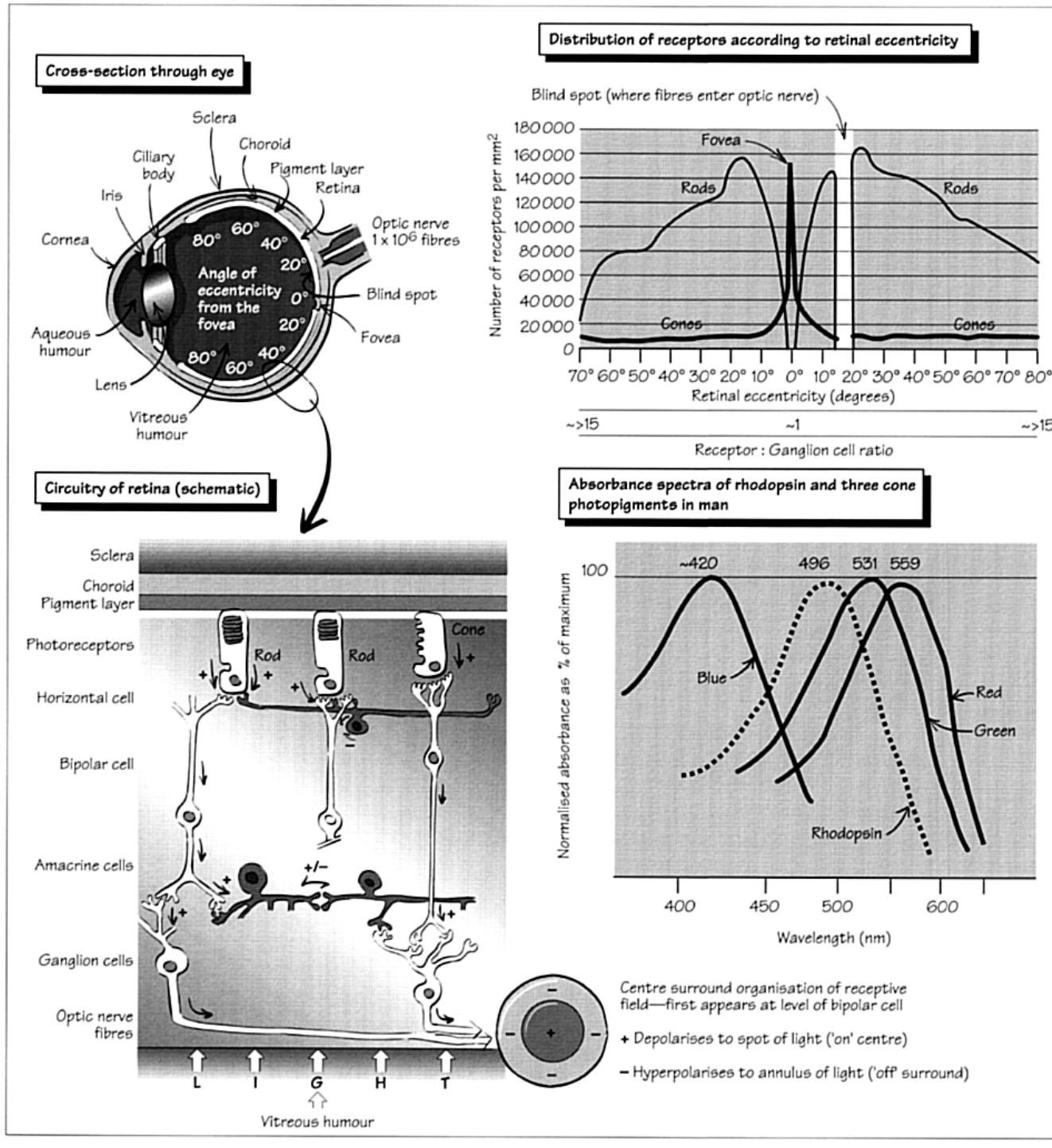
Furthermore, although pain typically arises from tissue damage, it can also occur with damage to the PNS and CNS. One such example is trigeminal neuralgia, which is characterised by paroxysms of facial pain. In this condition the patient experiences paroxysms of pain in one of the three divisions of the trigeminal nerve and although in the majority of cases the cause of the condition is not found, it can be seen in some people with ***multiple sclerosis***. It can be treated surgically by lesioning of the appropriate nerve root, although most cases respond to the anti-epileptic agent carbamazepine (see Chapter 45). Another example of a pain syndrome arising with damage to neural tissue is seen following trauma to a peripheral nerve trunk, where a

change in autonomic innervation to the traumatised limb results in the development of severe pain (so-called ***reflex sympathetic dystrophies***). The reason for the development of such states is not known, although the nociceptive nerve endings do appear to start expressing receptors for noradrenaline. Thus, local sympathectomies can be helpful in alleviating this pain, although this is not always the case (**Site III**).

Abbreviations

HTM	high threshold mechanoreceptor
PMN	polymodal nociceptors
PAG	periaqueductal grey matter
SmI	primary somatosensory cortex
SmII	second somatosensory area
SP	substance P
TENS	transcutaneous nerve stimulation

21 The visual system I: The eye and retina



The visual system is responsible for converting all incident light energy into a visual image of the world. This information is coded for in the retina that lies at the back of the eye, which then transmits that information to the visual cortical areas, the hypothalamus and upper brainstem (see Chapters 22 and 23). The process of visual transduction was detailed in Chapter 18.

Optical properties of the eye

On reaching the eye light has to be precisely focused on to the retina, and this process of **refraction** is dependent on the curvature of the cornea and the axial length of the eye. A failure to do this accurately leads to either an inability to see clearly when reading ***(long-sight or hypermetropia)***; or to see clearly distant objects ***(short-sight or myopia)*** or both. In the latter case there is often an additional problem of ***astigmatism***, in which the refraction of the eye varies in different meridians.

In addition to the need to be refracted precisely on to the retina, light must also be transmitted without any loss of quality and this relies on the cornea, anterior and posterior chambers and lens all being clear. Injuries or disease of any of these components can lead to a reduced **visual acuity**, i.e. the ability to discriminate detail. The commonest conditions affecting these parts of the eye are infections and damage to the cornea ***(keratitis)*** or opacification of the lens (***cataracts***).

Retinal anatomy and function

The light on striking the **retina** is transduced into electrical signals by the **photoreceptors** that lie on the innermost layer of the retina, furthest from the vitreous humour. There are two main types of photoreceptors: **rods and cones**. The rods are found in all areas of the retina, except the fovea, and are sensitive to low levels of light and are thus responsible for our vision at night **(scotopic vision)**. Many rods relay their information to a single ganglion cell, and thus this system is sensitive to absolute levels of illumination while not being capable of discriminating fine visual detail. Thus at night we can detect objects but not in any detail.

The cones are found at highest density in the **fovea** and contain one of three different **photopigments**. They are responsible for our daytime or **photopic vision**. This coupled to the high density of these receptors at the **fovea**, where they have an almost one-to-one relationship with ganglion cells, means that they are the receptors responsible for visual acuity and colour vision. Alterations in the photopigments contained within these receptors leads to ***colour blindness***. Diseases of the receptors leading to their death, such as ***retinitis pigmentosa***, lead to a progressive loss of vision, that typically affects the peripheral retina and rods in the early stages, resulting in night blindness and constricted visual fields.

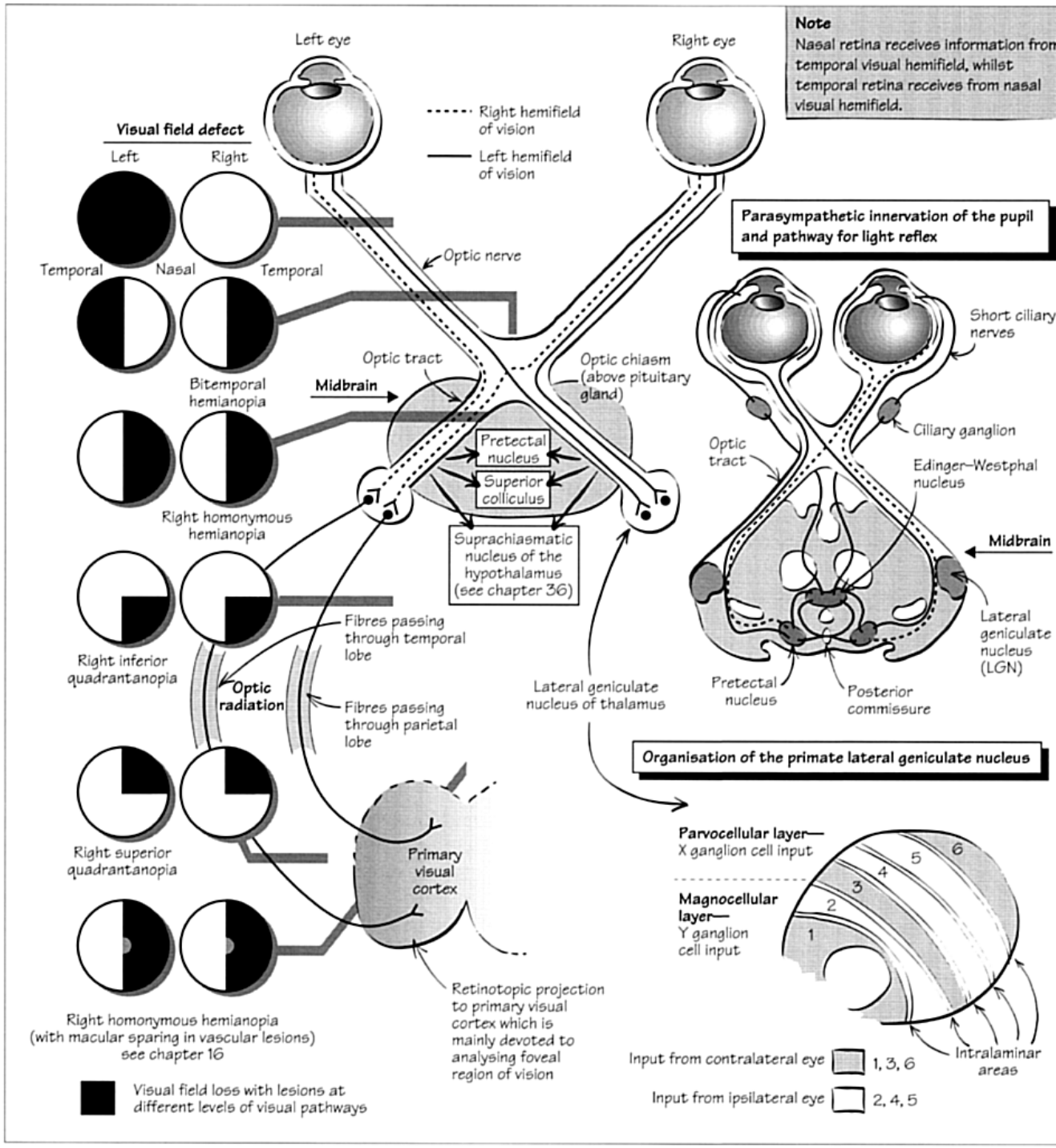
The photoreceptors make synapses with both horizontal and bipolar cells. The **horizontal cells** have two major roles: (i) they create the centre surround organisation of the receptive field of the bipolar cell; and (ii) they are responsible for shifting the spectral sensitivity of the bipolar cell to match the level of background illumination (part of the light adaptation response; see Chapter 18). The **centre surround receptive field** means that a bipolar cell will respond to a small spot of light in the middle of its receptive field in one way (depolarisation or hyperpolarisation), while an annulus or ring of light around that central spot of light will produce an opposite response. The horizontal cells, by receiving inputs from many receptors and synapsing on one bipolar cell, can provide the necessary information for this receptive field to be generated. The mechanism by which they fulfil their other role in light adaptation is not fully understood.

The **bipolar cells** relay information from the photoreceptors to the ganglion cells and receive synapses from photoreceptors, horizontal and amacrine cells. They can be classified according to the receptor they receive from (cone only, rod only or both) or their response to light. Bipolar cells that are hyperpolarised by a small spot of light in the centre of their receptive fields are termed **off-centre (on-surround)** while the converse is true for those bipolar cells that are depolarised by a small spot of light in the centre of their receptive field.

The **ganglion cells** are found closest to the vitreous humour, receive from both bipolar and amacrine cells and send their axons to the brain via the optic nerve. These nerve fibres course over the inner surface of the retina before leaving at a site which forms the **optic disc** and which is responsible for the **blind spot** as no receptors are located at this site. This blind spot is not usually apparent in normal vision. The ganglion cells can be classified in a number of different ways: according to their morphology; their response to light as for bipolar cells ('on' or 'off' centre); or a combination of these properties (the **XYW system**). The X ganglion cells, which make up 80% of the retinal ganglion cell population, are involved in the analysis of detail and colour while the Y ganglion cells are more involved in motion detection. The W ganglion cells that make up the remaining 10% of the population project to the brainstem but as yet have no clearly defined function. The various characteristics of these different types of ganglion cells are important as the segregation of these visual characteristics at this stage is reflected at higher levels of the visual pathway (see Chapters 22 and 23).

The **amacrine cells** of the retina, that make up the final class of retinal cells, receive synapses from the bipolar cells and other amacrine cells and relay that information to other amacrine and bipolar cells as well as ganglion cells. There are many different types of amacrine cells, some of which are exclusively related to rods and others to cones. They contain a number of different transmitters, which provides an alternative classification system. They often have complex responses to light stimuli and are important in generating many of the response properties of ganglion cells, including the detection and coding of moving objects and the onset and offset of illumination.

22 The visual system II: The visual pathways and subcortical visual areas



The **retina** conveys its information from the ganglion cells to a number of different sites, including several cortical areas via the thalamus, the hypothalamus and midbrain. The major cortical projection is via the lateral geniculate nucleus (LGN) of the thalamus to the primary visual cortex (V1 or Brodmann area 17). Other cortical areas (known collectively as the extrastriate areas) receive information from the LGN as well as the pulvinar region of the thalamus (see Chapter 23).

The projection from the retina to V1 maintains its retinotopic organisation, such that a lesion along the course of the pathway produces a predictable visual field defect. Lesions in front of the optic chiasm typically produce uniocular field defects while lesions of the chiasm (e.g. from pituitary tumours) cause a bitemporal hemianopia. Lesions behind the chiasm typically produce a field defect in both eyes, either a homonymous hemianopia or quandrantanopia.

Lateral geniculate nucleus (LGN)

The **LGN** consists of six layers in primates, with each layer receiving an input from either the ipsilateral or contralateral eye. The inner two with their large neurons form the magnocellular laminae while the remaining four layers constitute the parvocellular laminae. The morphological distinction between the neurons in these two laminae is also found electrophysiologically.

The parvocellular neurons display chromatic or colour sensitivity and sensitivity to high spatial frequency (detail) regardless of stimulus wavelength with sustained responses to visual stimuli. In contrast, the magnocellular neurons show no colour selectivity, respond best to low spatial frequencies and often have a transient response on being stimulated. Thus the magnocellular layer neurons have similar properties to the Y ganglion cells and the parvocellular neurons to the X ganglion cells, a similarity that is reflected in the retinogeniculate projection of these two classes of ganglion cells. The X ganglion cells and the parvocellular laminae neurons are responsible for the detection of colour and form the **P channel**, while the **M channel** of the Y ganglion cells and the magnocellular laminae of the LGN are responsible primarily for motion detection.

The LGN mainly projects to the **V1** where the afferent fibres synapse in layer IV, and to a lesser extent layer VI, with the M and P channels having different synaptic targets within these laminae. In addition there is a projection from cells that lie between the laminae of cells in the LGN (so-called intralaminar part of the LGN) direct to layers II and III of V1 (see Chapter 23).

Superior colliculus

The superior colliculus in the midbrain is a multilayered structure, wherein the superficial layers are involved in mapping the visual field and the deep layers with complex sensory integration involving visual, auditory and somatosensory stimuli. The intermediate layers, however, are involved in saccadic eye movements and as such receive from the occipitoparietal cortex, the frontal eye fields and the substantia nigra (see Chapter 35). The saccadic eye movements are tightly mapped in the superior colliculus, so that stimulation at a given point in it will cause a saccadic eye movement to bring the point of fixation to that point in the visual field which is represented in the more superficial layers of this structure. This ability to line up different sensorimotor representations in the superior colliculus in register even extends down into the deeper layers. In other words, a vertical descent through this structure encounters, in order: (i) neurons that respond to visual stimuli in a given part of the visual field; (ii) neurons that cause saccadic eye movements which bring the fovea to bear on to that same part of the visual scene; (iii) auditory and somatosensory neurons that are maximally activated by sounds that originate from that part of the environment and by areas of skin that would most likely be activated by a physical contact with an object located in that part of the extrapersonal space. This latter feature accounts for the fact that in the superior colliculus the somatosensory representation is primarily skewed towards the nose and face. Thus the superior colliculus not only codes for saccades, but tends to code specifically for those saccades that are triggered by stimuli of behavioural significance as well as having a more widespread function in orienting responses. This role for the superior colliculus is reflected in its efferent connections to a number of brainstem structures as well as the spinal cord (tectospinal tract). Clinically, damage is rarely confined to this structure, but when it is, there is a profound loss of saccadic eye movements with neglect.

Pretectal structures and the pupillary response to light

There is a projection from the optic tract to the pretectal nuclei of the midbrain which in turn project bilaterally to the Edinger–Westphal nucleus which provides the parasympathetic input to the pupil allowing it to constrict. Light shone in one eye will cause constriction of both pupils (so-called direct and consensual response). Damage to one of the optic nerves will cause a reduced direct and consensual response but that same eye will constrict normally to light shone in the unaffected eye, producing a ***relative afferent pupillary defect***.

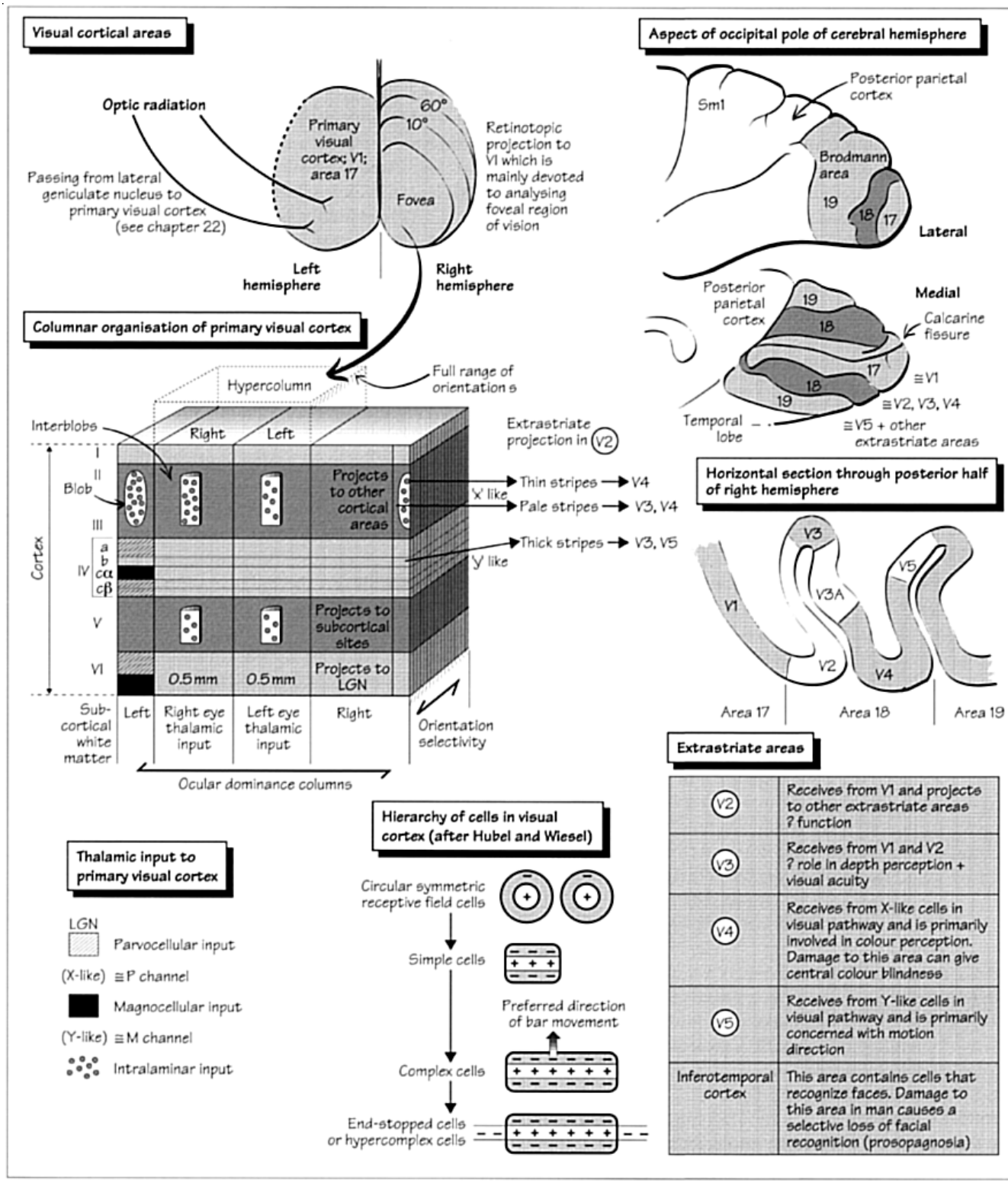
Suprachiasmatic nucleus of the hypothalamus

This nucleus receives a direct retinal input and is important in the generation and control of circadian rhythms (see Chapter 37).

Abbreviations

LGN lateral geniculate nucleus of the thalamus
V1 primary visual cortex or Brodmann area 17

23 The visual system III: Visual cortical areas



Primary visual cortex (V1 or Brodmann area 17)

The primary visual cortex (V1) lies along the calcarine fissure of the occipital lobe and receives its major input from the lateral geniculate nucleus (LGN). These connections are organised **retinotopically** so that adjacent areas of the retina project up the visual pathway via neighbouring axons. This retinal projection is, however, not a simple map, as the critical factor is the relationship of the photoreceptors to the projecting ganglion cell of the retina. This means that the centre of vision (especially the fovea) dominates the retinal projection to V1.

The LGN projection to V1 is mainly to layer IV and is different for the M and P channels, while the projection from intralaminar part of the LGN is to layers II and III of V1 (see below). The LGN input to layer IV of V1 is so great that this cortical layer is futher subdivided into IVa, IVb, IVcα and IVcβ, with each subdivision having slightly different connections. However, in general the cortical neurons in layer IVc of V1 have **centre surround or circular symmetric receptive field organisation** (see Chapter 21). These layer IVc neurons then project on to other adjacent neurons within the cortex, in such a way that several neurons of this type converge on to a single neuron whose receptive field is now more complex in terms of the stimulus that best activates it. These cells respond most effectively to a line or bar of illumination of a given orientation and were termed **simple cells**. These cell in turn project in a convergent fashion on to other neurons (complex cells), that are predominantly found in layers II and III, and which are maximally activated by stimuli of a given orientation moving in a particular direction, that direction often being orthogonal to the line orientation.

The complex cells project to the **hypercomplex or end-stopped cells** which respond to a line of a given orientation and length. Thus in the original model of Hubel and Wiesel the organisation of the cells of V1 was strictly hierarchical with each cell deriving its receptive field from the cells immediately beneath it in the hierarchy.

Hubel and Wiesel then discovered that these neurons were organised into columns of cells with similar properties; the two properties that they originally studied being the eye that provides the dominant input to that neuron (giving **ocular dominance columns**) and the orientation of the line needed to activate neurons maximally (giving **orientation selective columns**). They represented these two sets of columns as running orthogonal to each other, and the area of cortex containing an ocular dominance column from each eye with a complete set of orientation selective columns being termed the **hypercolumn**. This hypercolumn, which is 1 mm^2 in size, is capable of analysing a given section of the visual field that is defined by the corresponding retinal inputs from both eyes. In the case of the fovea where there is near unity of photoreceptors to ganglion cells, this visual field is very small, while the converse is true for more eccentric retinal inputs. Therefore a shift of 1 mm in the cortex from one hypercolumn to another leads to a shift in the location of the visual field being analysed, with most of these being concerned with foveal vision (see below).

However, there are two main major complicating factors with this model. One is the accommodation of the M and P channels and the second relates to the discovery of cytochrome oxidase rich neurons in layers II, III and IVb (and to a lesser extent layers V and VI) which show no orientation selectivity but colour and high spatial frequency sensitivity. These cytochrome oxidase rich neurons in layers II and III are grouped together to form **'blobs'**, at least one of which is associated with each ocular dominance column, with the areas between them being termed **interblobs**. Both the blobs and interblobs, together with the cytochrome rich layer IVb, have distinct projections to V2 and other extrastriate areas—projections that correlate well with the M and P channels. This arrangement of channels and connections suggests that visual information is not so much processed in a hierarchical fashion, but by a series of parallel pathways (see Chapter 14).

The major function of V1, apart from being the first site of binocular interactions, is to deconstruct the visual field into small line segments of various orientation as well as segregating and integrating components of the visual image which can then be relayed to more specialist visual areas. These areas perform more complex visual analysis but rely on their interaction with V1 for the conscious perception of the whole visual image. This occasionally presents itself clinically in patients with bilateral damage to V1, in which they deny being able to see any visual stimulus even though on formal testing they are capable of localising visual targets accurately (a phenomenon known as ***blindsight***).

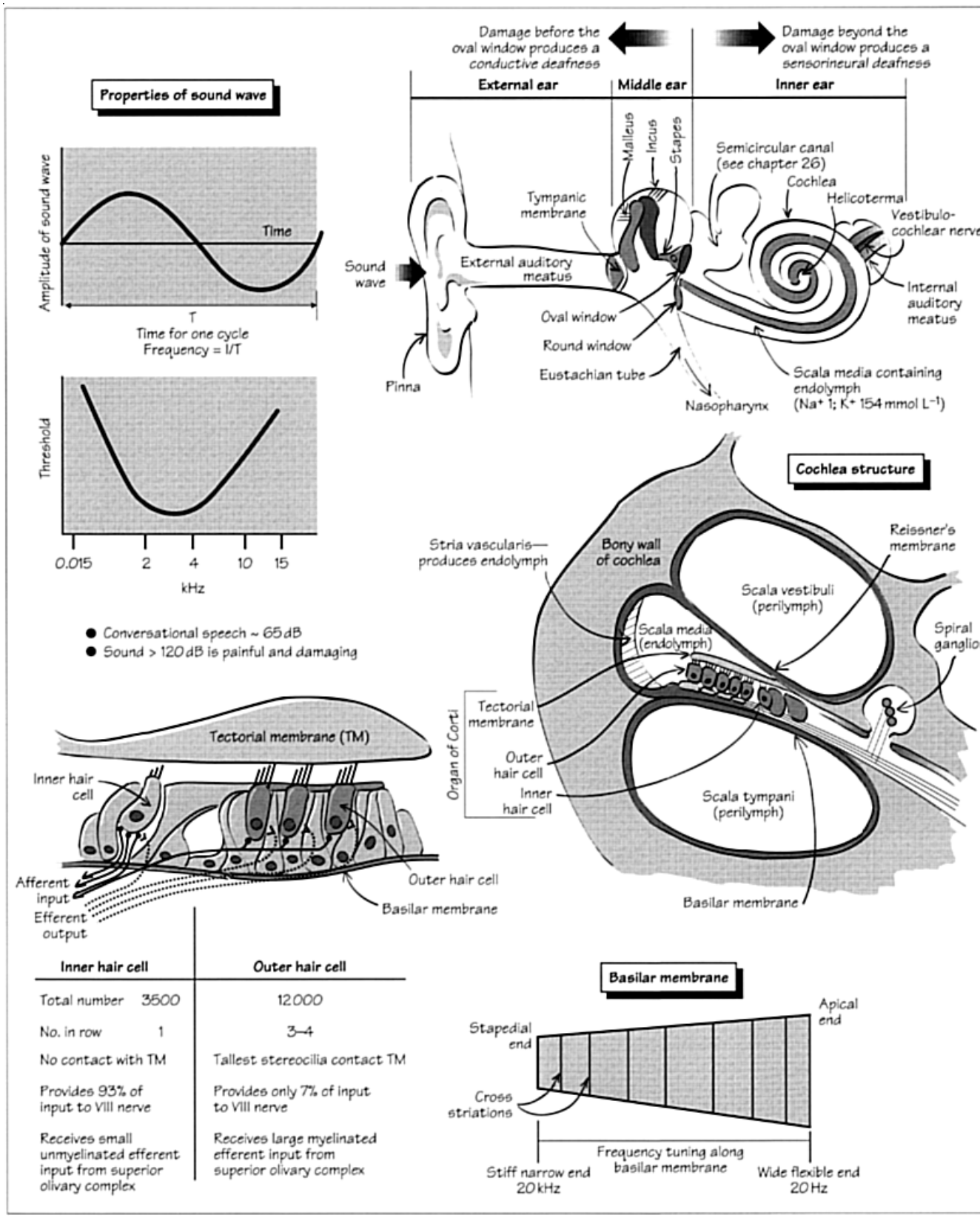
Visual association or extrastriate areas

The **extrastriate areas** are those cortical areas outside V1 which are primarily involved in visual processing. The number of such areas varies from species to species, with the greatest number being found in humans. These areas are found within Brodmann's areas 18 and 19 and the inferotemporal cortex and are involved in more complex visual processing than V1, with one aspect of the visual scene tending to be dominant in terms of the analysis undertaken by that cortical area (e.g. colour or motion detection). In addition, there are a number of other parts of the CNS that are associated with the visual system including the **posterior parietal cortex** (see Chapter 28); **the frontal cortex and frontal eye fields** (see Chapters 28 and 35); and the subcortical structures of the **hypothalamus** (see Chapter 37) and **upper brainstem** (see Chapter 22).

Abbreviations

LGN lateral geniculate nucleus of the thalamus
V1 primary visual cortex

24 The auditory system I: The ear and cochlea



Inner hair cell		Outer hair cell
Total number	3500	12000
No. in row	1	3–4
No contact with TM		Tallest stereocilia contact TM
Provides 93% of input to VIII nerve		Provides only 7% of input to VIII nerve
Receives small unmyelinated efferent input from superior olivary complex		Receives large myelinated efferent input from superior olivary complex

The **auditory system** is responsible for sound perception. The receptive end organ is the cochlea of the inner ear which converts sound waves into electrical signals by a process of mechanotransduction. The electrical signal generated in response to a sound is passed (together with information from the vestibular system; see Chapter 26) via the eighth cranial nerve (vestibulocochlear nerve) to the brainstem where it synapses in the cochlear nuclear complex (see Chapter 25).

Although the auditory system as a whole performs many functions, the primary site responsible for frequency discrimination is at the level of the cochlea.

Properties of sound waves

A **sound wave** is characterised by its **amplitude** or **loudness** (measured in decibels (dB)), **frequency** or **pitch** (measured in hertz (Hz)), **waveform, phase** and **quality** or **timbre**. The intensity of sound can vary enormously but in general we can discriminate changes in intensity of around 1–2 dB.

The arrival of a sound at the head creates phase and intensity differences between the two ears unless the sound originates from the midline. The degree of delay and intensity change between the two ears as a result of their physical separation is useful, but probably not necessary, for the localisation of sounds (see Chapter 26).

External and middle ear

On reaching the ear the sound passes down the **external auditory meatus** to the **tympanic membrane or eardrum**, which vibrates at a frequency and strength determined by the impinging sound. This causes the **three ear ossicles** in the **middle ear** to move, displacing fluid within the **cochlea** as the stapedial foot process moves within the oval window of the cochlea. This process is essential in reducing the acoustic impedance of the system and in enhancing the response to sound, because a sound hitting a fluid directly is largely reflected.

There are two small muscles associated with the ear ossicles which protect them from damage by loud noises as well as modifying the movement of the stapedial foot process in the oval window. Damage to the ear ossicles (e.g. ***otosclerosis***), middle ear (e.g. infection or ***otitis media***) or external auditory meatus (e.g. blockage by wax) all lead to a reduction in hearing or ***deafness*** that is **conductive** in nature.

Inner ear and cochlea

The displacement of the stapedial foot process in the **oval window** generates waves in the perilymph-filled scala vestibuli and tympani of the cochlea. These two scalae are in communication at the apical end of the cochlea, the helicotrema, but are separated for the rest of their length by the scala media that contains the transduction apparatus in the organ of Corti.

The organ of Corti sits on the floor of the scala media on a structure known as the **basilar membrane (BM)**, the width of which increases with distance from the stapedial end. This increase in width coupled to a decrease in stiffness of the BM means that sounds of high frequency maximally displace the BM at the stapedial end of the cochlea while low frequency sounds maximally activate the apical end of the BM. Thus frequency tuning is, in part, a function of the BM although it is greatly enhanced and made more selective by the hair cells of the organ of Corti that lie on this membrane.

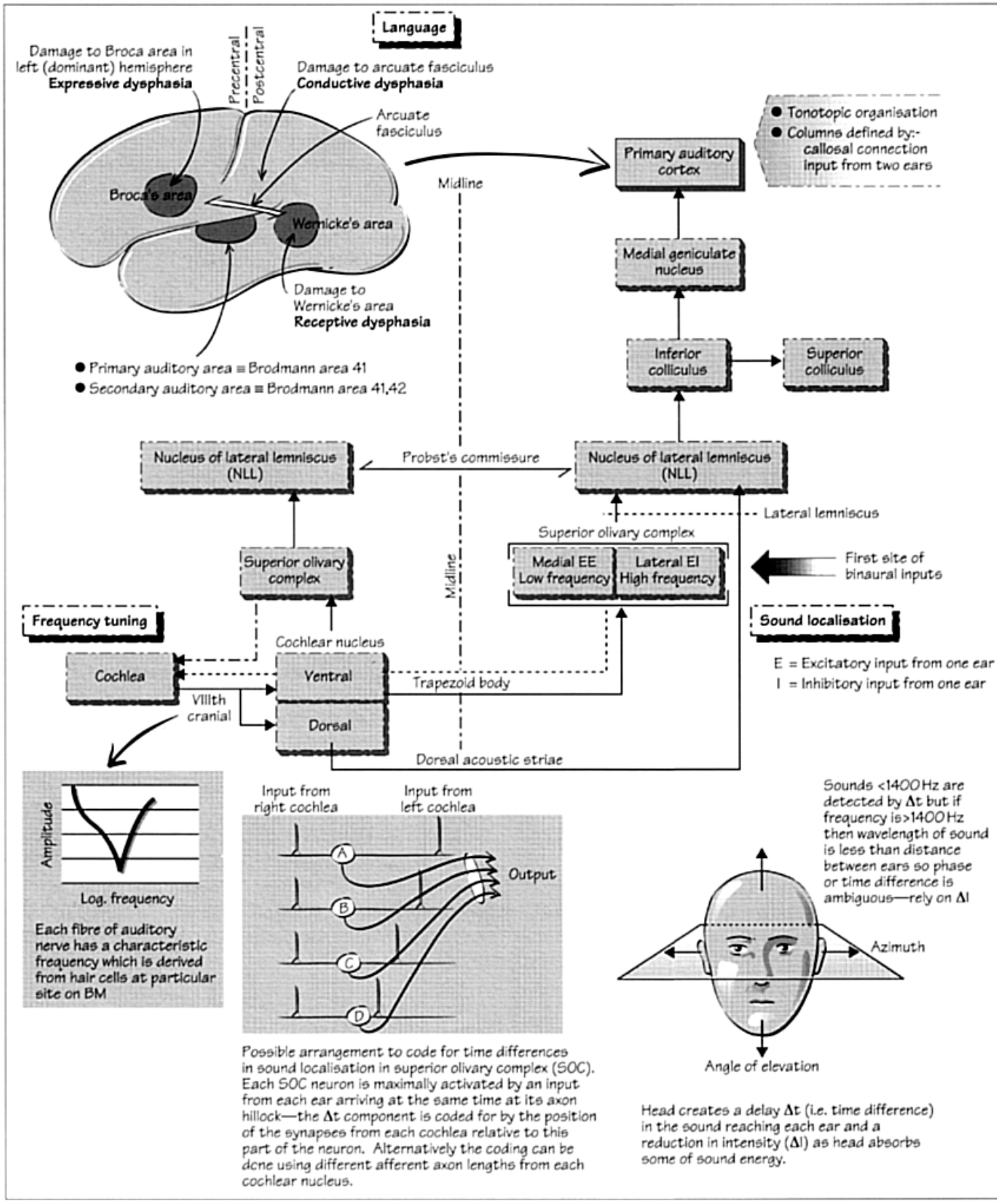
The **organ of Corti** is a complex structure that contains the cells of **auditory transduction**, the **hair cells** (see Chapter 18), which are of two types in this structure: a single row of inner hair cells (IHCs) that provide most of the signal in the eighth cranial nerve; and 3–4 rows of outer hair cells (OHCs) that have a role in modulating the response of IHCs to a given sound. These two types of hair cells are morphologically and electrophysiologically distinct. While the IHCs receive little input from the brainstem, the OHCs do so in the form of an input from the superior olivary complex which has the effect of modifying the shape and response properties of these cells. Some of the OHCs make direct contact with the overlying **tectorial membrane (TM)** in the organ of Corti which may be important in modifying the response of the IHCs to sound, as these cells do not contact the TM but do provide 95% of the afferent input of the cochlear nerve. One afferent fibre receives from many OHCs, but a single IHC is associated with many afferent fibres. In addition to these differences between OHCs and IHCs, there are subtle alterations in the hair cells themselves with distance along the scala media. These alterations in shape alter their tuning characteristics which adds a degree of refinement to frequency tuning, beyond that imparted by the resonance properties of the BM.

Damage to the cochlea, hair cells or cochlear part of the vestibulocochlear nerve leads to ***deafness*** that is described as being **sensorineural** in nature. Trauma, ischaemia and tumours of the eighth cranial nerve can all cause this. Certain hereditary causes of deafness have been associated recently with defects in the proteins found in the stereocilia of hair cells.

Abbreviations

A1	primary auditory cortex
BM	basilar membrane
dB	decibel
IHC	inner hair cell
MGN	medial geniculate nucleus of the thalamus
OHC	outer hair cell
TM	tectorial membrane

25 The auditory system II: The auditory pathways and language



The **vestibulocochlear or eighth cranial nerve** transmits information from both the cochlea and vestibular apparatus; the latter will be discussed in Chapter 26. Each fibre of the cochlear nerve is selectively tuned to a characteristic frequency, which is determined by its site of origin within the cochlea (see Chapter 24). These fibres are then arranged according to the location of their innervating hair cells along the basilar membrane, and this tonotopic organisation is maintained throughout the auditory pathway.

On entering the brainstem the cochlear nerve synapses in the cochlear nuclear complex of the medulla.

Auditory pathways

The **cochlear nucleus** is divided into a ventral (VCN) and dorsal (DCN) part. The VCN projects to the SOC bilaterally whilst the DCN projects via the dorsal acoustic striae to the contralateral nucleus of the lateral lemniscus and inferior colliculus.

The **superior olivary complex (SOC)** contains spindle-shaped neurons with a lateral and medial dendrite, which receive an input from each ear. It is the first site of binaural interactions and thus, this structure is important in sound localisation. In the **medial part of the SOC** this input is excitatory from each ear **(EE cells)** whereas in the **lateral SOC** the neurons have an excitatory input from one ear and an inhibitory input from the other **(EI cells)**.

The EE cells by virtue of their input are important in the localisation of sounds of low frequency (less than 1.4 kHz) where the critical factor is the delay (Δt) in the sound reaching one and then the other ear. One possible arrangement which could be employed is shown in the figure and relies on the differential localisation of the synaptic inputs to a single SOC neuron from the two ears.

The EI cells are important in the localisation of higher frequency sounds where the difference in intensity (ΔI) of sound between the two ears is important (ΔI being generated as a result of the head acting as a shield). Sounds of frequencies greater than 1.4 kHz (in the case of humans) rely on ΔI for localisation. In the case of sounds originating in the midline, there will be no Δt and no ΔI and there is some confusion in localisation which can be overcome to some extent by moving the head or using other sensory cues.

The elevation of the sound within the plane of the midline is probably detected in some way with the help of the pinna.

The SOC not only projects rostrally to the **inferior colliculus (IC)** but also has an important input to the cochlea (see Chapter 24). The projection to the IC is tonotopic and this structure also receives an input from the primary auditory cortex (A1) and other sensory modalities. In this respect it interacts with the superior colliculus and is involved in the orienting response to novel audiovisual stimuli (see Chapters 22 and 35).

The IC projects to the **MGN** which projects to the **A1** in the superior temporal gyrus. This area corresponds to Brodmann's areas 41 and 42, with the thalamic afferent input synapsing in layers III and IV of the cortex. The columnar organisation of A1 is poorly developed but the tonotopic map is maintained so that low-frequency sounds are located posteriorly and high-frequency sounds anteriorly.

Secondary auditory cortical areas and language

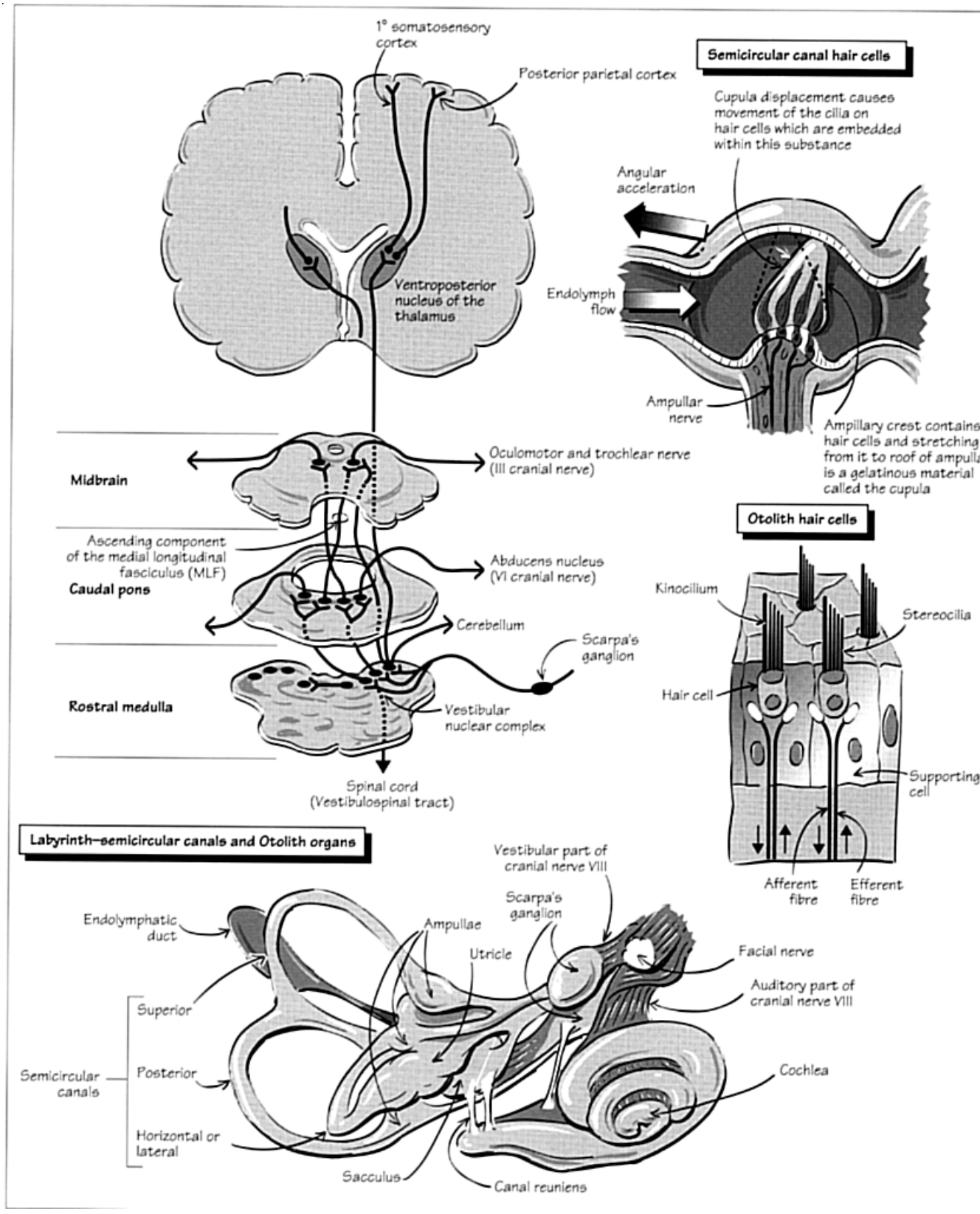
In A1, apart from neurons with relatively simple afferent inputs, there are some cells which respond to complex sounds. These neurons are more frequently found in the **secondary auditory areas**, and reach their most complex in **Wernicke's area**, the cortical site of language comprehension. This area is found in the dominant hemisphere (usually left) and when damaged (e.g. in cerebrovascular accidents (CVAs); see Chapter 16) leads to a ***receptive dysphasia***, or an inability to understand what is being said. This area is connected, via the **arcuate fasciculus**, to an area in the dominant hemisphere frontal lobe known as **Broca's area**. This frontal area is responsible for the expression of speech and damage to it causes an ***expressive dysphasia*** or an inability to speak fluently in the absence of damage to the motor apparatus of articulation. ***Aphasia*** is an inability to generate any speech and in a large middle cerebral artery CVA of the dominant hemisphere this can occur as both Wernicke's and Broca's areas are involved. Selective lesions of the arcuate fasciculus are said to produce a ***conduction aphasia***, where the patient understands and can speak but cannot repeat words and sentences. However, current evidence points to a more complex interaction among brain regions in the recognition and production of speech.

Aphasia and dysphasia are to be distinguished from deficits in the activation and execution of the motor acts of speaking (e.g. weakness of the palate and tongue in ***motorneuron disease***), which is termed ***dysarthria*** (or anarthria when no speech can be generated).

Abbreviations

A1	primary auditory cortex
BM	basilar membrane
CVA	cerebrovascular accident
DCN	dorsal cochlear nucleus
IC	inferior colliculus
MGN	medial geniculate nucleus of the thalamus
NLL	nucleus of the lateral lemniscus
SOC	superior olivary complex
VCN	ventral cochlear nucleus

26 The vestibular system



The vestibular system is concerned with balance, postural reflexes and eye movements. It consists of a peripheral transducer component which projects to the brainstem, (including the oculomotor nuclei) and from there to the thalamus and sensory cortex as well as to the cerebellum. Disruption to the system results in the symptoms of dizziness, vertigo, nausea ± blurred vision with signs of eye movement abnormalities (typically nystagmus; see Chapter 35) and unsteadiness. In the comatose patient clinical testing of the vestibular system can provide useful information on the integrity of the brainstem.

Vestibular transduction

The peripheral transducer component consists of the **labyrinth** which is made up of two **otolith organs** (the **utricle** and the **sacculus**) together with the **ampullae** located in the three **semicircular canals**. The otolith organs are primarily concerned with static head position and linear acceleration while the semicircular canals are more concerned with rotational (angular) acceleration of the head.

Hair cells are found both in the otolith organs and the ampullae and are similar in structure to those found in the cochlea (see Chapters 18 and 24). As in the cochlea, deflection of the stereocilia towards the kinocilium depolarises the cell and allows transmitter to be released from the hair cell, leading to activation of the associated afferent fibre. The converse is true if the stereocilia are deflected in the opposite direction. Movement of the cilia is associated with rotational movement of the head (ampullae receptors in the semicircular canals) and acceleration or tilting of the head (otolith organs in utricle), as although head movement causes the **endolymph** bathing the hair cells to move, it 'lags behind' and so distorts the stereocilia.

Spontaneous activity in the afferent fibres is high, reflecting the spontaneous leakage of transmitter from the cell at the synapse. Hyperpolarisation of the hair cell therefore results in a reduced afferent discharge, while depolarisation is associated with an increase in firing. Efferent fibres from the brainstem terminating on the hair cells can change the sensitivity of the receptor end organ.

Peripheral disorders of the vestibular system

Damage to the peripheral vestibular system is not uncommon. An example of such a disorder is ***benign positional vertigo*** which commonly occurs after trauma or infection of the vestibular apparatus with the deposition of debris (e.g. otolith crystals or otoconia) in the posterior semicircular canal. This condition, which is characterised by paroxysms of vertigo, nausea and ataxia induced by turning the head into certain positions—such as lying down or rolling over in bed—is therefore the consequence of distortion of endolymph flow in this canal secondary to the debris. Treatment and cure can be effected if a series of head manoeuvres are followed which allows the debris to fall out of the semicircular canal and into the ampullae.

Bilateral damage to the vestibular apparatus can result in **oscillopsia**, a condition in which there is an inability to visually fixate on objects (see Chapter 35). In contrast, powerful excitation of the vestibular system such as that encountered during motion sickness produces dizziness, vomiting, sweating and tachycardia, caused by discrepancies between vestibular and visual information.

Vestibular function can be tested by introducing water into the external meatus **(caloric testing)**. When warm water is applied to a seated subject whose head is tilted back by about 60°, nystagmus towards the treated side is observed. Cold water produces a nystagmus towards the opposite side. These effects reflect the changes in the temperature of the endolymph and an effect resembling head rotation away from the irrigated side.

The central vestibular system and vestibular reflexes

Afferent vestibular fibres in the eighth cranial nerve have their cell bodies in the vestibular **(Scarpa's) ganglion** and terminate in one of the **four vestibular nuclei** in the medulla which also receive inputs from neck muscle receptors and the visual system.

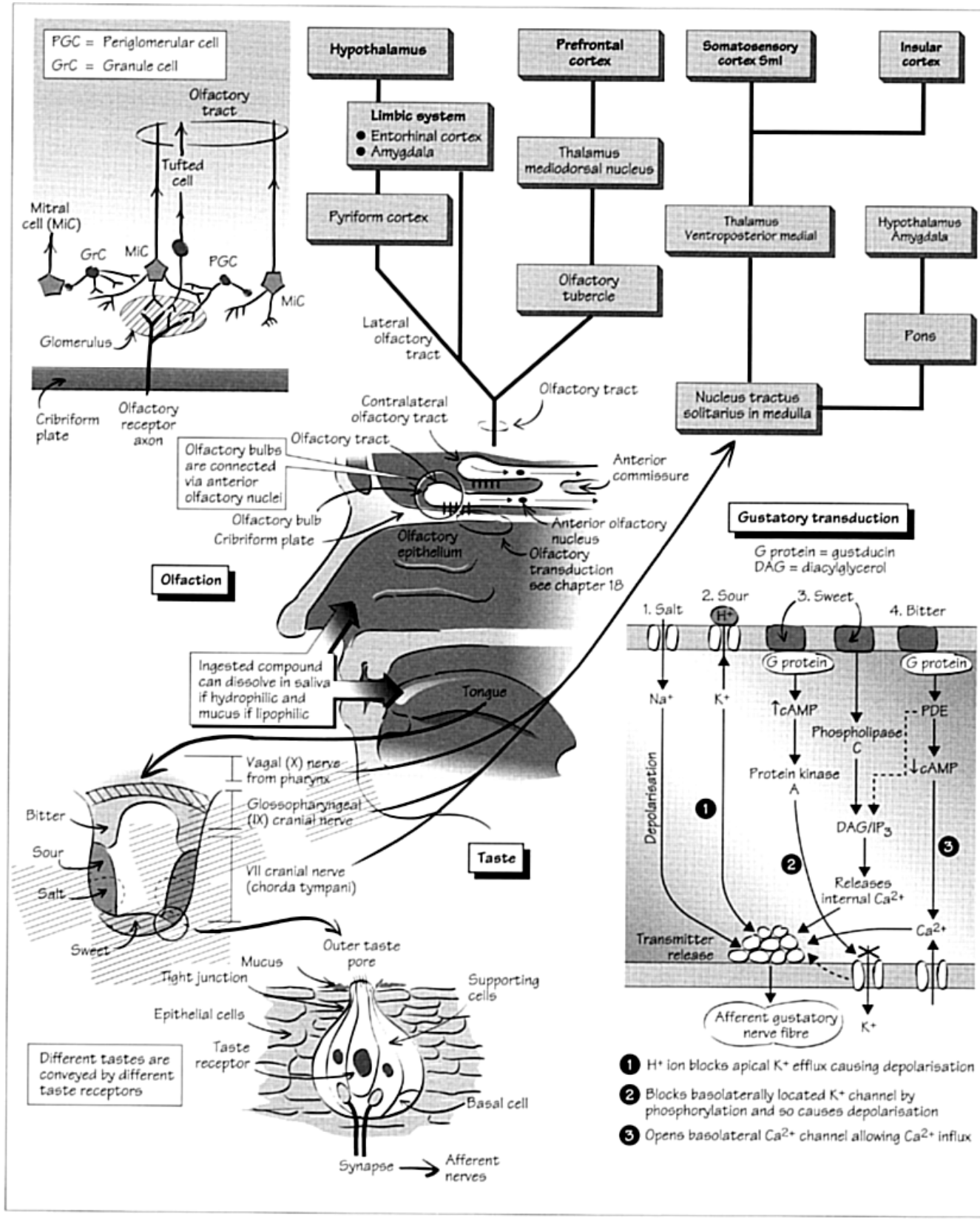
The vestibular nuclei project to the spinal cord (see Chapters 11, 31 and 32), the ipsi- and contralateral thalamus, the cerebellum, the oculomotor nuclei and contralateral vestibular nuclei. These latter structures are important in reflex eye movements such as the ability to maintain visual fixation while moving the head—the vestibuloocular reflex (VOR; see Chapters 34 and 44). Other projections of the vestibular nuclei are important in maintaining posture and gait. The cortical termination of the vestibular input to the CNS is SmI and the posterior parietal cortex (see Chapter 28).

Caloric testing of the vestibular system examines the integrity of the vestibular apparatus and its brainstem connections so it can be useful in comatosed patients when the degree of brainstem function needs to be ascertained. Less severe central damage to the vestibular apparatus can occur in a number of conditions including ***multiple sclerosis*** (see Chapter 46) and vascular insults (see Chapter 16). In most cases other structures are involved and so there are other symptoms and signs on examination.

Abbreviations

SmI primary somatosensory reflex
VOR vestibuloocular reflex

27 Olfaction and taste



The **olfactory or first cranial nerve** contains more fibres than any other sensory nerve projecting to the CNS, while **taste** is relayed via the seventh, ninth and tenth cranial nerves (see Chapter 13).

Olfaction

The olfactory system as a whole is able to discriminate a great diversity of different chemical stimuli or odours, and this is made possible through thousands of different olfactory receptors. These receptors are located in the apical dendrite of the olfactory receptor cell and the axon of this cell projects directly into the CNS via the cribriform plate at the top of the nose to the olfactory bulb.

The **olfactory stimulus or odour**, on binding to the olfactory receptor, depolarises it (see Chapter 18) which, if sufficient, leads to the generation of action potentials at the cell body which are then conducted down the olfactory nerve axons to the olfactory bulb.

The **olfactory nerve** passes through the roof of the nose through a bone known as the cribriform plate. Damage to this structure can shear the olfactory nerve axons causing a loss of smell or ***anosmia***. However, the commonest cause of a loss of smell is local trouble within the nose, usually infection and inflammation. The olfactory receptor axons then synapse in the olfactory bulb that lies at the base of the frontal lobe. Damage to this structure, as occurs in frontal ***meningiomas***, produces anosmia that can be unilateral.

The **olfactory bulb** contains a complex arrangement of cells. The axons from the olfactory nerve synapse on the apical dendrites of mitral, and to a lesser extent, tufted cells, both of which project out of the olfactory bulb as the olfactory tract. The olfactory bulb contains a number of inhibitory interneurons (granule and periglomerular cells) which are important in modifying the flow of olfactory information through the bulb.

The **olfactory tract** projects to the temporal lobe where it synapses in the **pyriform cortex** and **limbic system** which projects to the **hypothalamus**. This projection is important in the behavioural effects of olfaction, which are perhaps more evident in other species. In humans lesions in these structures rarely produce a pure anosmia, but activation of this area of the CNS as occurs in ***temporal lobe epilepsy*** (see Chapter 45) is associated with the abnormal perception of smells—(e.g. olfactory hallucinations).

The projection of the olfactory system to the thalamus is small and is via the olfactory tubercle to the mediodorsal nucleus, which projects to the prefrontal cortex. The role of this pathway is not clear.

Taste

The **taste** or **gustatory receptors** are located in the tongue. They are clustered together in fungiform papillae with support and stem cells; the latter dividing to replace those gustatory receptors that are damaged. The apical surface of the gustatory receptor contains microvilli covered in mucus, which is generated by the neighbouring goblet cells. Any ingested compound can therefore reach the gustatory receptor; hydrophilic substances are dissolved in saliva while lipophilic substances are dissolved in the mucus. Traditionally, taste is classified according to four modalities—salt, sour, sweet and bitter—which correlate well with the different transduction processes that are now known to exist for these different tastes.

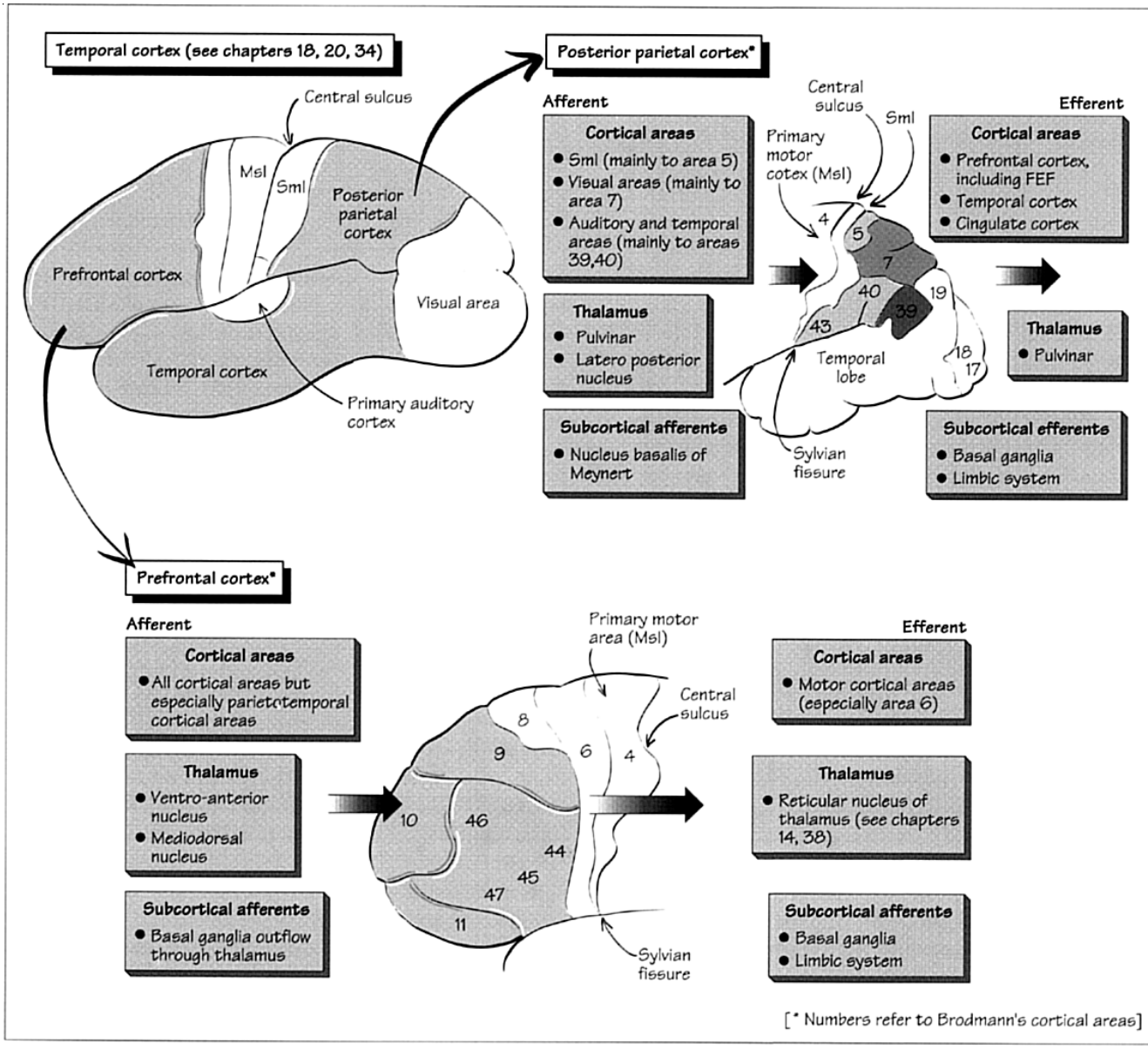
Salt stimuli cause a direct depolarisation of the gustatory receptors by virtue of the fact that Na^+ passes through an amiloride-sensitive apical membrane channel. The depolarisation leads to the release of neurotransmitter from the basal part of the cell which activates the afferent fibres in the relevant cranial nerve. **Sour stimuli**, in contrast, probably achieve a similar effect by the blocking of apical voltage-dependent H^+ channels. **Sweet stimuli** bind to a receptor that activates the G protein, gustducin, which then activates an adenyl cyclase with cAMP production. The rise in cAMP activates a protein kinase which phosphorylates and closes basolateral K^+ channels and by so doing depolarises the receptor. **Bitter stimuli** similarly rely on receptor binding and G-protein activation. One pathway involves gustducin but in this instance, this leads to activation of a cAMP phosphodiesterase which reduces the level of cAMP (and so the phosphorylating protein kinase) leading to opening of the basolateral Ca^{2+} channels and so transmitter release. An alternative pathway for both sweet and bitter tastes involves the activation of a phospholipase C and the production of IP_3 and diacylglycerol (DAG) which can release Ca^{2+} from internal stores within the receptor. The increased Ca^{2+} concentration promotes neurotransmitter release.

The receptors relay their information via the **chorda tympani** (anterior two-thirds of the tongue) and **glossopharyngeal nerve** (posterior third of the tongue) to **the nucleus of the solitary tract** in the medulla (see Chapters 12 and 13). The structure projects rostrally via the thalamus to the primary somatosensory cortex (SmI) and the insular cortex, with a possible further projection to the hypothalamus and amygdala. Some patients with ***temporal lobe epilepsy*** have an aura of an abnormal taste in the mouth which may be consequent of this latter projection (see Chapter 45).

Abbreviations

cAMP	cyclic adenosine monophosphate
DAG	diacylglycerol
IP_3	inositol triphosphate
PDE	phosphodiesterase

28 Association cortices: the posterior parietal and prefrontal cortex



The **association cortices** are those parts of the cerebral cortex that do not have a primary motor or sensory role, but instead are involved in the higher order processing of sensory information necessary for perception and movement initiation.

These association areas include the posterior parietal cortex (PPC) (defined in monkeys as corresponding to Brodmann's areas 5 and 7, and in humans including areas 39 and 40); the prefrontal cortex (corresponding to Brodmann's areas 9–12, 44–47) and the temporal cortex (corresponding to Brodmann's areas 21, 22, 37 and 41–43). The temporal cortex is involved in audition and language, complex visual processing (such as face recognition) and memory and is discussed in Chapters 23, 25 and 39.

Posterior parietal cortex

This area has developed greatly during evolution and is related to specific forms of human behaviour, such as the extensive use of tools, collaborative strategic planning and the development of language. It has two main

subdivisions within it: one involved mainly with somatosensory information (centred on area 5); and the other with visual stimuli (centred on area 7).

Neurophysiologically, **area 5** contains many units with a complex sensory input often with a convergence of different sensory modalities, such as proprioceptive and cutaneous stimuli. These units with such a dual input are probably involved to some extent in the sensory control of posture and movements, a function shared with the multijoint units found in this area. In contrast, some units with multiple cutaneous inputs are probably more involved in object recognition as they respond best to object movement across their receptive fields. However, in addition to having these complex sensory inputs, units in this area are often only maximally activated when the sensory stimulus is of interest or behavioural significance. Damage to this area produces a contralateral sensory loss that is often subtle — e.g. a failure to recognise objects on tactile manipulation ***(astereognosis)***. In addition, patients often demonstrate an inattention to stimuli received on the contralateral side of the body. This can be so severe that the patient denies the existence of that part of his or her body which can then interfere with the actions of the normal non-neglected side (so-called intermanual conflict or alien limb). More commonly the patient fails to perceive sensory stimuli contralaterally when stimuli are simultaneously applied to both sides of the body (so-called extinction).

In contrast, **area 7** is more involved in complex visual processing, with many of the units in this area responding to stimuli of interest or behavioural significance (e.g. food). Many different units are found in this cortical area some of which maximally respond to the visual fixation and tracking, while others are more involved in the process of switching attention from one visual object of interest to another (light sensitive or visual space neurons). There are individual neurons in area 7 that respond to both sensory and visual stimuli. Some of these neurons are maximally activated when a stimulus is moved towards the neuron's cutaneous receptive field from extrapersonal (distant) space, while others are maximally activated during visual fixation of a desired object in which there is concomitant movement of the arm towards that object. In humans damage to this area produces a neglect of visual stimuli in the contralateral hemifield, as well as defects in eye movement and the visual control of movement. However, a more striking deficit which may occur in some patients is in the realm of complex visual processing such as route finding and the construction of complex shapes.

Finally in humans, and to a lesser extent in other primates and animals, units are found in the posterior parietal cortex which are maximally activated by vestibular and auditory inputs (see Chapters 25 and 26). Therefore damage to this area in humans can lead to complex difficulties in vision and visually guided movements, balance and language processing, including arithmetic skills. This includes an inability to write ***(agraphia)***, to read ***(alexia)*** and calculate simple sums ***(acalculia)***.

In summary, **the function of the PPC** is in combining information on personal (somatic) awareness with information on extrapersonal (visual) space, and in coupling internal purpose with external stimuli. Such machinery must deal with behavioural mechanisms, two of which (awareness and intention) are personal in nature and two of which (spatial representation and attention towards stimuli) are externally orientated towards the environment.

Prefrontal cortex

This cortical area has increased in size with phylogenetic development and has its greatest representation in humans. It is involved in the purposive behaviour of an organism and thus is intimately involved in the planning of responses to stimuli which includes a motor component (see Chapter 29). Within this structure are specialised cortical areas such as the frontal eye fields (FEF; see Chapter 35) and Broca's area (see Chapter 25). Although the prefrontal cortex is treated as a functional whole this is a gross simplification.

Many different types of units are encountered neurophysiologically in this area of cortex, but they generally respond to complex sensory stimuli of behaviourial relevance which can then be translated into a cue for movement.

Damage to this site in animals leads to increased distractability with corresponding deficits in working memory (the ability to retain information for more than a few seconds) and a change in locomotor activity and emotional responsiveness. A patient with frontal lobe damage anterior to the motor areas has a characteristic syndrome without insight. The patient is often disinhibited, which results in him or her speaking and behaving in an atypical, often childish, fashion. The patient has very poor attention and is easily distractable, cannot retain information and is sometimes unable to form new memories, with a tendency to perseverate (the repetition of words or phrases and actions) and pursue old patterns of behaviour even in the face of environmental change. He or she is unable to formulate and pursue goals and plans, to generalise and deduce. There is often a marked reduction in verbal output which is also reflected in motor behaviour as evidenced by a lack of spontaneous movement. The patient can become apathetic with severe blunting of his or her emotional responses, although in some cases the converse is true with the patient becoming aggressive. Overall the patient's personality changes and it is typically others who bring the patient to medical attention, as the patient usually denies there is any problem (no insight).

The reliance on the clinical symptomatology to describe the function of the prefrontal cortex relates to the fact that

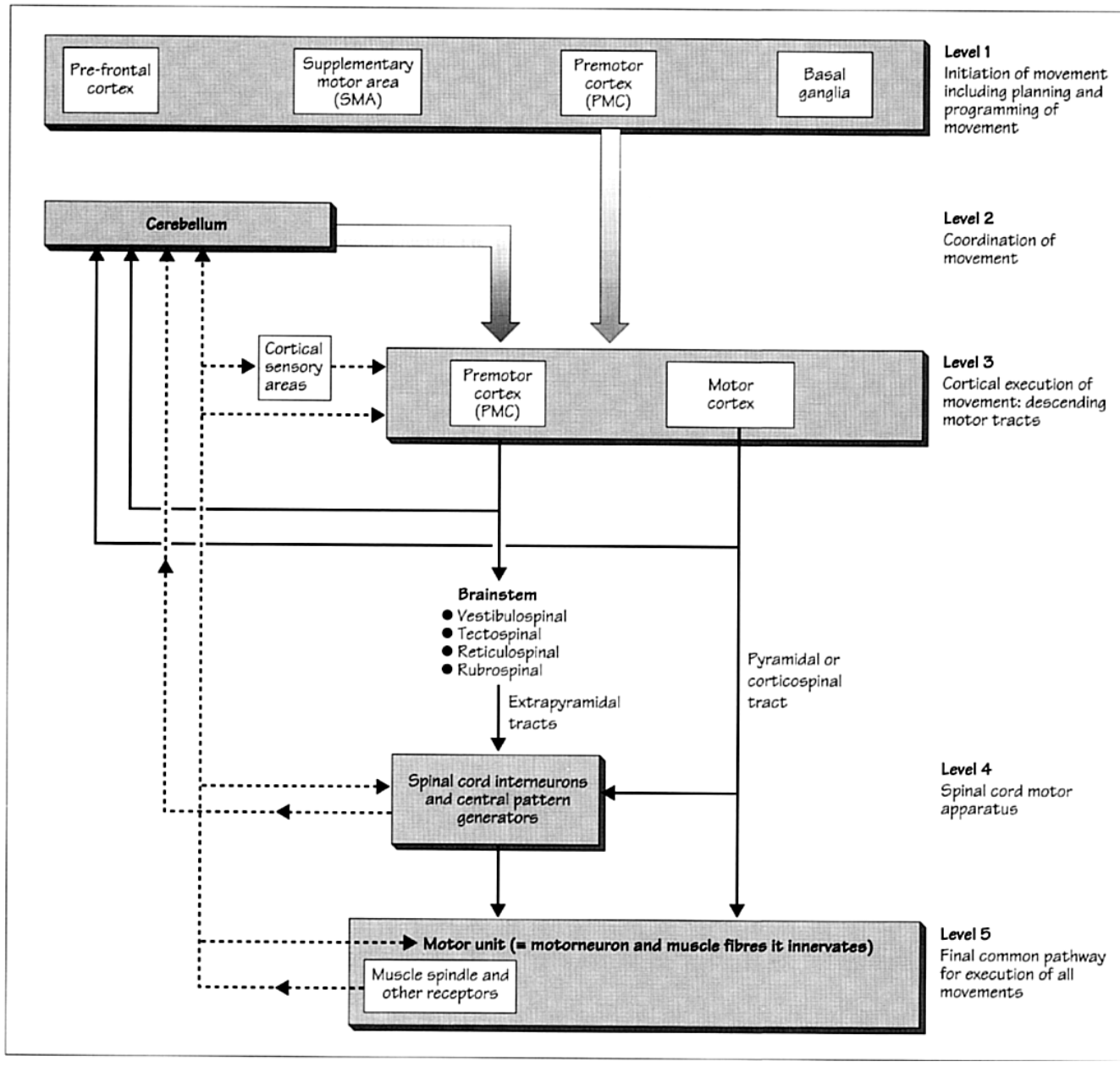
this part of the cortex is most developed in humans. However, extensive damage of the frontal lobes can also affect the cortical motor areas (see Chapter 32), eye movements (see Chapter 35), the ability to talk (an expressive dysphasia; see Chapter 25) and the control of micturition.

Abbreviations

FEF	frontal eye field
MsI	primary motor cortex
PPC	posterior parietal cortex
SmI	primary somatosensory cortex

Part 3 **Motor systems**

29 The organisation of the motor systems



The **motor systems** are those areas of the nervous system that are primarily responsible for controlling movement. The movement can be either guided by inputs from the sensory systems **(closed-loop or reflexly controlled)** or triggered by a sensory cue or some internal desire to move **(open-loop or volitional movement)**. In practice, most motor acts involve both types of movement, with closed-loop movements predominantly involving the axial or proximal muscles responsible for balance, posture and locomotion while the open-loop movements are typically associated with the distal musculature concerned with the control of fine skilled movements

The organisation of the motor structures is best viewed in terms of a hierarchy.

Level 1

The highest level of motor control is concerned with the **initiation, planning and programming of movements** in

response to an internal desire to move. This desire probably originates in the **limbic system** (Chapter 39) and **posterior parietal cortex** (Chapter 28), while the structures primarily responsible for translating that desire into a movement are the **basal ganglia** (Chapter 34) and their cortical projection areas in the frontal lobe (Chapter 32). These cortical areas include the **supplementary motor area** (SMA) and **premotor cortex** (PMC); the latter also has a specific role in the control of proximal muscles (see below).

Damage to the basal ganglia and their cortical projection sites leads to a range of complex movement disorders, which includes ***Parkinson's disease*** as well as the development of abnormal involuntary movements such as ***chorea***, ***dystonia*** and ***ballismus*** (see Chapter 34 for the definition of these terms). Damage to these areas does *not* produce any specific weakness or changes in the monosynaptic tendon reflexes (see Chapter 30).

Level 2

The next level is occupied by the **cerebellum**, which is responsible for the **coordination of movement**. It achieves this by comparing the intended movement descending from the motor areas in the cerebral cortex with the actual movement as detected by the activity of muscle afferents and interneurons (INs) in the spinal cord. It is capable of storing motor information, and this motor memory is not only useful in the learning of new movements but also in the correct timing of muscle activations during complex movements.

Damage to this structure leads primarily to a breakdown in the coordination of movement, without any specific weakness (see Chapter 33).

Level 3

The middle level is concerned with the control of the lower motorneurons by the supraspinal **descending motor pathways**. This can broadly be divided into two sets of pathways.

1 The **corticospinal (CoST) or pyramidal tract** which originates in the **motor**, **premotor** and **somatosensory** cortices and synapses directly on to the motorneuron (MN) in the brainstem, cranial nerve nuclei and ventral (or anterior) horn of the spinal cord and to a lesser extent INs.

2 The extrapyramidal tracts which originate from subcortical structures and have a more complex distribution of synaptic contacts with both MNs and INs. These **extrapyramidal pathways** include the **vestibulo- (VeST), reticulo- (ReST), tecto- (TeST) and rubrospinal tracts (RuST)** and are all in receipt of an input from the primary motor cortex.

Damage in the CNS is rarely specific to a single tract but interruption of the descending motor pathways produces a pattern of weakness in the limbs that is more pronounced in the extensor muscles in the arms and flexor muscles in the legs—the so-called (but misnamed) ***pyramidal distribution of weakness***. In association with the weakness, there is increased tone in the muscles and brisk reflexes; all three features characterising an ***upper motorneuron lesion***. In contrast to the higher levels in the hierarchy, this is the first level where damage is actually associated with weakness.

Level 4

A low level of motor organisation is to be found in the **spinal cord** itself. The descending motor pathways from the brain synapse not only on the MNs, but also the INs and while some of these mediate the spinal cord **reflexes**, others are capable of generating their own outputs to MNs independently of any descending or peripheral sensory input—so-called **central pattern generators**. These are important in locomotion (see Chapter 31).

Level 5

The lowest level or **final common pathway of the motor system** is the output neuron of the CNS to the muscle, namely the **motorneuron (MN)**. The MN receives information not only from the brain via the descending pathways and spinal cord INs but also has an important input from sensory organs in the periphery, especially the **muscle spindle** and **Golgi tendon organ** that are found in the muscle and tendon, respectively. The muscle spindle in particular is important in mediating the **simple stretch reflex** that underlies the tendon jerks of the clinical examination.

Damage to the MN or its axon to the muscle produces a ***lower*** (as opposed to upper) ***motorneuron lesion***, characterised by weakness and wasting, hypotonia and reduced or absent reflexes (see Chapter 30).

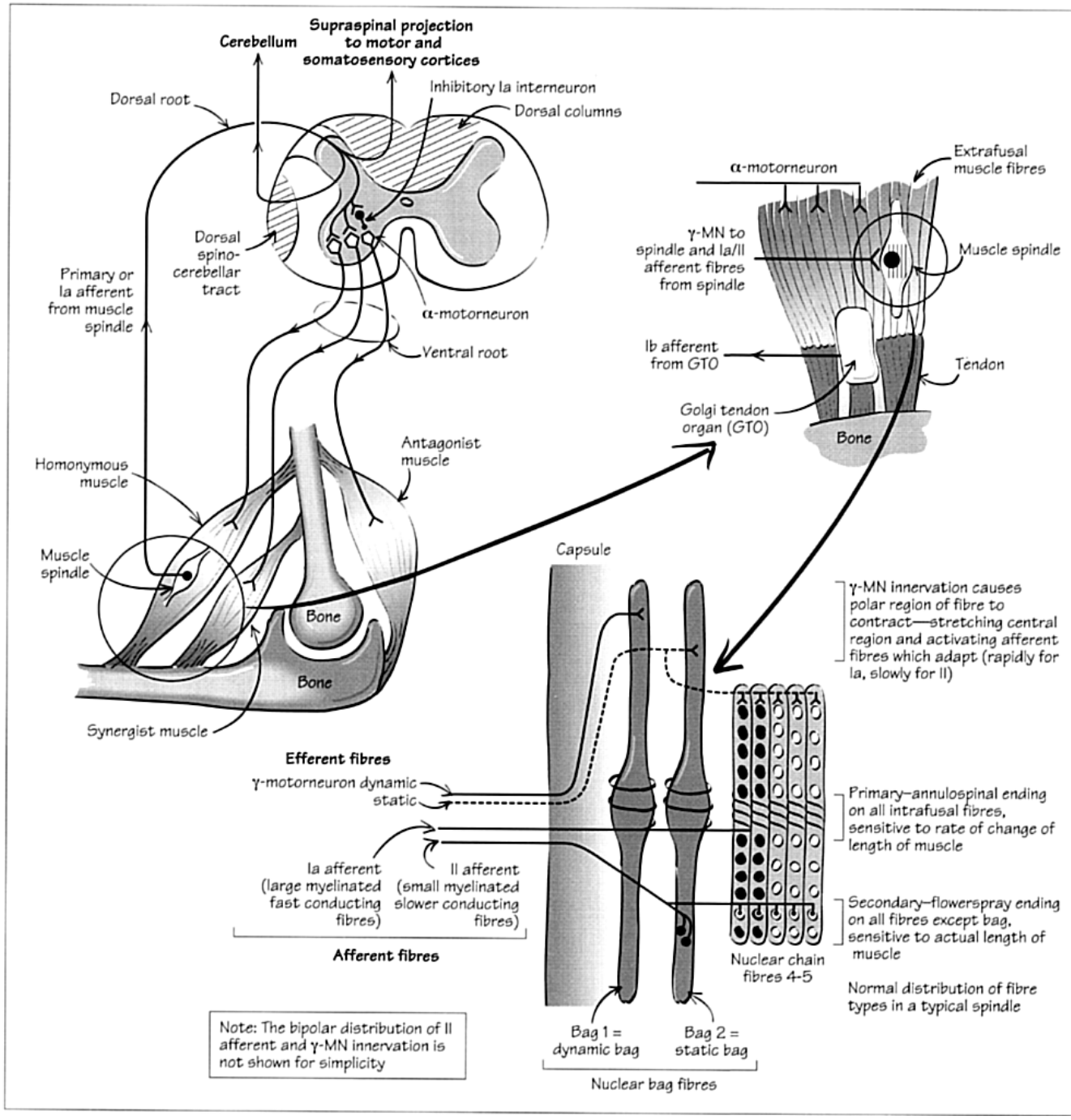
A cautionary note

It is important to remember that the division of the CNS into motor and sensory functions is a gross simplification as all the motor areas have some sensory input. It is difficult to know the point at which a highly processed sensory input becomes the impulse for the initiation of a movement. It should also be realised that the division of the motor systems into various levels and different motor pools is a convenient but not strictly accurate device for understanding the control of movement and the pathophysiology of disorders of the motor system.

Abbreviations

CoST	corticospinal tract
IN	interneuron
MN	motorneuron
PMC	premotor cortex
ReST	reticulospinal tract
RuST	rubrospinal tract
SMA	supplementary motor area
TeST	tectospinal tract
VeST	vestibulospinal tract

30 The muscle spindle and lower motorneuron



Lower motorneuron

The **lower motorneuron (LMN)** is defined as the neuron whose cell body lies in either the anterior or ventral horn of the spinal cord or the cranial nerve nuclei of the brainstem and which directly innervates the muscle via its axon. The number of muscle fibres innervated by a single axon is termed the **motor unit**. The smaller the number of fibres per MN axon, the finer the control (e.g. the extraocular muscles).

The MNs of the anterior horn are divided into two types: the **α-MN** (70 μm in diameter) which innervate the muscle itself (the force generating extrafusal fibres); and the **γ-MN** (30 μm in diameter) which innervate the intrafusal fibres of

the muscle spindle. The **muscle spindle** is an encapsulated sense organ found within the muscle which is responsible for detecting the extent of muscle contraction by monitoring the length of muscle fibres.

It is the muscle spindle and its connections to the spinal cord that mediates the **tendon reflexes**; sudden stretching of a muscle by a sharp tap of a tendon hammer transiently activates the **Ia afferent nerve endings** which, via an excitatory monosynaptic input to the MN, causes that muscle (the **homonymous muscle**) to contract briefly (e.g. the knee jerk). In addition, the Ia afferent input from the muscle spindle while activating other **synergistic muscles** with a similar action to the homonymous muscle also inhibits muscles with opposing actions **(antagonist muscles)** through a **Ia inhibitory interneuron (IN)** in the spinal cord. However, it must be stressed that tendon jerks reflect not only the integrity of this circuit but the overall excitability of the MN, which is increased in cases of an upper motorneuron lesion (see Chapter 29).

Muscle spindle

The **muscle spindle** lies in parallel to the extrafusal muscle fibres and consists of the following.

- **Nuclear bag and chain fibres** which have different morphological properties: the bag 1 or dynamic fibres which are very sensitive to the rate of change in muscle length; while the bag 2 or static bag fibres are like the nuclear chain fibres in being more sensitive to the absolute length of the muscle.
- A **γ-MN** that synapses at the polar ends of the intrafusal muscle fibres and which can be one of two types: **dynamic or static,** with the latter innervating all fibres other than the bag 1 fibres. Both types of γ-MN are usually coactivated with the α-MN so that the intrafusal fibres contract at the same time as do the extrafusal fibres, thus ensuring that the spindle maintains its sensitivity during muscle contraction. Occasionally, the γ-MN can be activated independently of the α-MN, typically when the animal is learning some new complex movement, which increases the sensitivity of the spindle to changes in length.
- Two types of afferent fibres and nerve endings: a **Ia afferent fibre** associated with an annulospiral nerve winding around the centre of all types of intrafusal fibres **(primary ending)**; and a slower conducting **type II fibre** which is associated with flowerspray endings on the more polar regions of the intrafusal fibres (with the exception of the bag 1 fibres; the **secondary ending**). The stretching of the intrafusal fibre activates both types of fibre. However, the Ia fibre is most sensitive to the rate of change in fibre length, while the type II fibres respond more to the overall length of the fibre rather than the rate of change in fibre length.

The spindle relays via the dorsal root to a number of CNS sites including: (i) the MNs innervating the homonymous and synergistic muscles (the basis of the stretch reflex); (ii) interneurons inhibiting the antagonist muscles; (iii) the cerebellum via the dorsal spinocerebellar tract; (iv) the somatosensory cortex; and (v) the primary motor cortex via the dorsal column–medial lemniscal pathways. Thus the muscle spindle is not only responsible for mediating simple stretch or tendon reflexes but is also involved in the coordination of movement, the perception of joint position (proprioception) and the modulation of long-latency or transcortical reflexes (see Chapter 32).

Damage to the spindle afferent fibres (e.g. in large fibre ***neuropathies***) produces hypotonia (as the stretch reflex is important in controlling the normal tone of muscles), incoordination, reduced joint position sense and occasionally tremor with an inability to learn new motor skills in the face of novel environmental situations. In addition, large fibre neuropathies disrupt other somatosensory afferent inputs (see Chapter 19).

The **Golgi tendon organ (GTO)** is found at the junction between muscle and tendon and thus lies in series with the extrafusal muscle fibres. It monitors the degree of muscle contraction in terms of the muscular force generated and relays this to the spinal cord via a **Ib afferent fibre**. This sensory organ in addition to providing useful information to the CNS on the degree of tension within muscles also serves to prevent excessive muscular contractions (see Chapter 31).

Motorneuron recruitment and damage

The **'principle of recruitment'** corresponds to the order in which different types of muscle fibres are activated. The smallest α-MNs, which are those most easily excited by any input, innervate the so-called type 1 (*not* to be confused with the bag 1 intrafusal fibres found in the spindle) or slow-contracting fibres which are responsible for increasing and maintaining the tension in a muscle.

The next population of MNs to be activated are those that innervate the type 2A or fast-contracting/resistant to fatigue fibres which are responsible for virtually all forms of locomotion. Finally, the largest MNs are only activated by maximal inputs, which innervate the type 2B or fast-contracting/easily fatigued fibres that are responsible for running or jumping.

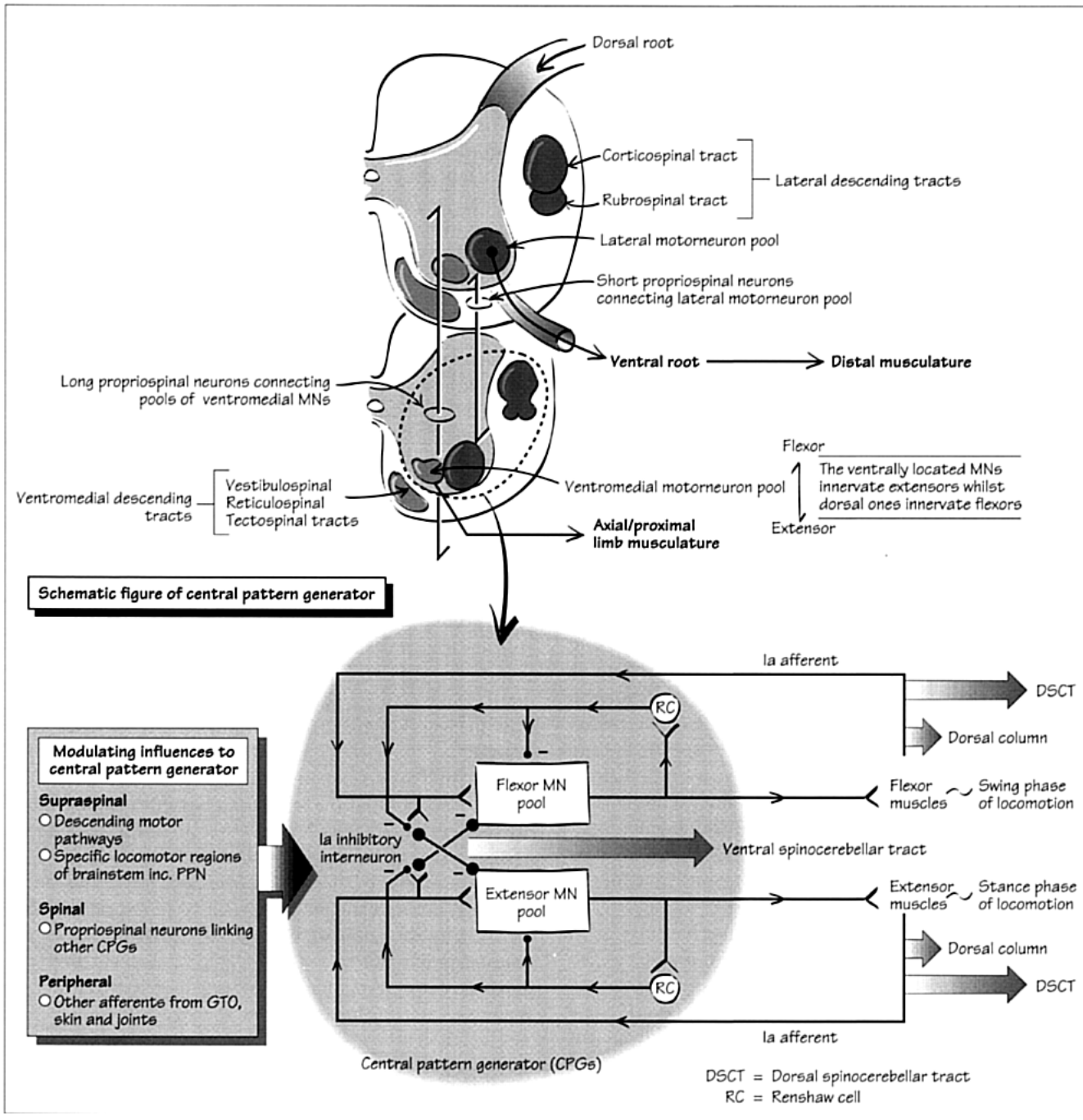
The order of recruitment of MNs to a given input follows a simple relationship known as the **size principle**, which allows muscles to contract in a logical sequence.

The **α-MN itself can be damaged** in a number of different conditions but in all cases the clinical features are the same, namely there is wasting of the denervated muscles with weakness, and reduced or absent reflexes (i.e. a lower motorneuron lesion).

Abbreviations

GTO	Golgi tendon organ
IN	interneuron
LMN	lower motorneuron
MN	motorneuron

31 Spinal cord motor organisation and locomotion



Spinal cord motor organisation

In addition to containing the **α- and γ-motorneurons (MNs),** the spinal cord also contains a large number of **interneurons (INs)** which relay afferent information from the periphery and supraspinal sites. These INs can form networks which are intrinsically active and whose output governs the activity of MNs, so-called **central pattern generators (CPGs)**. These CPGs, which may underlie locomotion, while not requiring any afferent input in order to produce a patterned motor output, are nevertheless modu-

lated by both central and peripheral inputs (see Chapters 30, 32).

Descending motor pathways (see Chapter 11 for details of individual tracts)

The **descending motor pathways** can be classified:

- according to their site of origin, namely pyramidal or extrapyramidal tracts (although *clinically* extrapyramidal disorders refer to diseases of the basal ganglia; see Chapter 34); or
- according to their location within the cord and the muscles they ultimately innervate through the MNs. Thus the **pyramidal (corticospinal)** and **rubrospinal tract** are associated with a **lateral MN pool** that innervates the distal musculature, while the **vestibulo-, reticulo-** and **tectospinal tracts** are more associated with a **ventromedial MN pool** that innervates the axial and proximal musculature.

These latter MNs are linked by long **propriospinal neurons** while the converse is true for the lateral MN pool. Thus the **lateral motor system** is more involved in the control of fine distal movements, while the **ventromedial system** is more concerned with balance and posture.

The MNs of the anterior horn are further organised such that the most anteriorally located MNs innervate the extensor muscles while those found at more posterior locations innervate the flexor musculature.

Locomotion

The control of **locomotion** is complex, as it requires the coordinated movement of all four limbs.

Each cycle in locomotion is termed a **step** and involves a **stance** and a **swing** phase—the latter being that part of the cycle when the foot is not in contact with the ground. Each cycle requires the correct sequential activation of flexors and extensors. The simplest way to achieve this is to have **two CPGs (so-called half centres)** that activate flexors and extensors respectively, and which mutually inhibit each other.

This mutual inhibition can perhaps best be modelled using the **inhibitory Ia IN** and **Renshaw cells**. Renshaw cells are INs that, when activated by MNs, inhibit those same MNs (see Chapter 8). Thus the activation of an MN pool by a CPG leads to its own inhibition and the removal of an inhibitory input to the antagonistic CPG, thus switching the muscle groups activated. This half centre model for locomotion can be modulated by a range of descending and peripheral inputs. In this latter respect the Ib afferent from the GTO can switch the CPGs to prevent excessive tension developing in a muscle, while a range of cutaneous inputs can cause the cycle to be modified in the event of an obstacle being encountered. These afferents, termed **flexor reflex afferents**, cause the limb to be flexed so stepping over or withdrawing from the noxious or obstructive object.

CPGs within the spinal cord communicate with each other through propriospinal neurons. In contrast, supraspinal communication of information from and about the CPGs is relayed indirectly in the form of muscle spindle Ia afferent activity via the DSCT and dorsal columns and spinal cord interneuronal activity via the VSCT.

Clinical disorders of spinal cord motor control and locomotion

Although experimental animals can locomote in the absence of any significant supraspinal inputs (so-called **fictive locomotion**), this is not the case in humans. However, clinical disorders of gait are relatively common and may occur for a number of reasons.

Including, rarely, disorders of spinal cord INs such as occurs in ***stiff-person syndrome***. In this condition the patient presents with increased tone or rigidity in the axial muscles ± spasms caused by the continuous firing of the MNs as a result of the loss of an inhibitory interneuronal input primarily to the ventromedial MNs. This condition is associated with antibodies against the synthetic enzyme for γ-aminobutyric acid (GABA), namely glutamic acid decarboxylase (GAD).

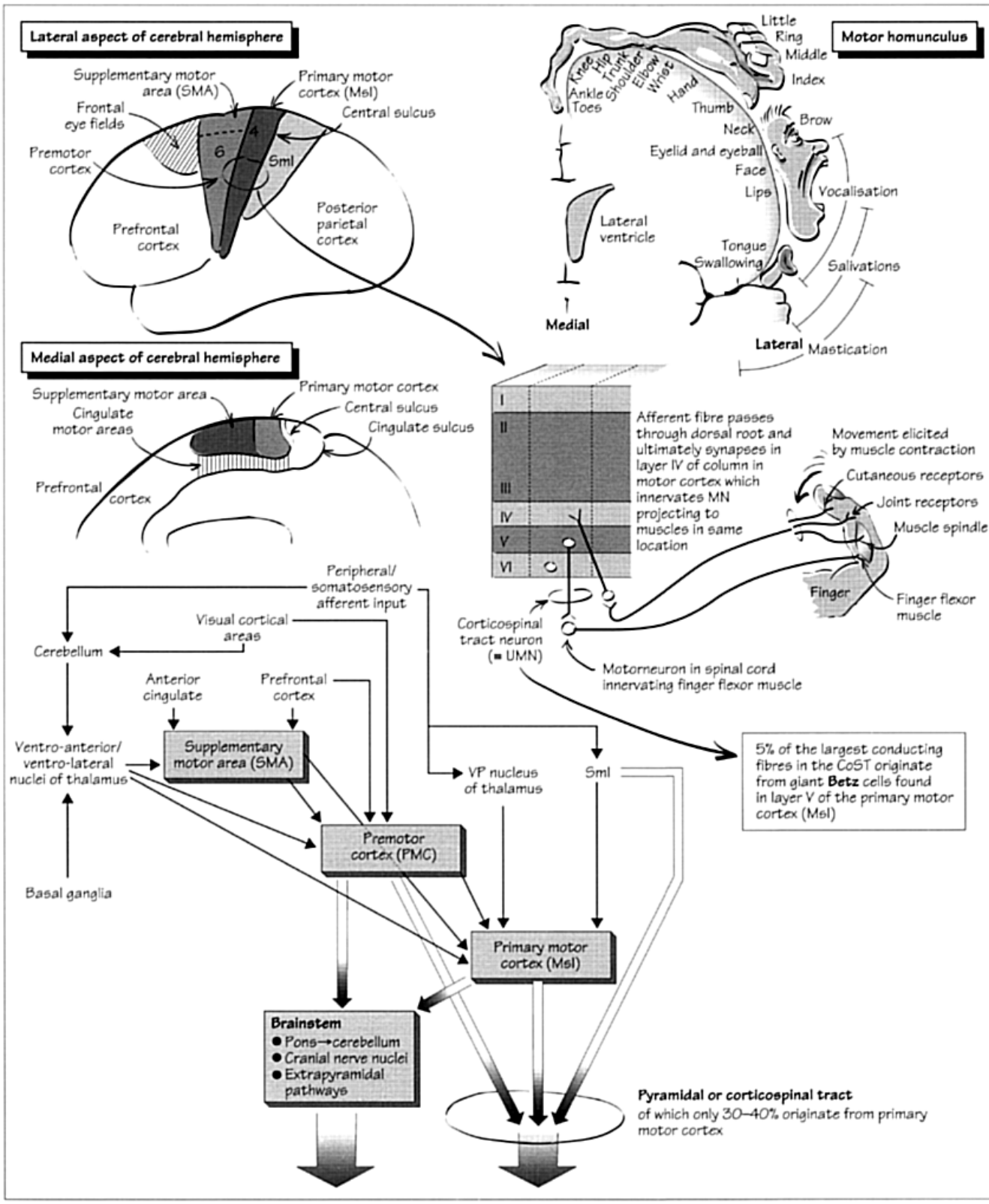
Damage to the descending pathways can produce a range of deficiencies. The most devastating is that seen with extensive brainstem damage when there is uninhibited extensor muscle activity and the patient adopts a characteristic ***decerebrate posture*** with arching of the neck and back and rigid extension of all four limbs. In contrast, a more rostrally placed lesion in one of the cerebral hemispheres produces weakness down the contralateral side (hemiplegia or hemiparesis) with increased tone (hypertonia) and increased tendon reflexes (hypereflexia) which may produce spontaneous or stretch-induced rhythmic involuntary muscular contractions (clonus). This situation is also seen with interruption of the descending motor pathways in the spinal cord (see Chapter 11).

The pattern of weakness in such lesions characteristically involves the extensors more than the flexors in the upper limb and the converse in the lower limb. This is misleadingly termed a **pyramidal distribution of weakness**, as damage confined to the pyramidal tract in monkeys leads only to a deficiency in fine finger movements with a degree of hypotonia and hyporeflexia.

Abbreviations

CPG	central pattern generator
DSCT	dorsal spinocerebellar tract
GABA	γ-aminobutyric acid
GAD	glutamic acid decarboxylase
GTO	Golgi tendon organ
IN	interneuron
MN	motorneuron
PPN	pedunculopontine nucleus
VSCT	ventral spinocerebellar tract

32 The cortical motor areas



Cortical motor areas

The **primary motor cortex (MsI)** is that part of the cerebral cortex which produces a motor response with the minimum electrical stimulation. It corresponds to Brodmann's area 4 and lies just in front of the central sulcus and projects to the motorneurons (MNs) of the brainstem via the **corticobulbar tracts** and to the MNs of the spinal cord directly via the **corticospinal tract (CoST)** and indirectly via the subcortical extrapyramidal tracts. Indeed MsI is particularly closely associated with the pyramidal tract (even though 60–70% of it originates in other cortical areas) and so has a role in the control of distal musculature and fine movements.

The MsI receives afferent information from the cerebellum (via the thalamus), more anteriorly placed motor cortical areas such as the supplementary motor area (SMA) and a sensory input from the muscle spindle as well as cortical sensory areas. This latter sensory input emphasises the artificial way in which the CNS is divided up into motor and sensory systems and in order to acknowledge this the primary motor cortex is termed the MsI while the primary somatosensory cortex is termed the SmI (see Chapter 19).

A range of other cortical areas are involved in the control of movement, including the **premotor cortex (PMC**; corresponding to the lateral part of Brodmann's area 6); the **supplementary motor area (SMA**; corresponding to the medial aspect of Brodmann's area 6); a number of motor areas centred on the **anterior cingulate cortex** on the medial aspect of the frontal lobe; the **frontal eye fields** (corresponding to Brodmann's area 8) and the **posterior parietal cortex** (especially Brodmann's area 7).

Some of these areas have specialist functions such as the frontal eye fields with eye movement control (see Chapter 35) and the posterior parietal cortex with the visual control of movement (see Chapter 28). The remaining areas in the frontal lobe are involved with more complex aspects of movement, with the possible exception of the PMC which may have an important role in directly controlling the proximal musculature. Most of these other cortical areas therefore occupy a higher level in the motor hierarchy than MsI, and their connections and functions are summarised in the figure and Table 32.1 (see also Chapter 28).

Primary motor cortex

Investigation of the **organisation of MsI** has shown that the motor innervation of the body is organised in a highly topographic fashion, with the cortical representation of each body part being proportional to the degree of motor innervation—so, for example, the hand and orobuccal musculature have a large cortical representation. The resultant distorted image of the body in MsI is known as the **motor homunculus**, with the head represented laterally and the feet medially.

This organisation may be manifest clinically in patients with ***epilepsy*** that originates in the motor cortex. In such cases the epileptic fit may begin at one site, typically the hand, and then spread so that the jerking marches out from the site of origin (so-called **Jacksonian march**, named after the neurologist, Hughlings Jackson). This is in contrast to the clinical picture seen with seizures arising from the SMA, in which the patient raises both arms and vocalises with complex repetitive movements suggesting that this area has a higher role in motor control.

These studies on the motor homunculus by Penfield and colleagues in the 1950s revealed the macroscopic organisation of MsI, but subsequent microelectrode studies in animals revealed that MsI is composed of **cortical columns** (see Chapter 14). The inputs to a column consist of afferent fibres from the joint, muscle spindle and skin which are maximally activated by contraction of those muscles innervated by that same area of cortex. So, for example, a group of cortical columns in MsI will receive sensory inputs from a finger when it is flexed – that input being provided by the skin receptors on the front of the finger, the muscle spindles in the finger flexors and the joint receptors of the finger joints. That same column will also send a projection to the MNs in the spinal cord that innervate the finger flexors. Thus, activation of the corticospinal neuron from that column will ultimately activate the receptors which project to that same column, and vice versa. Thus each column is said to have **input–output coupling** and this may be important in the more complex reflex control of movement as, for example, with the **long-latency or transcortical reflexes**. These reflexes refer to the delayed and smaller electromyographic (EMG) changes that are seen following the sudden stretch of a muscle—the first EMG change being the M1 response of the monosynaptic stretch reflex (see Chapter 30). The transcortical reflex has as its afferent limb the muscle spindle input via the Ia fibre (relayed via the dorsal column–medial lemniscal pathway) and the efferent pathway involves the CoST. The exact role of this reflex is not known but it may be important in controlling movements precisely, especially when unexpected obstacles are encountered which activate the muscle spindle.

There has been great controversy as to whether MsI controls individual muscles, simple movements or some other aspect of movements. Neurons within MsI fire before any EMG changes and appear to **code for the direction and force of a movement**, although this activity is dependent on the nature of the task being performed. Therefore, as a whole, the motor cortex controls movement by its innervation of populations of MNs, as individual corticospinal axons innervate many different MNs.

The MsI is capable of being remodelled after lesions or changes in sensory feedback, implying that it maintains a flexible relationship with the muscles throughout life. Thus cells in a region of MsI can shift from the control of one set

Table 32.1 Cortical motor areas — connections and functions.

Cortical area	Afferent input	Efferent output	Neurophysiology	Function
Primary motor cortex (MsI)	SMA PMC SmI Cerebellum via thalamus (VA–VL nuclei) Dorsal column–medial lemniscal system (VP via nucleus of thalamus)	Corticospinal or pyramidal tract Brainstem: Pons to cerebellum Cranial nerve nuclei Extrapyramidal tracts	Lesion of MsI results in a loss of placing, hopping reactions and skilled manipulative movements	Control of distal musculature and fine skilled movements Role in reflex control of movement (transcortical reflexes)
Premotor cortex (PMC)	SMA Prefrontal cortex Somatosensory and visual cortices Cerebellum via thalamus (VA–VL nuclei) Basal ganglia via thalamus (VA–VL nuclei)	MsI Corticospinal or pyramidal tract Brainstem: pons to cerebellum extrapyramidal pathways	Lesion of PMC produces a mild paresis and impairment of skilled movements; deficits in executing visuomotor tasks Regional blood flow studies show it is activated during tasks requiring directional guidance of a movement from sensory information	Control of proximal musculature Control of movement sequence and preparation for movement
Supplementary motor area (SMA)	Prefrontal cortex Basal ganglia via thalamus (VA–VL nuclei) Anterior cingulate cortex Contralateral SMA	SMA (contralateral) PMC MsI	Lesion of SMA produces a severe reduction in spontaneous motor activity with forced grasping and failure of bimanual coordination Stimulation of SMA produces vocalization and complex bilateral arm movements Activity in SMA precedes any changes in MsI Units in SMA respond maximally to sensory cues being used as an instruction for a movement Regional blood-flow studies have shown an increased flow with the planning or thinking of a motor act	Role in the initiation and planning of movement Role in bimanual coordination

of muscles to a new set. Within given areas of cortex there is some evidence that synaptic strengths can be altered with long-term potentiation (see Chapter 39), which suggests that the MsI may be capable of learning new movements, a function traditionally ascribed to the cerebellum (see Chapter 33).

Damage to MsI in isolation is rare and experimentally tends to produce deficiencies similar to those seen with selective pyramidal tract lesions. However, damage to both MsI and adjacent premotor areas, as occurs in most CVAs involving the middle cerebral artery (see Chapter 16), produces a much more significant deficiency, with a significant hemiparesis. Lesions, however located to the SMA, produce a distinct picture of bilateral failure to initiate movements, while lesions in the frontal eye field produce restrictions of eye movement.

Other cortical motor areas

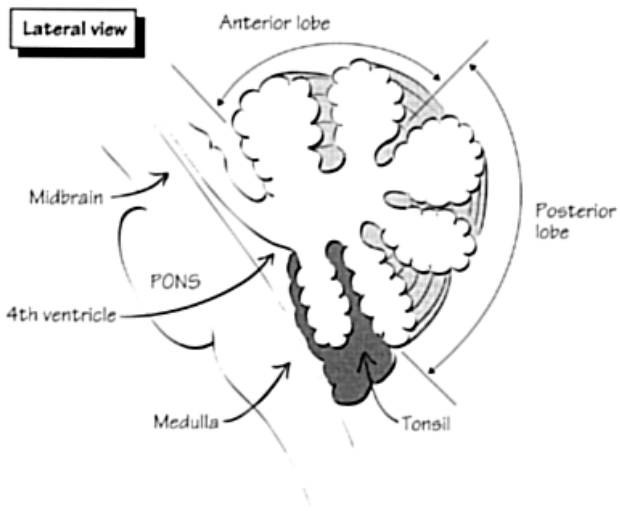
The premotor cortical areas refer to a number of different regions within the frontal lobe that lie anterior to the primary motor cortex. The PMC, in contrast, refers to a specific area of Brodmann area 6, and like the primary motor cortex has an input directly to the spinal motorneurons via the corticospinal or pyramidal tract. This area therefore

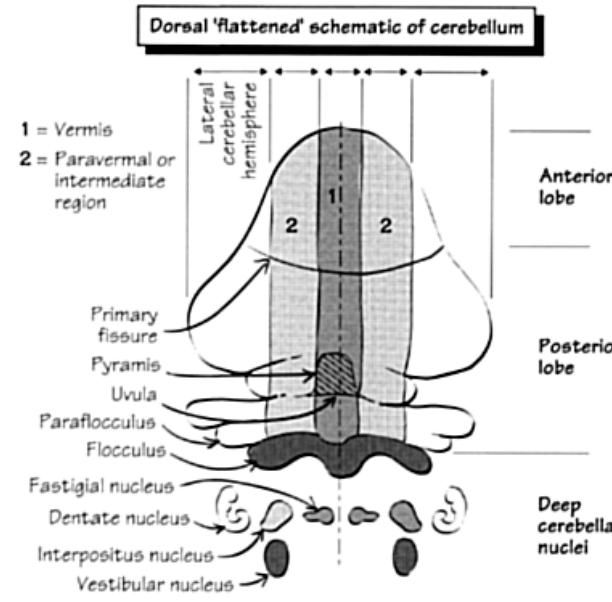
occupies two levels of the motor hierarchy as it also has a role in the planning of movement (see Chapter 29). In contrast, the SMA lies medial to the PMC, has a much more clearly defined role in the planning of movements especially in response to sensory cues. Furthermore, it is now clear that the SMA is part of a much larger number of higher order motor cortical areas that lie along the medial side of the frontal cortex and which are involved in the planning of movements more than their execution. It is these cortical areas that receive the predominant outflow of the basal ganglia (see Chapter 34), and helps explain the abnormal movements that are seen with diseases of this area of the brain. For example, in Parkinson's disease there is a slowness and poverty of movement that is associated with under-activation of these cortical areas, a situation that is rectified by the administration of anti-parkinsonian medication.

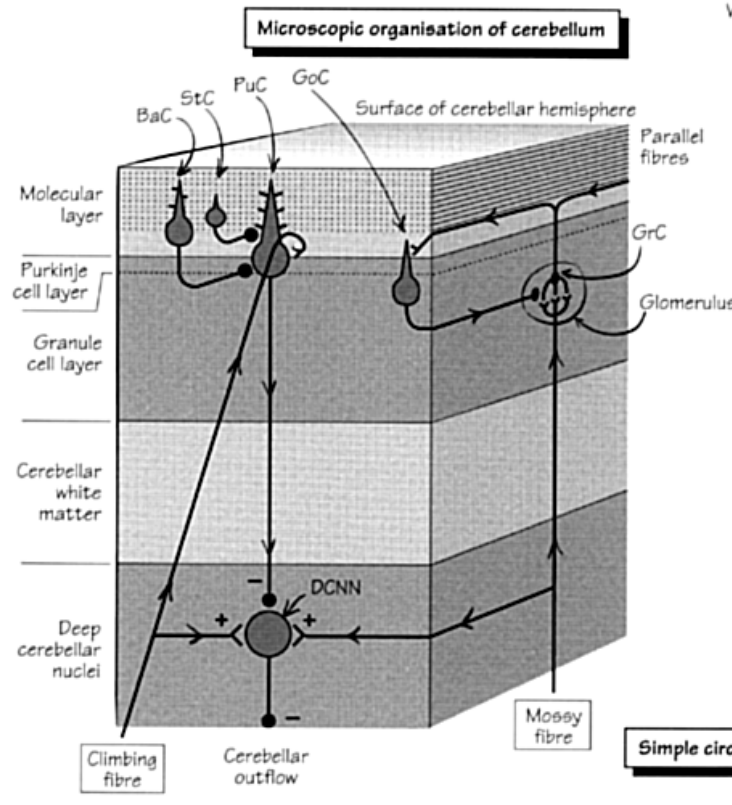
Abbreviations

CoST	corticospinal (or pyramidal) tract
CVA	cerebrovascular accident
EMG	electromyography
MN	motorneuron
MsI	primary motor cortex
PMC	premotor cortex
SMA	supplementary motor area
Sm1	primary somatosensory cortex

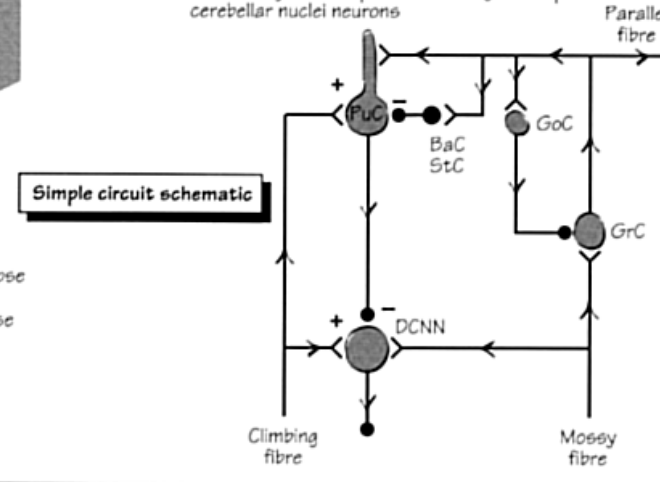
33 The cerebellum







1. Two types of interneuron in the molecular layer: stellate and basket cell with the larger Golgi cell found in the outer part of the granule cell layer.
   All three interneurons serve to inhibit the submaximally activated PuC, both directly and indirectly (via GrC), and by so doing increase the contrast i.e. highlight those PuC that are most active.
2. Parallel fibres run perpendicular to PuC dendritic tree
3. Purkinje cell is very large (soma: 50–80 μm in diameter)
4. Climbing fibre input originates from inferior olive
5. Cerebellar glomerulus are structures encompassing multiple mossy fibre inputs to granule cell
6. Deep cerebellar nuclei are tonically activated by collateral mossy and climbing fibres, and can therefore compare afferent information before and after it has been processed by the cerebellar cortex.
7. The Purkinje cell output is inhibitory to deep cerebellar nuclei neurons



StC = Inhibitory stellate cell
BaC = Inhibitory basket cell
PuC = Purkinje cell
DCNN = Deep cerebellar nuclei neuron
GoC = Golgi cell
GrC = Granule cell

Excitatory synapse
Inhibitory synapse

Organisation of the cerebellum

The **cerebellum (CBM)** is a complex structure found below the tentorial membrane in the posterior fossa and connected to the brainstem by three (cerebellar) peduncles (see Chapter 12). It is primarily involved in the coordination and learning of movements, and is best thought of in terms of three functional and anatomical systems:

1 **spinoCBM** that is involved with the control of axial musculature and posture;

2 **pontoCBM** that is involved with the coordination and planning of limb movements; and

3 **vestibuloCBM** that is involved with posture and the control of eye movements.

These three systems have their own unique pattern of connections. The spinoCBM can be divided into a vermal and paravermal (intermediate) region with the former having a close association with the axial musculature. It is therefore associated with the ventromedial descending motor pathways and MNs whilst the paravermal part of the spinoCBM is more concerned with the coordination of the limbs. The pontoCBM has a role in this coordination but is more concerned with the visual control of movement by relaying information from the posterior parietal cortex to the motor cortical areas. The vestibuloCBM has no associated deep cerebellar nucleus and is phylogenetically one of the oldest parts of the cerebellum. It, like the vermal part of the spinoCBM, is more concerned with balance through its connections with the ventromedial motor pathways but in addition also has a role in the control of eye movements (see also Chapter 35).

In general the CBM compares the intended movement originating from the motor cortical areas with the actual movement as relayed by the muscle afferents and spinal cord interneurons while receiving an important input from the vestibular system. The comparison having been made, an error signal is relayed via descending motor pathways, and the correction factor stored as part of a motor memory in the synaptic inputs to the Purkinje cell (PuC). This modifiable synapse at the level of the PuC is an example of **long-term depression** (LTD; see also Chapters 39 and 44). It describes the reduced synaptic input of the parallel fibre (pf) to PuC when it is activated in phase and at low frequency with the climbing fibre input to that same PuC and which persists for several hours at least. In other words, at times of new movements the climbing fibre input to the PuC increases which has a modifying effect on the pf input to that same PuC. As the movement becomes more routine, the cf fibre lessens but the modified (reduced) pf input persists: it is this modification that is thought to underlie the learning and memory of movements.

This modifiable synapse was first proposed by Marr in 1969 and subsequently has been verified, especially with respect to the vestibulo-ocular reflex (see Chapters 26 and 44). The biochemical basis of LTD in the CBM is unknown but appears to rely on the activation of different glutamate receptors in the PuC and the subsequent influx of calcium and the activation of a protein kinase. The presence of a modifiable synapse implies that the CBM is capable of learning and storing information in a motor memory (see Table 33.1).

The microscopic organisation of the cerebellum which allows for the generation of LTD is well characterised, even if the biochemical basis for it remains obscure. The excitatory input to the cerebellum is provided by a mossy and climbing fibre input. The mossy fibre indirectly activates Purkinje cells through parallel fibres that originate from granule cells. In contrast, the climbing fibre directly synapses on the Purkinje cell and, as with the mossy fibre input, there is an input to the deep cerebellar nuclei neurons. These neurons are therefore tonically excited by the input fibres to the cerebellum, and are inhibited by the output from the cerebellar cortex namely the Purkinje cell. The Purkinje cells in turn are inhibited by a number of local interneurons, whilst Golgi cells in the outer granule cell layer provide an inhibitory input to the granule cells. All of these interneurons have the effect of inhibiting submaximally activated Purkinje and granule cells, and by so doing highlight the signal to be analysed.

The final output of the cerebellum from the deep cerebellar nuclei to various brainstem structures is also inhibitory.

Clinical features of cerebellar damage

Much that can be deduced about the function of the CBM is derived from the clinical features of patients with cerebellar damage.

Dysfunction of the CBM is found in a large number of conditions, and the clinical features of cerebellar damage are as follows.

1 **Hypotonia or reduced muscle tone**. This is caused by a reduced input from the deep cerebellar nuclear neurons via the descending motor pathways to the muscle spindle (see Chapter 30).

2 **Incoordination/ataxia**. There are a number of manifestations of this including: ***asynergy*** (an inability to coordinate the contraction of agonist and antagonist muscles); ***dysmetria*** (an inability to terminate movements accurately which can result in an ***intention tremor*** and ***past pointing***); and ***dysdiadochokinesis*** (an inability to perform rapidly alternating movements). ***Ataxia*** is often used to describe incoordinated movements. In cases where the vermis is predominantly involved, as occurs in alcoholic cerebellar degeneration, this results in a staggering wide-based 'drunk-like' character to the gait. When there is involvement of the more lateral parts of the cerebellar hemisphere the incoordination involves the limbs.

3 **Dysarthria**. This is an inability to articulate words properly caused by incoordination of the oropharyngeal muscu-

Table 33.1 Functional and anatomical systems of the cerebellum.

System	SpinoCBM or paleoCBM: vermal region	SpinoCBM or paleoCBM: paravermal or intermediate region	PontoCBM or neoCBM	VestibuloCBM or ArcheoCBM
Major afferent connections	Vestibular nucleus Proximal limb Ia/Ib afferents and interneuronal activity relayed via DSCT and VSCT respectively Visual and auditory information to posterior lobe only	Ia/Ib afferents from distal limb via DSCT Interneuronal activity from distal spinal motor pools relayed in VSCT Primary motor and somatosensory cortex	Posterior parietal cortex Primary and premotor motor cortical area *Both* relayed via pontine nuclei	Semicircular canals via vestibular nucleus Visual information from superior colliculus, lateral geniculate nucleus and primary visual cortex relayed via pontine nuclei
Associated deep cerebellar nucleus	Fastigial	Interpositus (globose and emboliform)	Dentate	—
Major efferent projections	Reticular formation → ReST Vestibular nucleus → VeST (i.e. Ventromedial descending motor pathways)	Red nucleus (magnocellular part) → RuST VA–VL nucleus of the thalamus → PMC (Brodmann area 6) and MsI (Brodmann area 4) → corticospinal tract (Dorsolateral descending motor pathways)	VA–VL nucleus of thalamus → Area 4 and 6 → corticospinal tract Red nucleus (parvocellular part) → inferior olive → CBM (Mollaret's triangle)	Vestibular nucleus → VeST Vestibular nucleus → oculomotor nuclei
Specific role	Control of axial musculature Regulate muscle tone	Distal limb coordination Regulate muscle tone	Motor planning Visual control of movement Minor role in distal limb coordination	Posture Eye movement control

lature. The words are slurred and spoken slowly, so-called ***scanning dysarthia***.

4 **Nystagmus**. This describes rapid jerky eye movements caused by a breakdown in the outflow from the vestibular nucleus and its connections with the oculomotor nuclei (see also Chapters 26 and 35).

5 **Palatal tremor or myoclonus**. This is a rare condition in which there is hypertrophy of the inferior olive, with damage in a triangle bounded by this structure, the dentate nucleus of the CBM and the red nucleus in the midbrain (so-called Mollaret triangle). The patient characteristically has a low frequency tremor of the palate which oscillates up and down.

Function of the cerebellum

The **role of the CBM** can be defined by area and correlates well with the localising signs of cerebellar disease. Exactly how the CBM achieves these functions is unknown, but the repetition of the same elementary circuitry in all parts of the cerebellar cortex implies a common mode of function. Three possibilities exist which are not mutually exclusive.

1 **By acting as a comparator**. The CBM compares the descending supraspinal motor signals (**efference copy**, intended movement) with the ascending afferent feedback information (actual movement), and any discrepancy is corrected by the output of the CBM through descending motor

pathways. This allows the CBM to coordinate movements so that they are achieved smoothly and accurately.

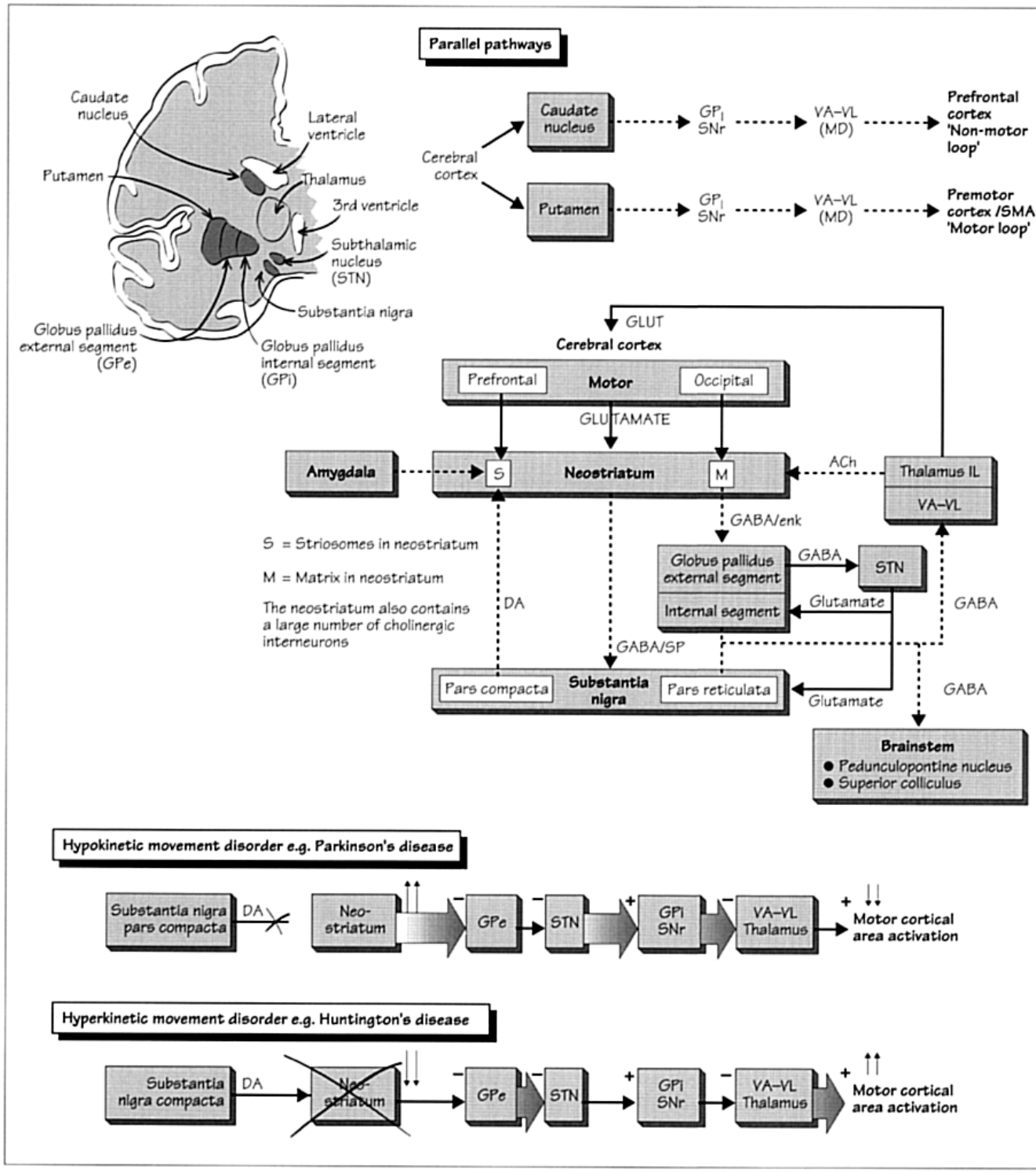
2 **By acting as a timing device**. The CBM (especially the pontoCBM) converts the descending motor signals into a sequence of motor activation so that the movement is performed in a smooth and coordinated fashion, with balance and posture being maintained by the vestibulo- and spinoCBM.

3 **By initiating and storing movements**. The existence of a modifiable synapse at the level of the PuC means that the CBM is capable of storing motor information and updating it. Therefore, under the appropriate circumstances, the right sequence for a movement can be accessed and fed through the supraspinal motor pathways, and by so doing initiate an accurate learnt movement.

Abbreviations

BaC	basket cell
CBM	cerebellum
DCNN	deep cerebellar nuclei neuron
DSCT	dorsal spinocerebellar tract
GoC	Golgi cell
GrC	granule cell
LTD	long-term depression
MsI	primary motor cortex
pf	parallel fibre
PMC	premotor cortex
PuC	Purkinje cell
ReST	reticulospinal tract
RuST	rubrospinal tract
StC	stellate cell
VA–VL	ventroanterior–ventrolateral nuclei of the thalamus
VeST	vestibulospinal tract
VSCT	ventral spinocerebellar tract

34 The basal ganglia



Anatomy and physiology of basal ganglia

The **basal ganglia** consist of the **caudate and putamen (dorsal** or **neostriatum; NS)**, the **internal** and **external segments of the globus pallidus** (**GPi** and **GPe**, respectively), the **pars reticulata and compacta of the substantia nigra** (**SNr** and **SNc**, respectively) and the **subthalamic nucleus (STN)**.

The NS is the main receiving area of the basal ganglia and receives information from the whole cortex in a somatotopic fashion as well as the intralaminar nuclei of the thalamus (IL). The major outflow from the basal ganglia is via the GPi and SNr to the ventroanterior and ventrolateral (VA–VL) nuclei of the thalamus which in turn project to the premotor cortex (PMC), supplementary motor cortex (SMA) and prefrontal cortex. In addition, there is a projection to the brainstem, especially to the pedunculopontine nucleus (PPN) that is involved in locomotion, and to the superior colliculus that is involved with eye movements (see Chapters 22, 35).

The basal ganglia also have a **number of loops** within them that are important. There is a striato-nigral-striatal loop with the latter projection being dopaminergic in nature. This pathway degenerates in ***Parkinson's disease*** (PD). There is also a loop from the GPe to the STN which then projects back to the GPi and SNr. This pathway is excitatory in nature and is important in controlling the level of activation of the inhibitory output nuclei of the basal ganglia to the thalamus. However, although a marked degree of convergence and divergence can be seen throughout the basal ganglia, the projections do form parallel pathways, which at the most simplistic level divide into a motor pathway through the putamen and a non-motor pathway through the caudate nucleus.

The NS consists of **patches or striosomes** that are deficient in the enzyme acetylcholinesterase (AChE). These are embedded in an otherwise AChE-rich striatum which forms the large extrastriosomal **matrix**. In general the striosomes are closely related to the dopaminergic nigrostriatal pathway and prefrontal cortex and amygdala, while the matrix is more involved with sensorimotor areas. However, the relationship of these two components of the neostriatum to any parallel pathways is not clear.

This non-motor role of the basal ganglia is perhaps more clearly seen with the **ventral extension of the basal ganglia** that consists of the ventral striatum (nucleus accumbens), ventral pallidum and substantia innominata (not shown in the figure). It receives a dopaminergic input from the ventral tegmental area that lies adjacent to the SNc in the midbrain, and projects via the thalamus to the prefrontal cortex and frontal eye fields.

The **neurophysiology** of the basal ganglia shows that many of the cells within it have complex properties which are not clearly sensory or motor in terms of their response properties. For example, some units in the neostriatum respond to sensory stimuli but only when that sensory stimulus is a trigger for a movement. In contrast many units in the pallidum respond maximally to movement about a given joint before any EMG changes. Thus from a neurophysiological point of view the basal ganglia take highly processed sensory information and convert it into some form of motor programme. This is supported by the clinical disorders that affect the basal ganglia.

Clinical disorders of the basal ganglia

Parkinson's disease

Parkinson's disease is a degenerative disorder that typically affects people in their sixth and seventh decades of life. The primary pathological event is the loss of the dopaminergic nigrostriatal tract, with the formation of characteristic histological inclusion bodies, known as Lewy Bodies. In the vast majority of cases the disease develops for reasons that are not clear (so-called idiopathic Parkinson's disease—see also Chapter 42). However in some cases clear aetiological agents are identified such as vascular lesions in the region of the neostriatal pathway or the administration of the anti-dopaminergic drugs in schizophrenia (see Chapter 40).

Over 75% of the dopaminergic nigrostriatal neurons need to be lost before the classical clinical features of idiopathic PD are manifest and these are: slowness to move (bradykinesia), increased tone in the muscles (so-called cogwheel rigidity) and tremor that is present at rest.

Neurophysiologically these patients have increased activity of the neurons in the GPi which results from increased activity in the STN secondary to the loss of the predominantly inhibitory dopaminergic input to the NS. The increased inhibitory output from the GPi (and presumably the SNr as well) to the VA–VL nucleus of the thalamus results in reduced activation of the SMA and other adjacent cortical areas. Thus patients with PD are unable to initiate movement because of their failure to activate the SMA although the explanation for the tremor and rigidity is less clear. These patients can, however, be treated successfully in the early stages of the disease with various drugs.

Antiparkinsonian drugs

No drug slows the progression of Parkinson's disease. In the early stages of the disease, especially where tremor predominates, **antimuscarinic drugs** (e.g. benzhexol, procyclidine) may be effective. These drugs are believed to correct a relative overactivity of central cholinergic activation that results from the progressive decrease of (inhibitory) dopaminergic activity. Adverse effects are common and include dry mouth, urinary retention, constipation and confusional states.

For most patients, **dopamine replacement therapy** with

levodopa (L-dopa) is the treatment of choice (dopamine itself does not pass the blood–brain barrier). Levodopa is the immediate precursor of dopamine and is converted in the brain by decarboxylation to dopamine. Orally administered levodopa is largely metabolised outside the brain and so it is given with an extracerebral decarboxylase inhibitor (carbidopa or benserazide) which greatly reduces the effective dose and peripheral adverse effects (e.g. hypotension, nausea). Levodopa frequently produces adverse effects which are mainly caused by widespread stimulation of dopamine receptors. They include nausea and vomiting (as a result of stimulation of the chemoreceptor trigger zone), psychiatric side effects (e.g. hallucinations, confusion) and dyskinesias. After 5 years' treatment about half the patients will have deteriorated. In some, the akinesia gradually recurs, while in others various dyskinesias may appear. The duration of action of each dose of levodopa may shorten ('end of dose' deterioration) and there may be rapid oscillations in mobility ('on–off' effect).

Selegiline is a selective monoamine oxidase type B (MAO_B) inhibitor that reduces the metabolism of dopamine in the brain and potentiates the action of levodopa. It may be used in conjunction with levodopa to reduce 'end of dose' deterioration. Catecholamine-O-methyltransferase (COMT) inhibitors have recently been developed for use in PD, they reduce the peripheral metabolism of L-dopa and by so doing increase the amount that can enter the brain.

Dopamine agonists (e.g. pergolide) are also used often in combination with levodopa in the later stages of PD in an attempt to reduce the late adverse effects of levodopa. Dopamine agonists directly bind to the dopamine receptors in the striatum (and substantia nigra) and by so doing activate the post-synaptic output neurons of the striatum. These agents are gaining favour as the treatment of choice in young onset PD because of their L-Dopa sparing effects which in turn may delay the development of 'on–off' effects.

Although most patients with PD are best treated with drugs, surgical approaches have been undertaken in advanced PD. In PD, there is increased activation of the internal part of the globus pallidus and substantia nigra pars reticulata, which in part is mediated by an input from the excitatory subthalamic nucleus. The consequence of this increased inhibitory outflow from the basal ganglia to the thalamus is that it results in under-activation of the premotor cortical areas which control movement initiation (see Chapter 32). Therefore recent interest has focused on the surgical manipulation of these basal ganglia nuclei in the form of lesions in the GPi (pallidotomy) or the insertion of electrodes for deep brain stimulation into the GPi or subthalamic nucleus. This latter approach generates a temporary lesion possibly by inducing a conduction block (see Chapters 6 & 8). Both these approaches have now been shown to be successful in advanced PD, although the extent to which they ameliorate drug-induced problems as opposed to the fundamental motor manifestations of the disease is unclear. An alternative surgical approach to lesioning or deep-brain stimulation is the implantation of dopamine-rich tissue into the striatum to replace and possibly restore the damaged nigrostriatal pathway. This has been done successfully with fetal nigral tissue in a small number of PD patients, although earlier attempts using autografts of the catecholamine-rich adrenal medulla proved unsuccessful. In all cases successful treatment is associated with evidence for a reactivation of the appropriate cortical areas.

Huntington's disease

Huntington's disease (HD) is an inherited autosomal dominant disorder associated with a trinucleotide expansion in the gene coding for the protein huntingtin on chromosome 4 (see Chapter 47).

The disease presents typically in mid-life with a progressive dementia and abnormal movements that usually takes the form of chorea—rapid dance-like movements, typically of the hands and neck. This type of movement is described as being hyperkinetic in nature, unlike the hypokinetic deficits seen in PD, and reflects the fact that the primary pathology is the loss of the output neurons of the striatum. This results in relative inhibition of the STN and thus reduced inhibitory outflow from the GPi and SNr, which leads to the cortical motor areas being over-activated generating an excess of movements.

Treatment in HD is designed to reduce the level of dopaminergic stimulation within the basal ganglia, but is seldom successful. As in PD, some progress has been made in the possible use of fetal tissue for transplantation into the diseased basal ganglia.

Other disorders of the basal ganglia

Another example of a hyperkinetic movement disorder is ***hemiballismus*** which is the rapid flailing movements of the limbs contralateral to damage to the subthalamic nucleus.

A number of other conditions can affect the basal ganglia including ***Wilson's disease*** (an autosomal recessive condition associated with copper deposition); ***Sydenham's chorea*** (a sequelae of rheumatic fever); defects in mitochondrial function (***mitochondrial cytopathies***; see Chapter 47); a number of toxins (e.g. carbon monoxide and manganese) and ***choreoathetoid cerebral palsy***; athetosis is defined as an abnormal involuntary slow writhing movement.

The spectrum of movement disorders seen with these diseases is variable as the damage is rarely confined to one structure, so patients may exhibit either ***parkinsonism, chorea*** and ***ballismus*** or ***dystonia*** which is where a limb is held in an abnormal fixed posture.

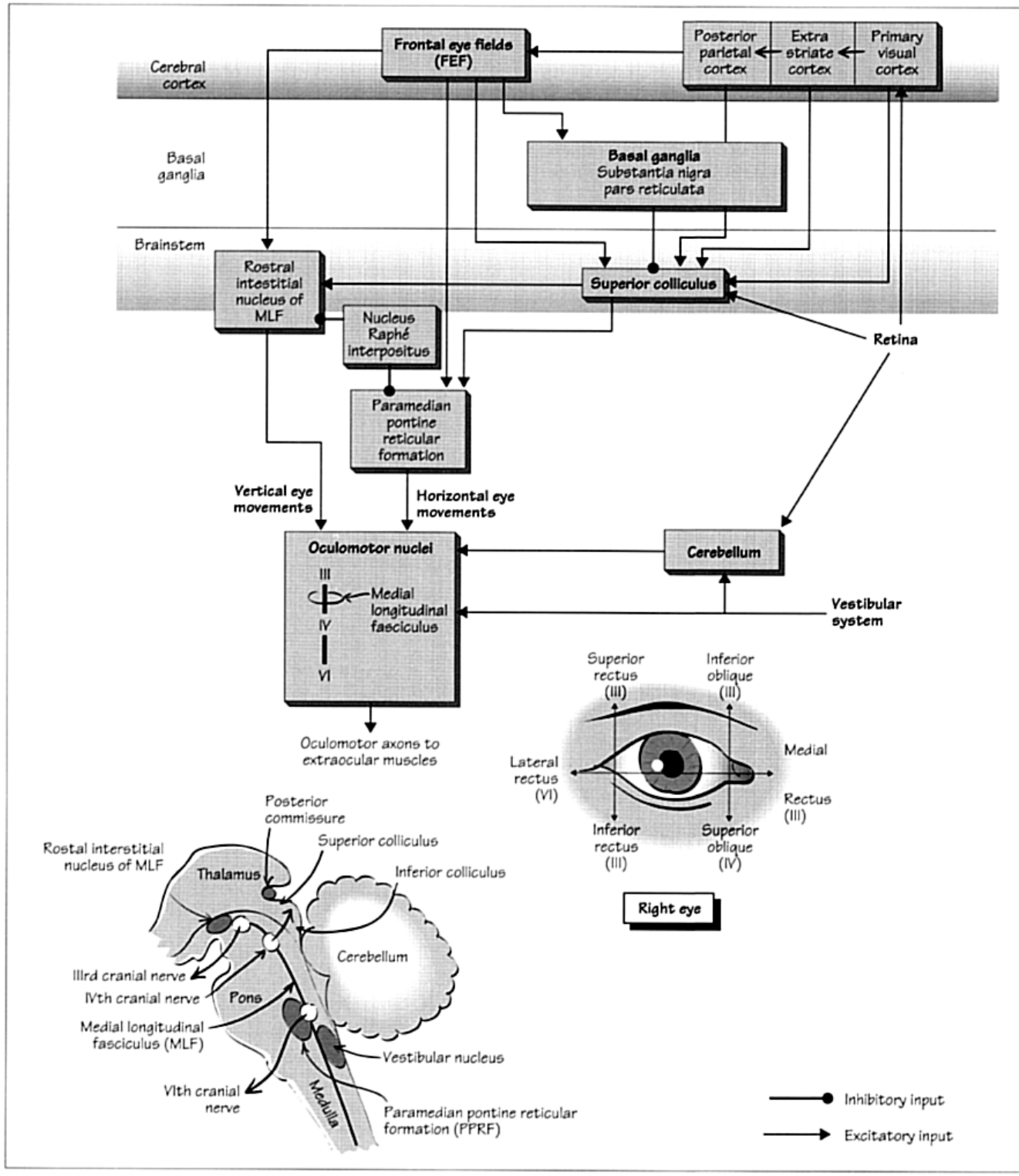
Many of these conditions including PD and HD have a degree of cognitive impairment, if not frank dementia, and while this may relate to coincidental damage in the cerebral cortex, there is increasingly evidence that it may be as a direct result of basal ganglia damage. In this respect the ventral extension of the basal ganglia may be important.

Finally, it should be mentioned that the basal ganglia have a major role in the control of eye movements (see Chapter 35) and thus many patients with diseases of the basal ganglia have abnormal eye movements which may be helpful in establishing their clinical diagnosis.

Abbreviations

ACh	acetylcholine
AChE	acetylcholinesterase
COMT	catecholamine-O-methyltransferase
DA	dopamine
EMG	electromyography
Enk	enkephalin
GABA	γ-aminobutyric acid
GLUT	glutamate
GPe	globus pallidus external segment
GPi	globus pallidus internal segment
HD	Huntington's disease
IL	intralaminar nucleus of the thalamus
MAO_B	monoamine oxidase type B
NS	neostriatum
PD	Parkinson's disease
PMC	premotor cortex
PPN	pedunculopontine nucleus
SMA	supplementary motor area
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
SP	substance P
STN	subthalamic nucleus
VA–VL	ventroanterior–ventrolateral nucleus of the thalamus

35 Eye movements



The accurate **control of eye movements** involves a number of different structures from the extraocular muscles to the frontal cortex and the failure to achieve this control results symptomatically in either double vision (diplopia), blurred vision or oscillopsia (a perception of an oscillating image or environmental movement). In clinical practice disruption of the final pathway from the oculomotor nuclei (third, fourth and sixth cranial nerves) to the extraocular muscle represents one of the major causes of diplopia (e.g. ***myasthenia gravis***; see Chapter 7), as does disruption, in ***multiple sclerosis,*** of the medial longitudinal fasciculus (MLF) pathway linking the oculomotor nuclei.

Types of eye movement

There are three major types of eye movement:

- **smooth pursuit** or the following of a target accurately, which is controlled primarily by posterior parts of the cortex in conjunction with the cerebellum;
- **saccadic eye movements** where there is a sudden shift of the eyes to a new target and which is controlled by more anterior cortical areas, the basal ganglia and superior colliculus in the midbrain;
- **sustained gaze** where the eyes are fixed in one direction and which is primarily a function of the brainstem (especially the paramedian pontine reticular formation (PPRF) and rostral interstitial nucleus of the MLF).

Eye movements, like the motor system in general, can be either **voluntary** (when the command comes from the frontal eye field) or **reflex** (when the command originates from subcortical structures and posterior parietal cortex).

Manifestations of disordered eye movement include: a loss of conjugate movements; broken pursuit movements; inaccurate saccades; gaze palsies; and nystagmus. **Nystagmus** is defined as a biphasic ocular oscillation containing an abnormal slow and corrective fast phase, the latter defining the direction of the nystagmus.

Anatomy and physiology of the CNS control of eye movements

- The **frontal eye fields** (FEF; predominantly Brodmann's area 8) are found anterior to the premotor cortex (PMC; see Chapter 32). Stimulation of this structure produces eye movements, typically saccades, to the contralateral side, and may be seen clinically in some epileptic patients.

Damage to this area reduces the ability to look to the contralateral side so the patient tends to look towards the side of the lesion. The FEF primarily receives from the posterior parietal cortex and projects to the superior colliculus, other brainstem centres and the basal ganglia.

- The **posterior parietal cortex** (corresponds to Brodmann's area 7 in monkeys) contains a large number of neurons responsive to complex visual stimuli, as well as coding for some visually guided eye movements (see Chapter 28). It is especially important in the generation of saccades to objects of visual significance via its connections with the FEF and superior colliculus.

Damage to this area in addition to causing deficiencies in visual attention and saccades to objects in the contralateral hemifield, can also impair smooth pursuit eye movements as evidenced by loss of the **optokinetic reflex**. This is a reflex in which the eyes fixate by a series of rapid movements on a moving target such as a rotating drum with vertical lines as fixation targets.

- The **primary visual cortex and its associated extrastriate areas** are involved in both saccadic and smooth pursuit eye movements (see also Chapters 22 and 23). The role in saccadic movements is primarily through the projection of V1 to the superior colliculus, while the role in smooth pursuit is via extrastriate area V5 (see Chapter 23), and projections to the FEF, posterior parietal cortex and pons.

Damage to the striate and extrastriate areas in addition to producing field defects and specific deficiencies of visual function (see Chapter 23), can also cause major abnormalities in smooth pursuit eye movements.

- The **basal ganglia** have a major role in the control of saccadic eye movements (see Chapter 34). The caudate nucleus receives from the FEF and projects via the substantia nigra pars reticulata to the superior colliculus.

Abnormalities in saccadic eye movements are seen clinically in a number of basal ganglia disorders. For example, in ***Parkinson's disease*** the saccadic eye movements tend to be slightly inaccurate with undershooting to the target (hypometric saccades).

- The **superior colliculus** in the midbrain is important in the accurate execution of saccades (see Chapter 22).
- The **cerebellum and vestibular nuclei** have important complex inputs into the brainstem oculomotor system and are especially important in the control of pursuit movements, as well as mediating the vestibulo-ocular reflex (see Chapters 26, 33 and 44).

Damage to the cerebellum and vestibular system causes broken pursuit eye movements, inaccurate saccades and nystagmus.

- The **rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF)** is important in the control of vertical saccades and vertical gaze (both up- and downgaze) and receives important inputs from the FEF and superior colliculus while projecting to all the oculomotor nuclei.

Damage to this structure, or disruption of its afferent inputs therefore produces deficiencies in both these eye movements, and this can occur in a number of conditions including some neurodegenerative diseases.

- The **paramedian pontine reticular formation (PPRF)** receives from the FEF, superior colliculus and cerebellum and is responsible for horizontal saccades and gaze. It is thought that this structure may work in conjunction with another pontine nucleus, the **nucleus raphé interpositus**.

This latter nucleus contains so-called omnipause neurons, which normally exert tonic inhibition on the burst neurons of the PPRF (and riMLF) mediating the saccadic impulse.

Damage to nucleus raphé interpositus results in random chaotic eye movements or ***opsoclonus***. In contrast, damage to the PPRF causes deficiencies in saccadic eye movements as well as an ipsilateral gaze paresis.

- The **medial longitudinal fasciculus (MLF)** mediates conjugate eye movements through interconnections between all the oculomotor nuclei and is commonly affected in some diseases of the CNS, such as ***multiple sclerosis*** (see Chapter 46).

A lesion in this structure causes an ***internuclear ophthalmoplegia***, with nystagmus in the abducting eye and slowed or absent adduction in the other ipsilateral eye.

Abbreviations

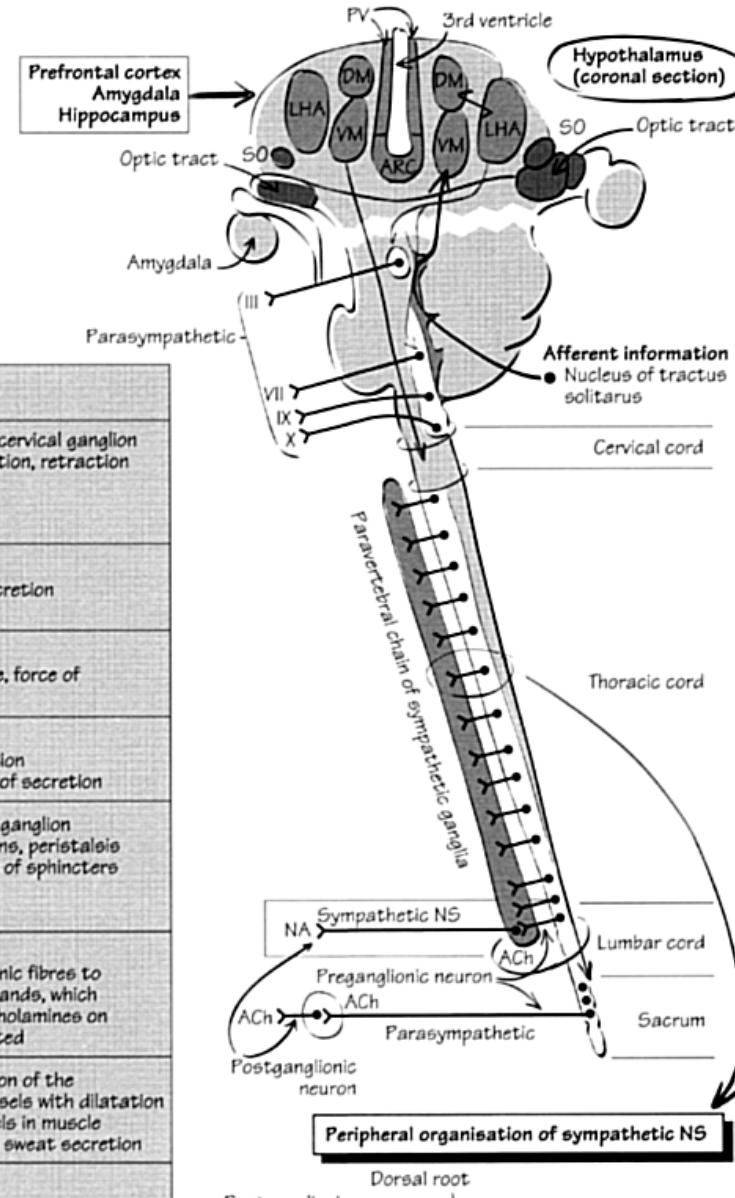
FEF	frontal eye fields
MLF	medial longitudinal fasciculus
PMC	premotor cortex
PPRF	paramedian pontine reticular formation
riMLF	rostral interstitial nucleus of the MLF

Part 4 **Autonomic, limbic and brainstem systems**

36 Autonomic nervous system

CNS control and organisation of autonomic nervous system

PV = Paraventricular nucleus
SO = Supraoptic nucleus
DM = Dorsomedial nucleus
VM = Ventromedial nucleus
LHA = Lateral hypothalamic area
ARC = Arcuate nucleus



Organ	Parasympathetic innervation	Sympathetic innervation
Eye	IIIrd cranial nerve—ciliary ganglion • Pupillary constriction and ↑ refractory power of the lens	T1–T2—superior cervical ganglion • Pupillary dilatation, retraction of eyelid
Lacrimal + salivary glands	VII/IX cranial nerve • Stimulation of salivary secretion	T1–T2 • Inhibition of secretion
Heart	X cranial nerve • Reduction in rate of contraction	T1–T6 • Increase in rate, force of contraction
Bronchial tree	• Bronchoconstriction and stimulation of secretions	T3–T6 • Bronchodilatation and inhibition of secretion
Upper G.I. tract	• Increase in peristaltic rate with relaxation of sphincters and stimulation of secretions	T5–T12—Coeliac ganglion • Inhibit secretions, peristalsis + contraction of sphincters
Adrenal gland		T8–T11 • No postganglionic fibres to the adrenal glands, which release catecholamines on being stimulated
Skin + peripheral vasculature		• Vasoconstriction of the skin blood vessels with dilatation of blood vessels in muscle • Pilorection and sweat secretion
Lower bowel, bladder, reproductive organs	S2–S4 sacral plexus • Contraction of smooth muscles of lower bowel • Contraction of bladder detrusor muscle and relaxation of internal urethral sphincter • Erection	T9–L2 • Inhibit peristalsis • ? role in inhibiting micturition • Ejaculation

Anatomy of the autonomic nervous system

The **autonomic nervous system (ANS)** includes those nerve cells and fibres which innervate internal and glandular organs. They subserve the regulation of processes which usually are not under voluntary influence. The **efferent conducting pathway** from the CNS to the innervated organ always consists of two succeeding neurons; **one preganglionic** and the other **postganglionic** with the former having its cell body in the CNS (see Chapter 1).

The ANS is subdivided into the **enteric, sympathetic** and **parasympathetic nervous systems** with the latter two systems commonly exerting opposing influences on the structure they are both innervating. The sympathetic nervous system preganglionic neurons are found in the intermediate part (lateral horn) of the spinal cord from the upper thoracic to mid-lumbar cord (T1–L3). The preganglionic parasympathetic neurons have their cell bodies in the brainstem and sacrum. The postganglionic cell bodies are found in the vertebral and prevertebral ganglia in the sympathetic nervous system but in the parasympathetic system they are situated either adjacent to or in the walls of the organ they supply.

In addition to these anatomical differences, there are pharmacological ones with the sympathetic nervous system using **noradrenaline** as its postganglionic transmitter while the parasympathetic nervous system uses **acetylcholine** (ACh). Both systems use ACh at the level of the ganglia.

CNS control of the autonomic nervous system

The **CNS control of the ANS** is complex, involving a number of brainstem structures as well as the **hypothalamus** (see Chapter 37). The main hypothalamic areas involved in the control of the ANS are the ventromedial hypothalamic area in the case of the sympathetic nervous system and the lateral hypothalamic area in the parasympathetic nervous system. These controlling pathways can be direct or indirect via a number of brainstem structures such as the periaqueductal grey matter and parts of the reticular formation (see Chapter 12).

Clinical features of damage to the autonomic nervous system

Damage to the ANS can either be local to a given anatomical structure or generalised when there is loss of the whole system caused by either a central or peripheral disease process. **Focal** peripheral lesions are not uncommon and the deficiencies resulting from these lesions can be easily predicted. For example, loss of the sympathetic innervation to the eye results in pupillary constriction (miosis), drooping of the upper eyelid (ptosis) and loss of sweating around the eye (anhydrosis)—a triad of signs known as ***Horner's syndrome***. Other examples include the ***reflex sympathetic dystrophies*** where there is severe pain and autonomic changes confined to a single limb, often in response to some trivial injury. The exact role of the sympathetic nervous system in the genesis of these conditions is not known, as local sympathectomies are not always effective treatment. However, in some instances the nociceptors start expressing receptors for noradrenaline (see Chapter 20).

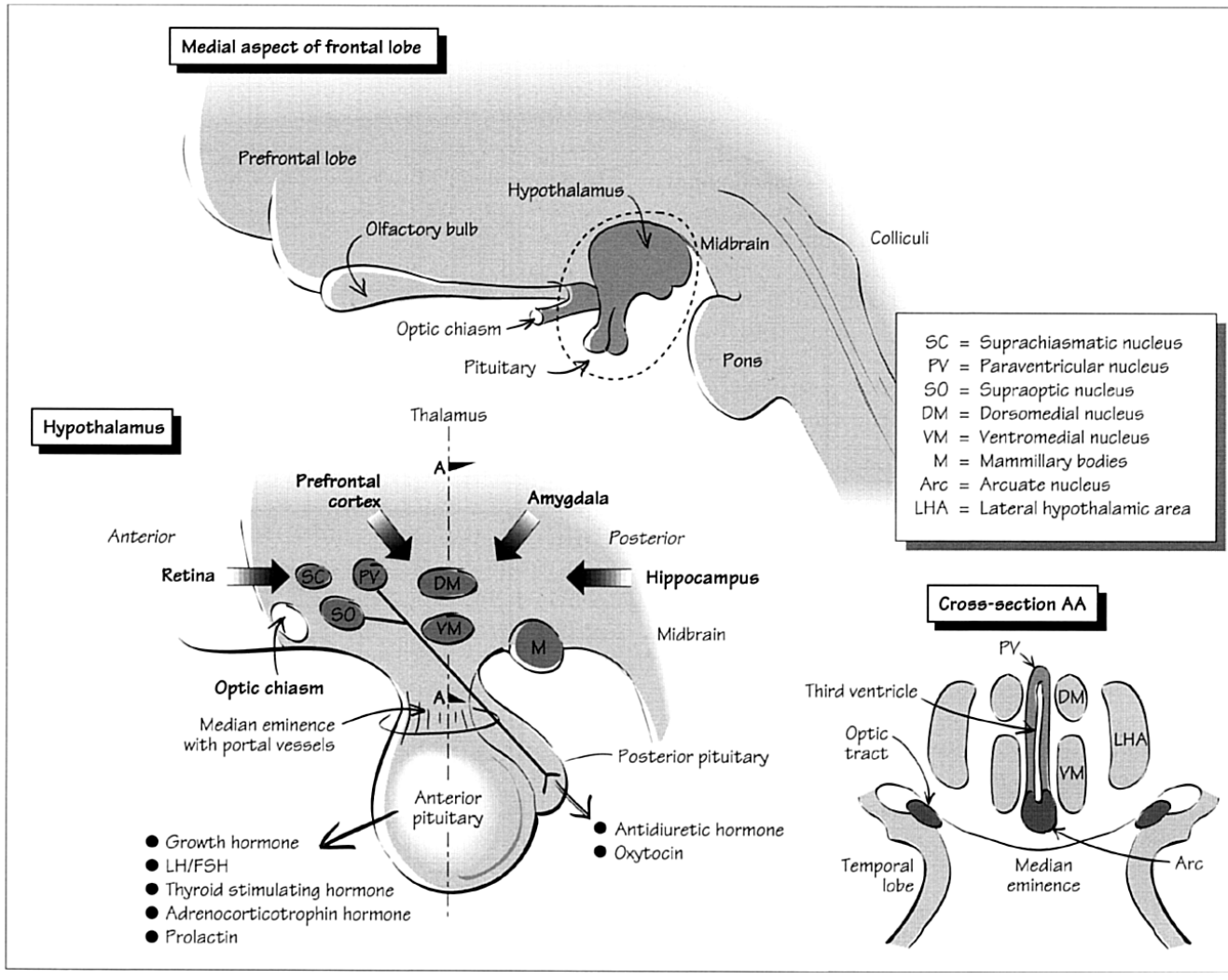
More **global** damage to the ANS can occur because of degeneration of the central neurons either in isolation (e.g. ***pure autonomic failure***) or as part of a more widespread degenerative process as is seen, for example, in ***multi-system atrophy (MSA)*** where there may be additional cell loss in the basal ganglia and cerebellum. Alternatively, the autonomic failure may result from a loss of the peripheral neurons as can occur, for example, in diabetes mellitus, alcoholism and the ***Guillain–Barré syndrome***.

In all these cases the patient presents with orthostatic and postprandial hypotension (syncopal or presyncopal symptoms on standing, exercising or eating a big meal) with a loss of variation in heart rate, bowel and bladder disturbances (urinary urgency, frequency and incontinence), impotence and loss of sweating and pupillary responses. The symptoms are often difficult to treat and a number of agents are employed to try and improve his or her postural hypotension and sphincter abnormalities. Such agents for the postural hypotension include fludrocortisone, ephedrine and vasopressin analogues (all of which cause fluid retention) and cisapride (a potentiator of ACh release) for the gastrointestinal paresis.

Abbreviations

ACh	acetylcholine
ANS	autonomic nervous system
MSA	multi-system atrophy
NA	noradrenaline (norepinephrine)

37 The hypothalamus



The hypothalamus lies on either side of the third ventricle, below the thalamus and between the optic chiasm and the midbrain, and receives a significant input from limbic system structures (see Chapter 39). It also receives from the retina, as well as containing a large number of neurons which are sensitive to changes in hormone levels, electrolyte changes and temperature changes. In addition to an efferent output to the ANS, it also has a critical role in the control of pituitary endocrine function (a detailed discussion on the endocrinology of the hypothalamic–pituitary system is beyond the scope of this book).

Thus the hypothalamus, while being important in the control of the ANS, has a much greater role in the homeostasis of many physiological systems (e.g. thirst; hunger; sodium and water balance; temperature regulation), the control of circadian and endocrine functions, the ability to form anterograde memories (in conjunction with the limbic system; see Chapter 39) and the translation of the response to emotional stimuli into endocrinological and autonomic responses.

The hypothalamus performs a number of other functions all of which can be lost or deranged in the disease state. The commonest cause is surgical removal of ***pituitary tumours***.

The **functions of the hypothalamus** are as follows.

1 It controls the ANS and damage to it can cause autonomic instability. The ventromedial part of the hypothalamus has a major role in controlling the sympathetic nervous system while the lateral hypothalamic area controls the parasympathetic nervous system (see Chapter 36).

2 It controls the endocrine functions of the pituitary by the production of releasing and inhibiting hormones as well as producing anti-diuretic hormone (ADH, also known as vasopressin) and oxytocin. Hypothalamic damage can have profound systemic effects because of the endocrinological disturbances associated with it, of which perhaps the commonest example is ***diabetes insipidus*** where there is loss of ADH. In this condition the patient passes many litres of urine each day which needs to be compensated for by increased fluid intake.

3 The hypothalamus has a major role in coordinating autonomic and endocrinological responses, both under physiologically appropriate conditions, as well as in the expression of emotional states as coded for by the limbic system. In cases of hypovolaemia or extreme anxiety, for example, the hypothalamus not only mediates increased sympathetic activity but also enhanced cortisol production via the stimulated release of ACTH from the anterior pituitary.

4 It has an important role in thermoregulation. Lesions to the anterior hypothalamic area cause hyperthermia while stimulation of this same area lowers body temperature via the ANS, in contrast to the posterior hypothalamic area which behaves in an opposite fashion. It may also mediate some of the more long-term changes seen with prolonged changes in ambient temperature, such as increased thyrotrophin-releasing hormone (TRH) production in patients exposed to a chronically cold enviroment. Damage to the hypothalamus can lead to profound changes in the central control of temperature. In septic states the production of some cytokines (e.g. interleukin-1) may reset the thermostat in the hypothalamus to a higher than normal temperature, accounting for the paradoxical situation of a fever with physiological evidence of mechanisms designed to conserve or generate heat (e.g. shivering).

5 It has a role in the control of feeding. In simple terms, the ventromedial hypothalamus is often called the satiety centre, in that damage to it causes excessive eating (hyperphagia) and weight gain, while damage to the lateral hypothalamic (or hunger) area produces aphagia (no eating at all). The control of these centres involves a number of hormones, including insulin and the more recently described leptins.

6 It has a role in the control of thirst and water balance by virtue of its osmoreceptors; the afferent input from a host of peripheral sensory receptors (e.g. atrial stretch receptors in the heart, arterial baroreceptors); the activation of hypothalamic hormone receptors (e.g. angiotensin II receptors); and its efferent output via the autonomic nervous system (ANS) to the heart and kidney as well as the production of ADH.

7 It has a role in the control of circadian rhythms via the retinal input to the suprachiasmatic nucleus. This nucleus appears to be critical in setting the circadian rhythm as lesion and transplant experiments have shown. Although the exact mechanism by which these rhythms are mediated is not known, it may involve the production of melatonin by the pineal gland.

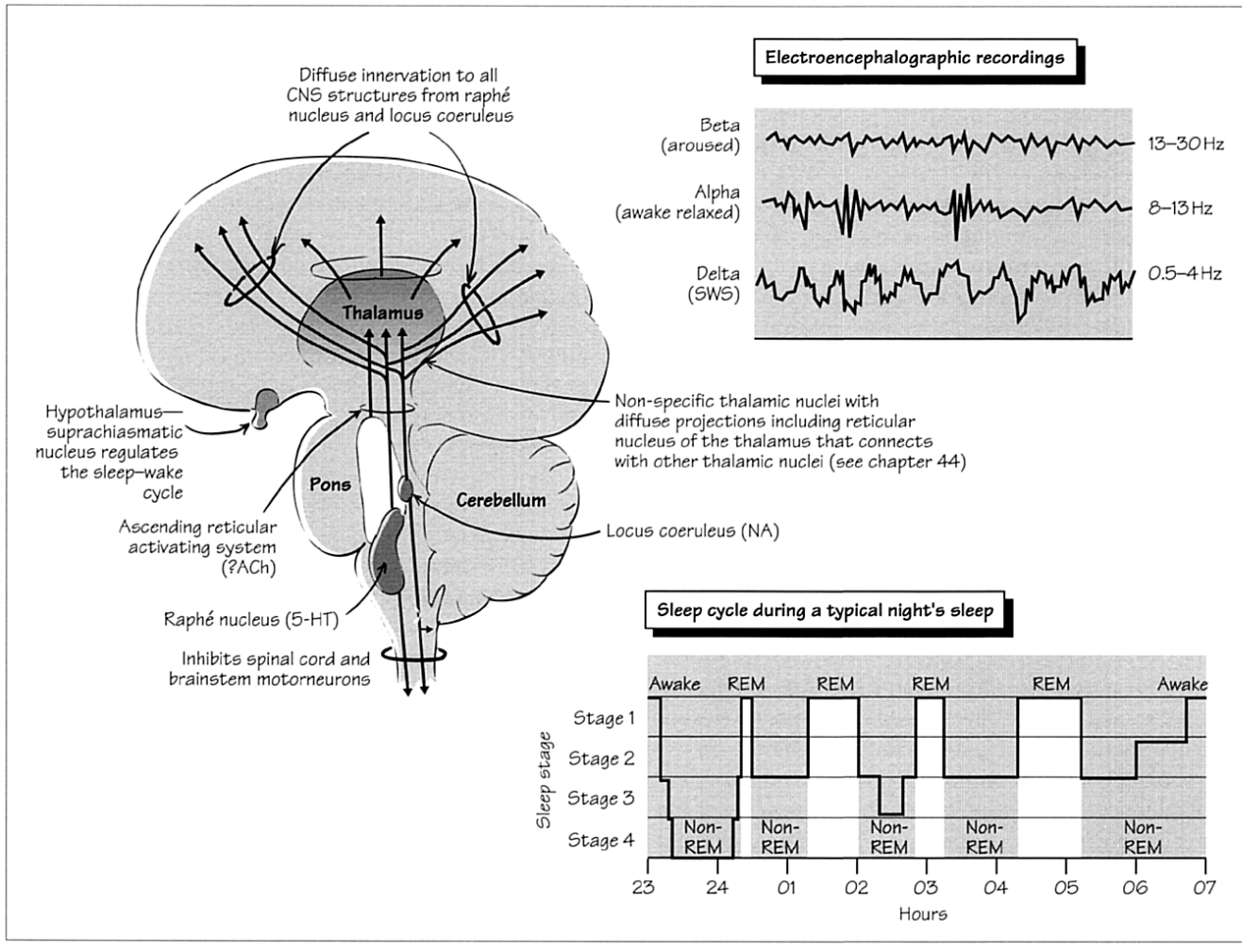
8 It has a role with the limbic system in memory. Damage to the mammillary bodies, which receive a significant input from the hippocampal complex as occurs in chronic alcoholism with thiamine deficiency, produces a profound amnesia ***(Korsakoff's syndrome);*** both anterograde (i.e. inability to lay down new memories) and retrograde (i.e. inability to recover old memories). The latter feature distinguishes these patients from those who have hippocampal damage (see Chapter 39) and may explain why patients with Korsakoff's syndrome tend to invent missing information (confabulation).

9 The hypothalamus may also have a role in sexual and emotional behaviour independently of its endocrinological influences.

Abbreviations

ACTH adrenocorticotrophic hormone
ADH antidiuretic hormone or vasopressin
ANS autonomic nervous system
TRH thyrotrophin releasing hormone

38 The reticular formation and sleep



Sleep

Sleep is a characteristic of all mammals and is defined behaviourally as a reduced responsiveness to environmental stimuli, and electrophysiologically by specific changes in electroencephalographic (EEG) activity. In addition, there are a number of changes associated with autonomic nervous system (ANS) function.

Normal patterns of sleep are essential for human well being, although, it is still unclear why we need to dream.

EEG patterns during states of consciousness and slow wave sleep

EEG recordings from normal subjects at rest show a characteristic high frequency (13–30 Hz, **beta activity**) low voltage pattern. This desynchronised activity changes as the subject closes his or her eyes and becomes drowsy, with the new EEG pattern having a lower frequency (8–13 Hz, **alpha activity**) but slightly higher voltage. This pattern is said to be synchronised and results from the simultaneous firing of many cortical neurons following thalamocortical activity.

EEG studies have revealed that sleep occurs in characteristic stages. As the subject falls asleep (stage 1) the EEG is similar to the awake EEG, i.e. low-voltage, fast activity. As sleep deepens through stages 2 and 3 to stage 4, the EEG amplitude progressively increases and its frequency falls. Stage 3 and 4 sleep is called collectively slow-wave sleep (SWS) or **non-rapid eye movement** (non-REM) sleep because the eyes are still. After about 90 min of sleep, the EEG changes back to a low voltage, fast pattern that is indistinguishable from stage 1 non-REM sleep. However, during this phase of sleep there are rapid eye movements.

This type of sleep is called **rapid eye movement sleep** (REM sleep), or paradoxical sleep because although the EEG is similar to that of an awake person, they are difficult to arouse and muscle tone is absent. It is during REM sleep that most dreaming occurs.

Neural mechanisms of sleep

Sleep is an active process, cholinergic neurons in the brainstem (forming part of the **ascending reticular activating system**) have been shown not only to regulate the desynchronised EEG of the awake state and REM sleep but also to produce PGO waves signalling the onset of REM sleep. In contrast serotonin- (5-hydroxytryptamine (5-HT)) containing neurons in the **raphé nuclei** appear to suppress this activity, suggesting that two pharmacologically different systems are responsible for initiating and terminating REM sleep. In addition, noradrenaline-containing neurons in the **locus coeruleus** are responsible for reducing spinal motorneuron excitability producing the associated atonia observed during REM sleep, while the pre-optic area and the suprachiasmatic nuclei of the **hypothalamus** are involved in controlling the sleep–wake cycle.

Sleep disorders

Insomnia is the commonest sleep disorder. It can be defined as the failure to obtain the required amount or quality of sleep to function normally during the day. ***Primary insomnia*** supposedly due to dysfunction of sleep mechanisms in the brain is rare, but these patients are the ones who may require treatment with hypnotic drugs. Causes of secondary insomnia include psychiatric disease (especially depression and anxiety disorders), physical disorders, chronic pain, drug misuse (e.g. excessive alcohol, caffeine) personal crises, and old age.

Management of insomnia

Psychological strategies may be effective alternatives to drugs.

Hypnotics are drugs which promote sleep. They include benzodiazepines, chloral hydrate, chlormethiazole and barbiturates. **Benzodiazepines** are by far the most widely used hypnotics. They also have anxiolytic, anticonvulsant, muscle relaxant and amnesic actions. All the actions of benzodiazepines are believed to be caused by the enhancement of GABA-mediated inhibition in the CNS. When GABA is released from presynaptic terminals, it acts on the postsynaptic ligand-gated $GABA_A$ receptor causing an increase in Cl^- conductance and inhibition. The $GABA_A$ receptors possess several 'modulatory' sites including one for benzodiazepines. Occupation of the benzodiazepine sites by benzodiazepine-receptor-agonists causes a conformational change in the GABA receptor. This increases the affinity of GABA binding and enhances the actions of GABA on the Cl^- conductance of the neuronal membrane.

Any benzodiazepine given at night will induce sleep but a rapidly eliminated drug (e.g. **temazepam**) is usually preferred to avoid daytime sedation. Some newer drugs do not have the benzodiazepine structure but are benzodiazepine-receptor agonists, e.g. **zopiclone** is a cyclopyrrolone with a short duration of action. The benzodiazepines are central depressants but their maximum effect when given orally does not normally cause fatal respiratory depression (in contrast to opioids or barbiturates). Adverse effects include drowsiness, impaired alertness and ataxia as well as a low grade dependence after a few weeks' use. Withdrawal of the drug may cause a physical withdrawal syndrome (anxiety, insomnia) which may last for weeks.

Hypersomnia (daytime sleepiness)

This is a serious but less common complaint than insomnia. Common causes of persistent daytime sleepiness include: narcolepsy, obstructive sleep apnoea, drugs (e.g. benzodiazepines, alcohol, etc.) and depression (20% have hypersomnia rather than insomnia).

Narcolepsy

Narcolepsy is characterised by irresistable sleep episodes lasting 5–30 min during the day, and cataplexy (loss of muscle tone and temporary paralysis) usually provoked by emotion, e.g. laughter, anger. It has a very strong HLA association (DR2/DQW1) and whilst no pathological abnormalities have been detected in these patients, it is probable that there are abnormalities in the brainstem structures underlying sleep, as there is evidence of short latency REM sleep during normal waking hours. The syndrome has a devastating effect on the quality of life which may be improved by long-term treatment with stimulants, e.g. dexamphetamine, methylphenidate. Clomipramine is used to treat the cataplexy.

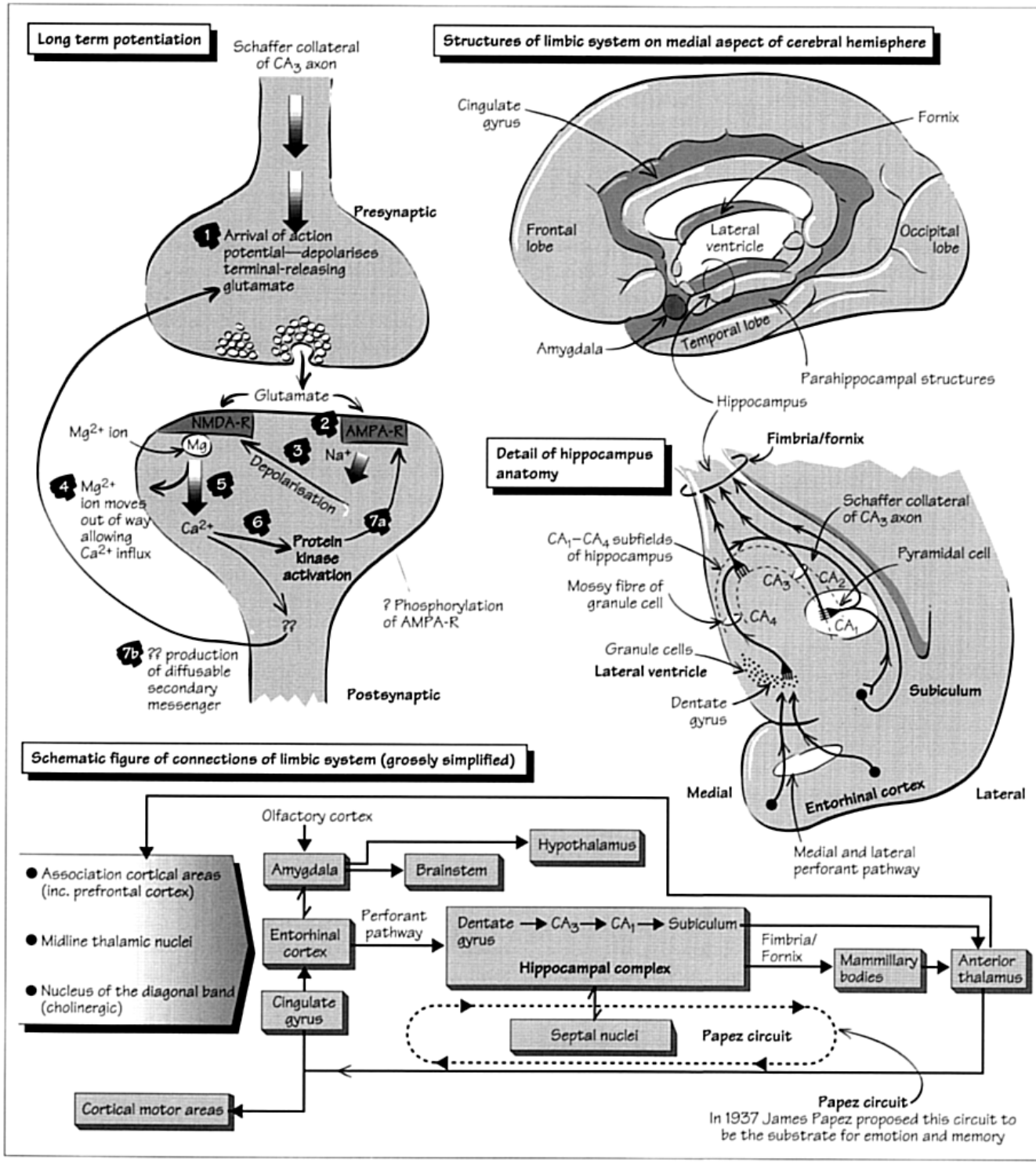
Obstructive sleep apnoea syndrome

This occurs if the upper airway at the back of the throat collapses when the patient breathes during sleep. This reduces the oxygen in the blood which arouses the patient causing him to momentarily awake and prevents a normal sleep pattern. The patient, usually an overweight man, is often unaware of these awakenings, but the disruption to sleep results in daytime sleepiness and impaired daytime performance.

Abbreviations

ACh	acetylcholine
EEG	electroencephalography
5-HT	5-hydroxytryptamine (serotonin)
HLA	histocompatibility locus antigen
NA	noradrenaline
PGO	pontine–geniculo-occipital
REM	rapid eye movement
SWS	slow wave sleep

39 The limbic system, long-term potentiation and memory



Anatomy of the limbic system

The **limbic system** refers to a collection of areas within the brain that lie primarily along the medial aspect of the temporal lobe and includes the **cingulate gyrus, parahippocampal structures (postsubiculum, parasubiculum, presubiculum and perirhinal cortex), entorhinal cortex, hippocampal complex (dentate gyrus, CA1–CA4 subfields and subiculum), septal nuclei and amygdala**. Additional structures are closely associated with the limbic system and include the mammillary bodies of the hypothalamus, olfactory cortex and nucleus accumbens (see Chapters 37, 27 and 34, respectively).

The **anatomical organisation** of the limbic system indicates that it performs some high-level processing of sensory information, given its input from the association cortices (see Chapter 28). This input is ultimately channelled through a trisynaptic pathway as it passes through the hippocampus; it is these synapses that have generated much interest with respect to long-term potentiation (LTP; see below).

The predominant outflow of the limbic system is to the prefrontal cortex and hypothalamus as well as to cortical areas involved with the planning of behaviour, including a motor response (see Chapters 29 and 32). Thus anatomically the limbic system appears to have a role in attaching a behavioural significance and response to a stimulus, especially with respect to its emotional content, and consequently damage to it has profound effects on the emotional responsiveness of the animal. The hippocampal complex has been shown to have both a high degree of susceptibility to hypoxia and yet a remarkable degree of plasticity which helps explain why this structure is important in the generation of epileptic seizures (see Chapter 45) as well as memory acquisition.

Function of the limbic system

Hippocampal complex and parahippocampal structures

The original description in the 1950s by Scoville and Milner of patient HM with bilateral anterior temporal lobectomy for intractable epilepsy and a resulting profound amnesic state suggested that this area of the brain had a major role in memory. Subsequently the hippocampus proper and parahippocampal areas have been shown to be critical in the ability of both experimental animals and patients to acquire information about events (so-called declarative memory).

However, the long-term storage of memories occurs at a site distant from the medial temporal lobe system and is probably within the overlying cerebral cortex—as demonstrated by the pattern of memory loss seen in ***dementia of the Alzheimer type*** (DAT; see Chapter 42). In this condition there is relatively well-preserved retrograde memory (for distant events such as childhood) in the face of severely impaired or absent anterograde memory (inability to remember what the patient has just done).

Amygdala

The amygdala is a small almond-shaped structure made up of many nuclei, that lies on the medial aspect of the temporal lobe and which is involved in the learning and possible storage of emotional aspects of experience.

Damage to this structure experimentally leads to blunted emotional reactions to normally arousing stimuli, and can even prevent the acquisition of emotional behaviour. In humans with selective amygdala damage there appears to be a profound impairment in the ability to recognise facial expressions of fear. Conversely, stimulation of this structure produces a pattern of behaviour typical of fear with increased autonomic activity. This is sometimes seen clinically in ***temporal lobe epilepsy*** where patients complain of brief episodes of fear.

Cingulate gyrus

The cingulate gyrus running around the medial aspect of the whole hemisphere has a number of functions, including a role in complex motor control (see Chapter 32), pain perception (see Chapter 20) and social interactions.

Damage to this structure can produce motor neglect, as well as reduced pain perception, reduced aggressiveness and vocalisation, emotional blunting and altered social behaviour which can result in a clinical state of ***akinetic mutism*** (not talking or moving). Stimulation of this area, either experimentally or during an epileptic seizure, produces alterations in the autonomic outflow and motor arrest, with vocalisation and complex movements.

Long-term potentiation

Long-term potentiation (**LTP**) is defined as an increase in the strength of synaptic transmission with repetitive use that lasts for more than a few minutes, and in the hippocampus it can be triggered by less than 1 second of intense synaptic activity and lasts for hours or much longer. It can be induced at a number of CNS sites but especially the hippocampus and it has therefore been postulated to be important in **memory acquisition**. However, it should be realised that different mechanisms may underlie LTP at different synapses within the hippocampal complex, and that most of the work is based on the excitatory glutamate synapse containing the *N*-methyl-D-aspartate glutamate (NMDA) receptor (see Chapter 9) in the CA1 subfield of the hippocampal complex.

The current model of LTP is as follows:

- An afferent burst of activity leads to the release of glutamate from the presynaptic terminal (stage 1 on figure).
- The released glutamate then binds to both NMDA and non-NMDA receptors in the postsynaptic membrane.

These latter receptors lead to a Na^+ influx (stage 2) which depolarises the postsynaptic membrane (stage 3).

- The depolarisation of the postsynaptic membrane leads not only to an EPSP, but also removes Mg^{2+} from the NMDA associated ion channel (stage 4). The Mg^{2+} normally blocks the NMDA receptor associated ion channel and thus its removal in response to postsynaptic depolarisation allows a further Na^+ and Ca^{2+} influx into the postsynaptic cell (stage 5).
- The Ca^{2+} influx leads to the activation of a postsynaptic protein kinase (stage 6), which is responsible for the initial **induction of LTP**—a postsynaptic event.
- The **maintenance of LTP** in addition to requiring a persistent activation of protein kinase activity (stage 7a) probably also requires an additional modification of neurotransmitter release (stage 7b); i.e. an increase in transmitter release in response to a given afferent impulse. The presynaptic modification, if necessary in the maintenance of LTP, means that the postsynaptic cell must produce a diffusible secondary signal which can act on the presynaptic terminal. Much controversy exists as to the nature of this diffusible messenger, but various candidates have been proposed including permeant arachidonic acid metabolites, nitric oxide, carbon monoxide and platelet activating factor. To date there is no agreement as to which, if any, of these are important in LTP.

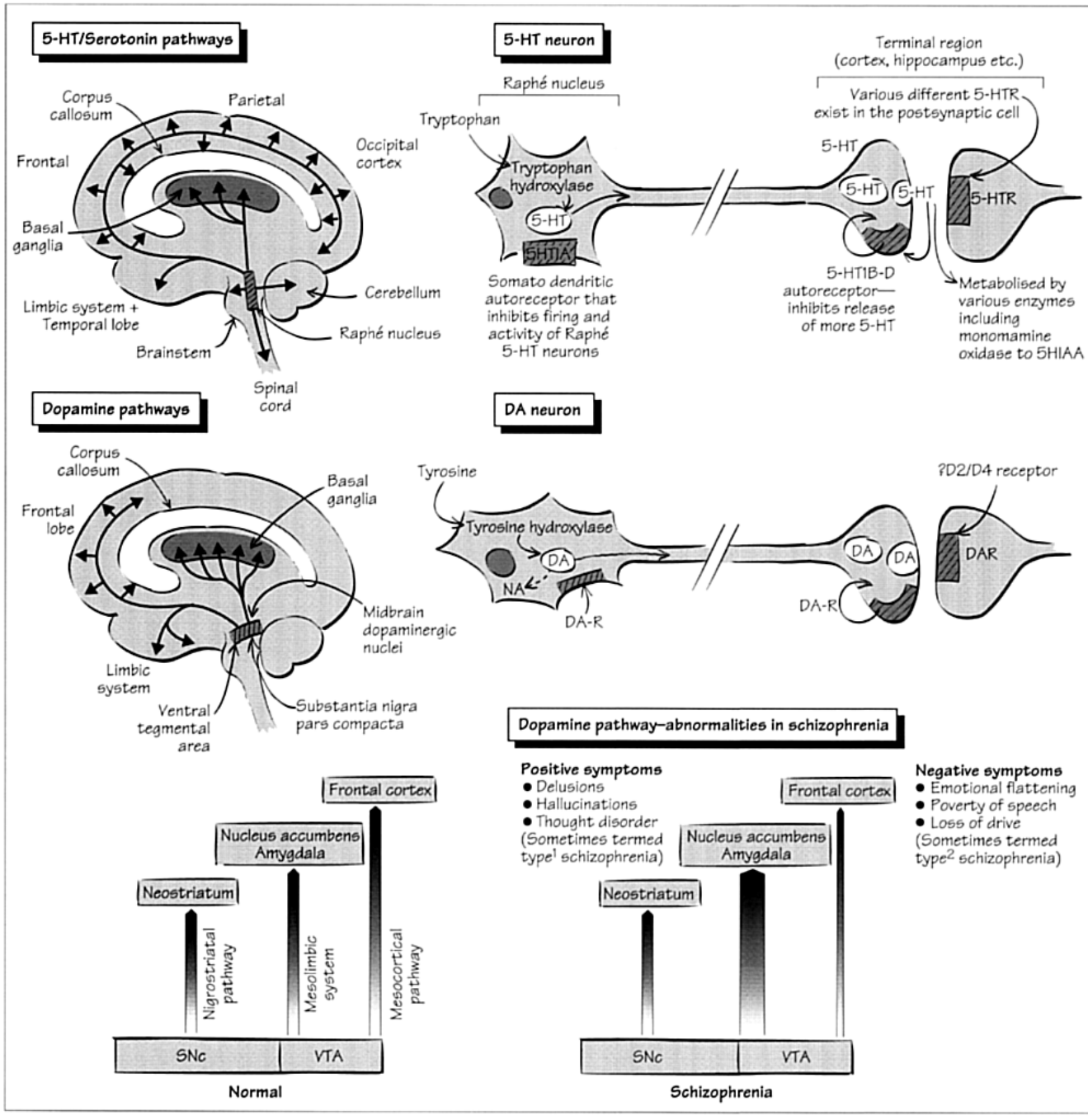
In some circumstances **long-term depression (LTD)** can be induced in the mossy fibre synapses in the CA3 subfield of the hippocampus. This, in contrast to LTP, is thought to be mediated by a presynaptic metabotropic glutamate receptor.

Abbreviations

AMPA-R	alpha amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid glutamate receptor
DAT	dementia of the Alzheimer type
EPSP	excitatory postsynaptic potential
LTD	long-term depression
LTP	long-term potentiation
NMDA-R	*N*-methyl-D aspartate glutamate receptor

Part 5 Neural plasticity and disorders of the nervous system

40 Neurochemical disorders: affective disorders and schizophrenia



There are a large number of psychiatric disorders which have many causes and treatments including affective disorders or disorders of mood such as ***depression*** and ***mania*** (when the mood oscillates between depression and mania it is termed a bipolar disorder). Depression is characterised by sadness, apathy, low self esteem and a tendency to withdraw from others coupled to a loss of libido, anorexia and early morning waking. Mania, on the other hand, is characterised by euphoria, delusions of grandeur and mental overactivity.

Schizophrenia is a syndrome characterised by specific psychological manifestations, including auditory hallucina-

tions, delusions, thought disorders and behavioural disturbances.

Depression

The cause of endogenous depression is not known and, although there is clearly a genetic component to the disorder, the nature of this is unclear.

A number of different therapies are employed for the treatment of depression, and while this includes psychotherapy and electroconvulsive therapy (ECT), the most commonly used approach is with antidepressant drugs. Most of the drugs in the treatment of depression inhibit the re-uptake of noradrenaline and/or serotonin (5-HT). Less used drugs are inhibitors of monoamine oxidase (MAOIs). Because both uptake inhibitors and MAOIs increase the amount of noradrenaline and/or 5-HT in the synaptic cleft and so enhance the action of these transmitters, it was argued that depression resulted from an 'under activity' of these monoaminergic systems. This simple idea is often referred to as the monoamine theory of depression and is a useful hypothesis, although not an entirely adequate explanation for this condition.

Amine uptake inhibitors

Tricyclic antidepressants (e.g. imipramine, amitriptyline) have proven antidepressant actions but no one drug has greater efficacy. Some have sedative actions, e.g. amitriptyline, and are more useful for agitated and anxious patients (see Chapter 20).

Drugs that are specific serotonin re-uptake inhibitors (SSRIs; e.g. fluoxetine) do not have the troublesome autonomic side effects of the tricyclics but may cause nausea and gastrointestinal problems.

Monoamine oxidase inhibitors (MAOIs)

The older MAOIs (e.g. phenelzine) are irreversible non-selective inhibitors of MAO. Their efficacy is similar to the tricyclics but unwanted side effects (e.g. postural hypotension) and potentially serious interaction with foods containing tyramine have limited their use. Moclobemide is a newer drug that selectively inhibits MAO_A and lacks most of the unwanted effects of phenelzine.

Schizophrenia

Schizophrenia has a significant genetic component with the risk for a first-degree relative developing the disease of 10%, rising to 40% for the offspring if both parents are affected.

The early theories of schizophrenia proposed that it was caused by the production of some endogenous psychotogen that may be a transmethylated derivative of dopamine. Subsequently this was modified to the theory that schizophrenia was caused by overactivity of the central dopaminergic pathways, especially the mesolimbic projections with relative sparing of the dopaminergic nigrostriatal pathway (see Chapter 34).

This has been further modified to the theory that the negative symptoms of schizophrenia may be caused by hypodopaminergic activity in the mesocortical system, while the psychotic symptoms result from hyperdopaminergic activity in the mesolimbic system. Indeed, schizophrenics show frontal hypoperfusion and this, coupled to previous studies showing non-progressive cerebral ventricular dilatation without gliosis, led to the proposal that schizophrenia may be a neurodevelopmental disorder.However, which part of the brain fails to develop normally is not known, although the amygdala, frontal and temporal lobes seem likely candidates.

The mainstay of therapy in schizophrenia remains the use of drugs that block the dopamine receptors, of which there are least five subtypes (D_1–D_5 receptors; see Appendix 1). These agents (e.g. chlorpromazine) are called antipsychotics or neuroleptics. It is not known how these agents reduce the severity of the symptoms in schizophrenia. A correlation between the clinical dose of antipsychotic drugs and their affinity to D_2-receptors suggests that blockade of this receptor subtype may be particularly important.

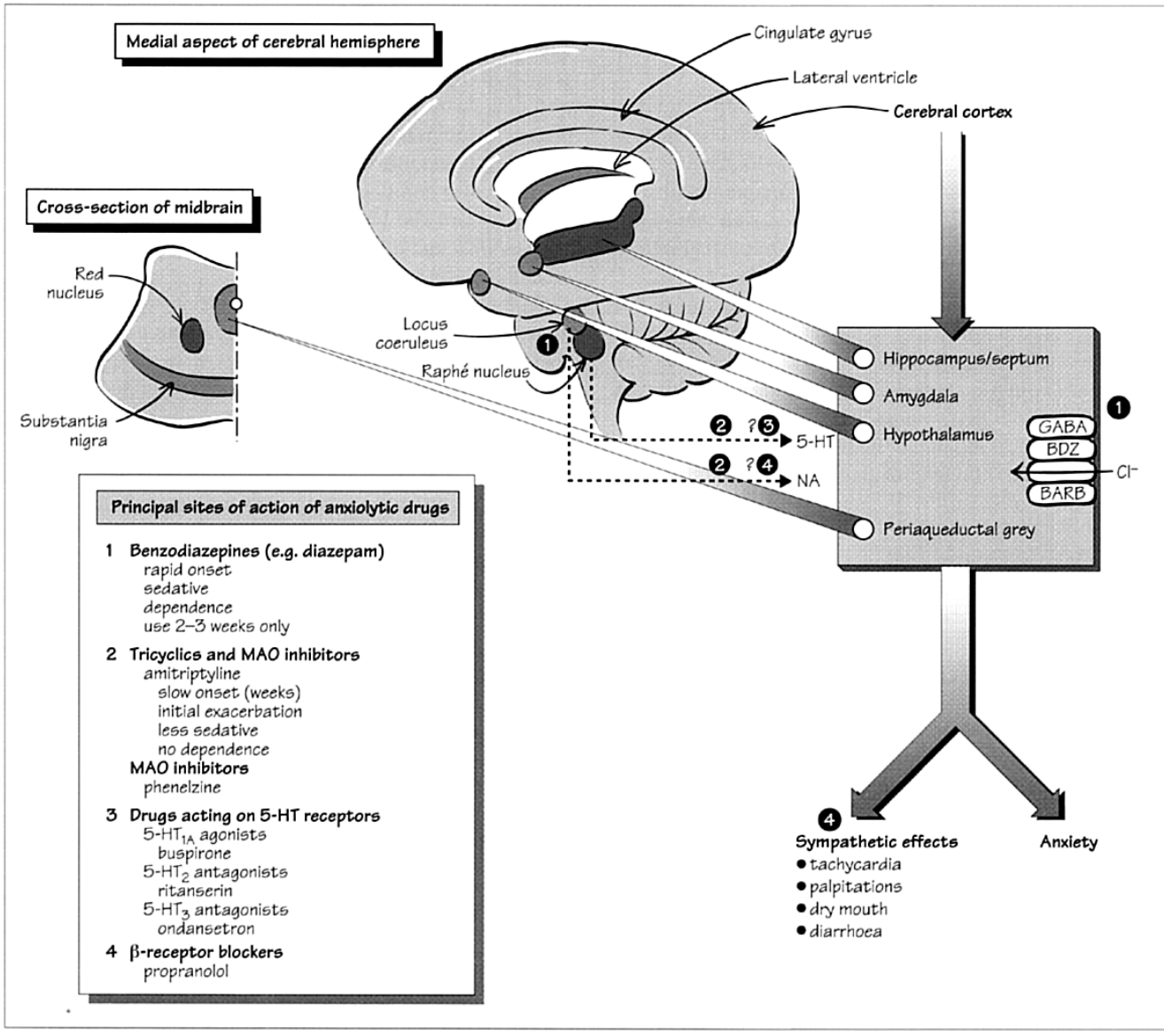
Antipsychotic drugs require several weeks to control the symptoms of schizophrenia and most patients will require maintenance treatment for many years. Relapses are common even in drug maintained patients. Unfortunately, neuroleptics also block DA receptors in the basal ganglia often producing distressing and disabling movement disorders (e.g. ***Parkinsonism***, see Chapter 34). Blockade of D_2-receptors in the pituitary gland causes an increase in prolactin release and endocrine effects (e.g. gynaecomastia, galactorrhoea, see chapter 37). Many neuroleptics also block muscarinic receptors (causing dry mouth, blurred vision, constipation), α-adrenoceptors (postural hypotension), and histamine H_1-receptors (sedation).

Some newer drugs (so-called 'atypical' agents) rarely cause movement disorders, e.g. clozapine, risperidone, olanzapine but the reason for this is unknown. Clozapine has a relatively high affinity for D_4-receptors (present mainly in limbic areas) but it seems that this is unlikely to explain the atypical action of clozapine because specific D_4-antagonists have recently been shown to be ineffective in schizophrenia.

Abbreviations

CSF	cerebrospinal fluid
DA	dopamine
ECT	electroconvulsive therapy
5-HT	5-hydroxytryptamine or serotonin
5-HIAA	5-hydroxy indole acetic acid
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
SSRI	selective serotonin re-uptake blockers

41 Neurochemical disorders: anxiety



Anxiety is a normal emotional reaction to threatening or potentially threatening situations, and is accompanied by sympathetic overactivity. In **anxiety disorders** the patient experiences anxiety that is disproportionate to the stimulus, and sometimes in the absence of any obvious stimulus. There is no organic basis for anxiety disorders, the symptoms resulting from overactivity of the brain areas involved in 'normal' anxiety. Psychiatric disorders which occur without any known brain pathology are called **neuroses**.

Anxiety disorders are subdivided onto four main types: ***generalised anxiety disorder***, ***panic disorder***, ***stress reactions*** and ***phobias***. Many transmitters seem to be involved in the neural mechanisms of anxiety, the evidence being especially strong for **GABA** and **5-HT**. Because intravenous injections of **cholecystokinin** (CCK_4) into humans cause the symptoms of panic it has been suggested that abnormalities in different transmitter systems might be involved in particular types of anxiety disorder. This remains to be seen.

Treatment of mild anxiety disorders may only require simple *supportive psychotherapy* but in severe anxiety, anxiolytic drugs given for a short period are useful. The **benzodiazepines** (e.g. *diazepam*) produce their effects by enhancing GABA mediated inhibition (Chapter 38) in many of the brain areas involved in anxiety, including the raphé nucleus (RN). **Tricyclic antidepressants** (e.g. *amitriptyline*) have anxiolytic activity but the mechanism involved in unknown. β-**Adrenoceptor antagonists** have a limited use in the treatment of situational anxiety (e.g. in musicians) where palpitations and tremor are the main symptoms. Efforts to discover non-sedative anxiolytics have led to the trial of several drugs that act on specific 5-HT receptors. They have not been very successful.

Anxiety disorders

Generalised anxiety disorders have both psychological and physical symptoms. The psychological symptoms include a feeling of fearful anticipation, difficulty in concentration, irritability, repetitive worrying thoughts that are often linked to awareness of sympathetic overactivity.

Phobic anxiety disorders have the same core symptoms as generalised anxiety disorders but occur only under certain circumstances, e.g. the appearance of a spider (arachnophobia). In contrast, ***panic attacks*** are episodic attacks of anxiety in which physical symptoms predominate (e.g. choking, palpitations, chest pain, sweating, trembling).

Benzodiazepines

Benzodiazepines (e.g. diazepam) are central depressants and will induce sleep when given in high doses at night and will provide sedation and reduce anxiety when given in divided doses during the day. The benzodiazepines are discussed in more detail in Chapter 38, their main adverse effects are drowsiness, impaired alertness, agitation and ataxia. In anxiety disorders, benzodiazepines should only be given for a maximum of 2–3 weeks because longer treatment risks the development of **dependence**. If this occurs, stopping the drug frequently leads to a **withdrawal syndrome** characterised by anxiety, tremor, sweating, and insomnia, i.e. symptoms similar to the original complaint.

Sites of action of benzodiazepines in the brain

The areas of the brain involved in the anxiolytic action of the benzodiazepines have been studied in rats by injecting tiny quantities of a drug through cannulae implanted in different brain areas. In general, limbic and brainstem structures seem important in mediating the anxiolytic actions of these drugs. In humans, cerebral blood flow and glucose metabolism studies using PET have not revealed consistent differences in anxious and non-anxious subjects.

Serotonin

Serotonin (5-HT) cell bodies are located in the raphé nuclei of the midbrain and project to many areas of the brain including those thought to be important in anxiety (hippocampus, amygdala, frontal cortex) (see Chapter 40). In rats, lesions of the raphé nuclei produce anxiolytic effects whilst stimulation of 5-HT receptors with agonists such as quipazine produce anxiogenic effects. A role for 5-HT in anxiety was strengthened when it was found that benzodiazepines reduce the turnover of 5-HT in the brain, and when micro-injected into the raphé nucleus, reduce the rate of neuronal firing and produce an anxiolytic effect. However, specific antagonists at 5-HT_3 receptors (e.g. ondansetron) and 5-HT_2 receptors (e.g. ritanserin) have little, if any, anxiolytic action. Buspirone, a 5-HT_{1A} partial agonist, has anxiolytic actions in man but only after several weeks' administration.

Noradrenaline

The evidence for the role of noradrenaline in anxiety is much less compelling than that for GABA and 5-HT. Nevertheless, β-adrenoceptor antagonists have a limited use in the treatment of patients with mild or transient anxiety and where autonomic symptoms such as palpitations and tremor are the most troublesome symptoms. The beneficial effects of β-blockers in these patients may result from a peripheral action because those (e.g. practolol) that do not pass the blood-brain barrier are equally effective.

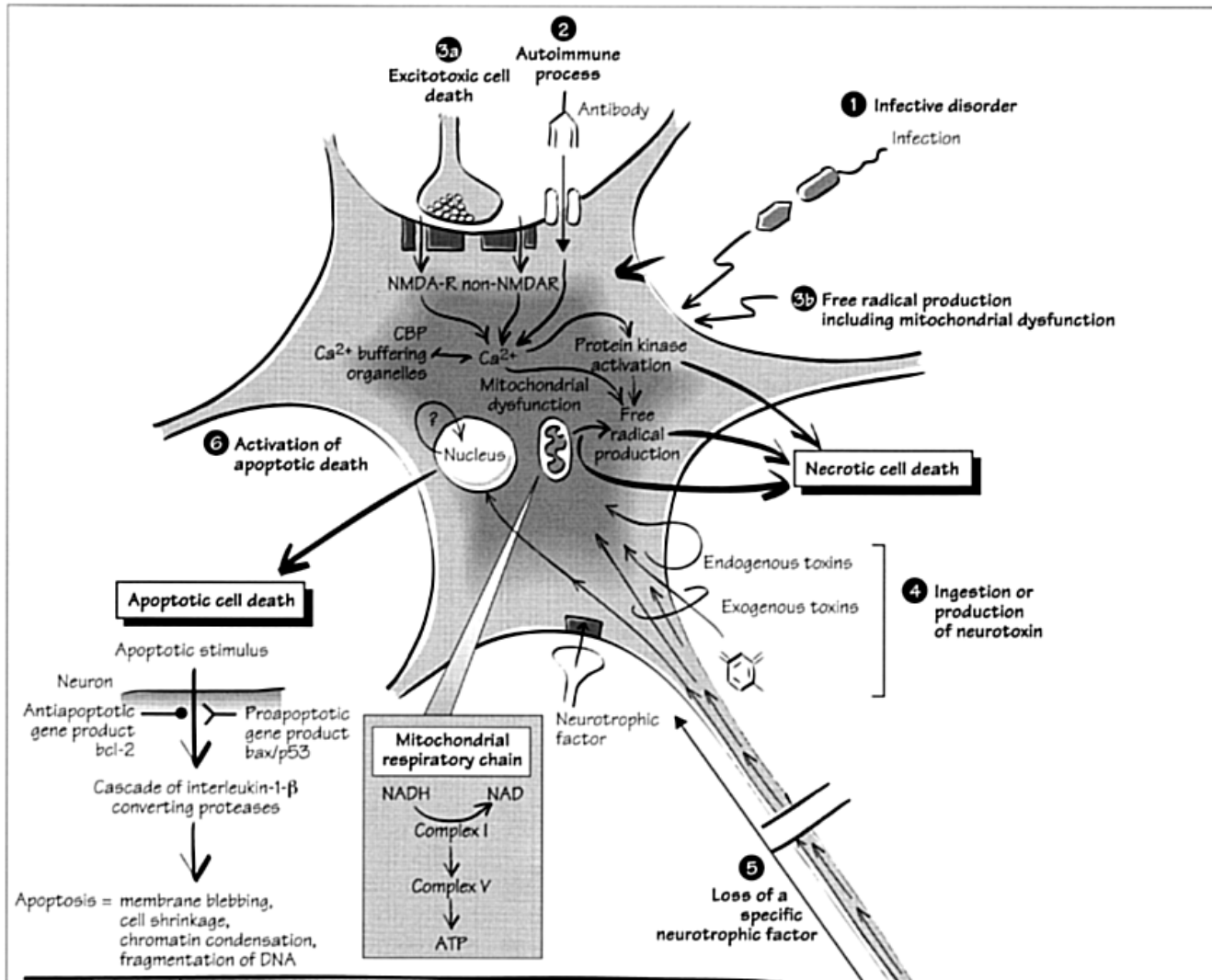
Cholecystokinin (CCK)

This is a gut peptide that occurs also in the brain. Two receptor subtypes have been identified. CCK_A receptors have a higher affinity than CCK_B receptors for the sulphated octapeptide fragment (CCK-8s) than for CCK_4. Intravenous CCK_4 consistently induces panic-like attacks in patients suffering from panic disorders and in about 70% of healthy volunteers. In contrast intravenous CCK_8 does not cause anxiety or panic (perhaps because of poor brain penetration) but does cause severe gastrointestinal symptoms. The panic attacks caused by CCK_4 can be prevented with benzodiazepines. The precise role of CCK as a transmitter involved in anxiety is unknown but since it is one of the very few agents (CO_2 is the other) that elicit genuine panic-like attacks in humans, CCK_B antagonists might prove to be particularly useful in the treatment of panic disorders.

Abbreviations

CCK	Cholecystokinin
GABA	γ-Aminobutyric acid
5-HT	5-Hydroxytryptamine (or serotonin)
MAOI	Monoamine oxidase inhibitor
PET	Positron emission tomography

42 Neurodegenerative disorders



Neurodegenerative disorder	Primary pathological findings	Clinical features
Dementia of the Alzheimer type* (DAT)	Cerebral cortex (esp. parietotemporal) and hippocampal complex contain neurofibrillary tangles and neuritic plaques with secondary cholinergic neuronal loss in the basal forebrain nuclei	Loss of anterograde memory Loss of language functions and with time global cognitive impairment
Parkinson's disease (PD)	Loss of the nigrostriatal dopaminergic pathway in basal ganglia with presence of Lewy bodies, especially in substantia nigra	Slowing up of movements (bradykinesia) Pill-rolling tremor Cogwheel rigidity of limbs (see chapter 34)
Motorneuron disease** (MND or ALS)	Loss of motoneurons in spinal cord, brainstem and cortical motor areas	Progressive weakness and wasting of the limb and bulbar muscles with some upper motor signs (hyperreflexia and hypertonia)

* Some forms of dementia have a more focal onset with selective involvement of the frontotemporal cortex, some cases of which have cortical inclusion (Pick) bodies at autopsy

** Motorneuron disease can present with either purely LMN or UMN features, but the commonest presentation is with a combination of the two –a condition also known as amyotrophic lateral sclerosis or ALS

Neurodegenerative disorders are those conditions in which the primary pathological event is a progressive loss of specific populations of CNS neurons over time.

Aetiology of neurodegenerative disorders

There are a number of theories on the aetiology of neurodegenerative disorders which may not be mutually exclusive.

1 *An infective disorder*

Neuronal death with a glial reaction (gliosis) is commonly seen in infective disorders (typically viral) with inflammation in the CNS. However, in neurodegenerative disorders such a reaction is not seen, although the observation that ***HIV infection*** can cause a dementia has raised the possibility that the neurodegenerative disorders may be caused by some retroviral infection. Furthermore, the development of dementia with spongiform changes throughout the brain in response to the proliferation of abnormal prion proteins as occurs in ***Creutzfeldt–Jakob disease*** has further fuelled the debate on an infective aetiology in neurodegenerative disorders.

2 *An autoimmune process*

Autoantibodies have been described in some neurodegenerative conditions, e.g. antibodies to calcium channels in ***MND***. However, the absence of an inflammatory response would argue against this hypothesis, although neuronal degeneration with a minimal inflammatory infiltrate can be seen in the ***paraneoplastic syndromes***; see Chapter 46.

3 *The result of excitotoxic cell death and free radical production*

Excitatory amino acids are found throughout the CNS (see Chapter 9) and act on a range of receptors that serve to depolarise the neuron and allow Ca^{2+} to influx into the cell. On entering the neuron calcium is normally quickly buffered; if the level of excitation is great then there may be an excessive influx of Ca^{2+} which can lead to the production of toxic free radicals and cell death. It is this cascade of events that may underlie some of the neurodegenerative disorders. For example in some cases of familial **MND** there is a loss of one of the free radical scavenger molecules—superoxide dismutase. Furthermore, in PD, deficiency in complex I activity of the mitochondrial respiratory chain in the substantia nigra may lead to the overproduction of free radicals as well as compromised cellular respiration—both of which contribute to neuronal death.

4 *The ingestion or production of a neurotoxin*

Many toxins can induce degenerative conditions (e.g. parkinsonism with manganese poisoning) but no such exogenous compound has consistently been found to cause any of the major neurodegenerative disorders.

DAT, on the other hand, is associated with the development of neurofibrillary tangles (NFTs) and senile neuritic plaques (SNPs) in the parahippocampal and parietotemporal cortical areas. The density of NFTs correlates well with the cognitive state of the patient. NFTs contain paired helical filaments made up of an abnormal form of the microtubule-associated protein τ—a protein that normally serves to maintain the neuronal cytoskeleton. In contrast, the SNPs contain abnormal forms of the protein β-amyloid, derived from the membrane bound glycoprotein amyloid precursor protein (APP) which is found in all neurons in normal brains and which performs some unknown function.

The reason as to why these abnormal proteins are produced and in what order is not clear, certainly some of the rare familial forms of **DAT** have genetic defects that influence the production of the amyloid protein. Whatever the reason for the development of these abnormal proteins, the result is cell death within the cortex. This leads to a secondary loss in the cholinergic innervation of the cortex with an associated atrophy of the cholinergic neurons in the basal forebrain, which has prompted clinical studies in the use of drugs that potentiate CNS cholinergic transmission, although these have met with only limited success. Clinically these patients usually present with progressive memory and language difficulties (see also Chapter 38).

5 *The loss of a specific neurotrophic factor*

Neurons are maintained by the production of a specific growth or neurotrophic factor (see Chapter 43), and the loss of one or some of these factors may underlie the development of the various neurodegenerative disorders. Clinical trials using neurotrophic factors in patients with neurodegenerative disorders have been undertaken.

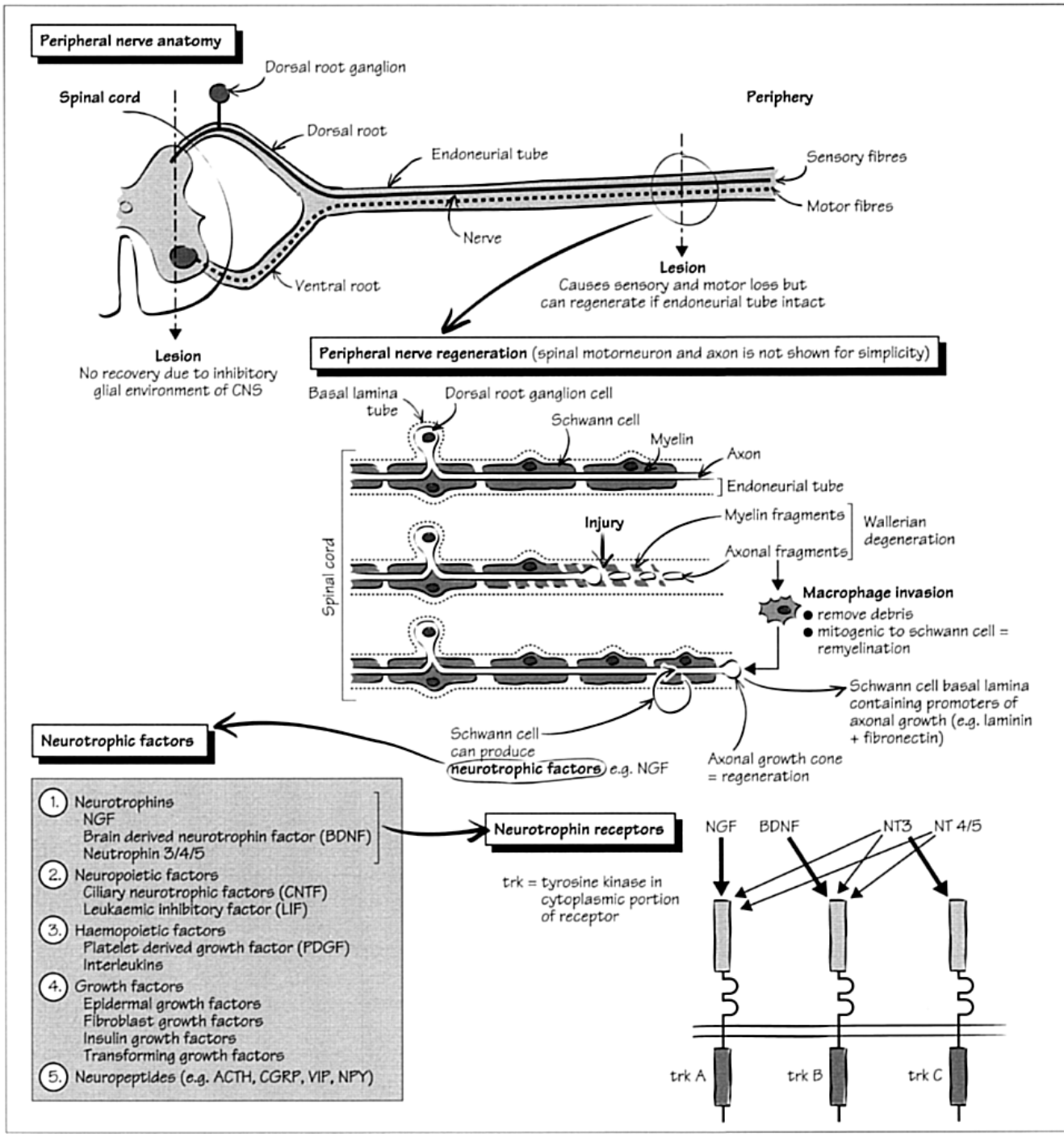
6 *The activation of a cell death programme (apoptosis)*

The loss of cells in most conditions (e.g. inflammation) is by a process of necrotic cell death but all cells contain the necessary machinery to initiate their own death, so-called programmed cell death or apoptosis. The pathways underlying this process are now relatively well understood although the triggers initiating them are not clear. It is therefore possible that the neurodegenerative disorders are caused by an inappropriate activation of this programme, possibly secondary to the loss of a neurotrophic factor.

Abbreviations

ALS	amyotrophic lateral sclerosis
APP	amyloid precursor protein
CBP	calcium-binding protein
DAT	dementia of the Alzheimer type
LMN	lower motor neuron
MND	motorneuron disease
NFT	neurofibrillary tangle
PD	Parkinson's disease
SNP	senile neuritic plaques
UMN	upper motor neuron

43 Neural plasticity and neurotrophic factors I: The peripheral nervous system



The PNS is capable of significant repair, to some extent independent of the age at which damage occurs. In contrast, the CNS has always been thought of as being unable to repair itself although there is now mounting evidence that there is considerable plasticity within it even in the adult state and that most, if not all, areas of the CNS are capable of some degree of reorganisation (see Chapter 44).

Repair in the PNS

Injury to a peripheral nerve if severe enough will cause permanent damage with loss of sensation, loss of muscle bulk and weakness. However, in many cases the nerve is able to repair itself, as the peripheral axon can regrow under the influence of the favourable environment of the Schwann cells. This is in contrast to the CNS where the neuroglial cells (astrocytes and oligodendrocytes) are generally inhibitory to axonal growth, even though most CNS neurons are capable of growing new axons.

When a peripheral nerve is damaged, the distal aspect of the axon is lost by a process of **Wallerian degeneration**. Wallerian degeneration leads to the removal and recycling of both axonal and myelin-derived material, but leaves in place dividing Schwann cells inside the basal lamina tube that surrounds all nerve fibres. These columns of Schwann cells surrounded by basal lamina are known as **endoneurial tubes**, and provide the favourable substrate for axonal growth.

Following injury, the degenerating nerve fibre elicits an initial macrophage invasion and this in turn provides the mitogenic input to the Schwann cell. The regenerating axon starts to sprout within hours of injury and contacts the Schwann cell basal laminae on one side, and the Schwann cell membrane on the other. The Schwann cell basal lamina is especially important in the process of axonal sprouting as it contains a number of molecules that are powerful promoters of axonal outgrowth *in vitro* (e.g. laminin and fibronectin).

In addition to providing a favourable substrate for axonal growth, Schwann cells also produce a number of neurotrophic factors, including nerve growth factor (NGF; see below). Thus the Schwann cell provides a substrate along which the regenerating axon can grow, as well as providing a favourable humoral neurotrophic environment. It also helps direct the regenerating axon back to its appropriate target, by means of the endoneurial tube. Occasionally the regrowth of the axons is inaccurate or incomplete so, for example, following damage to the third cranial nerve one can have aberrant regeneration such that there is elevation of the eyelid on looking down.

In contrast to axonal damage the loss of the cell body (in the ventral horn or dorsal root ganglia) leads to an irreversible and permanent loss of axons in the peripheral nerve. Examples of such disorders include ***poliomyelitis*** and ***motorneuron disease*** **(MND)** with respect to the α-MN, and a number of inflammatory and ***paraneoplastic syndromes*** in the case of the dorsal root ganglia (see Chapters 42 and 46). In all these cases the loss of axons is secondary to the loss of the cell body and so no regeneration is possible. Attempts to rescue dying α-MN in **MND** via the peripheral delivery of neurotrophic factors has been tried without much success (see also Chapter 42).

Neurotrophic factors

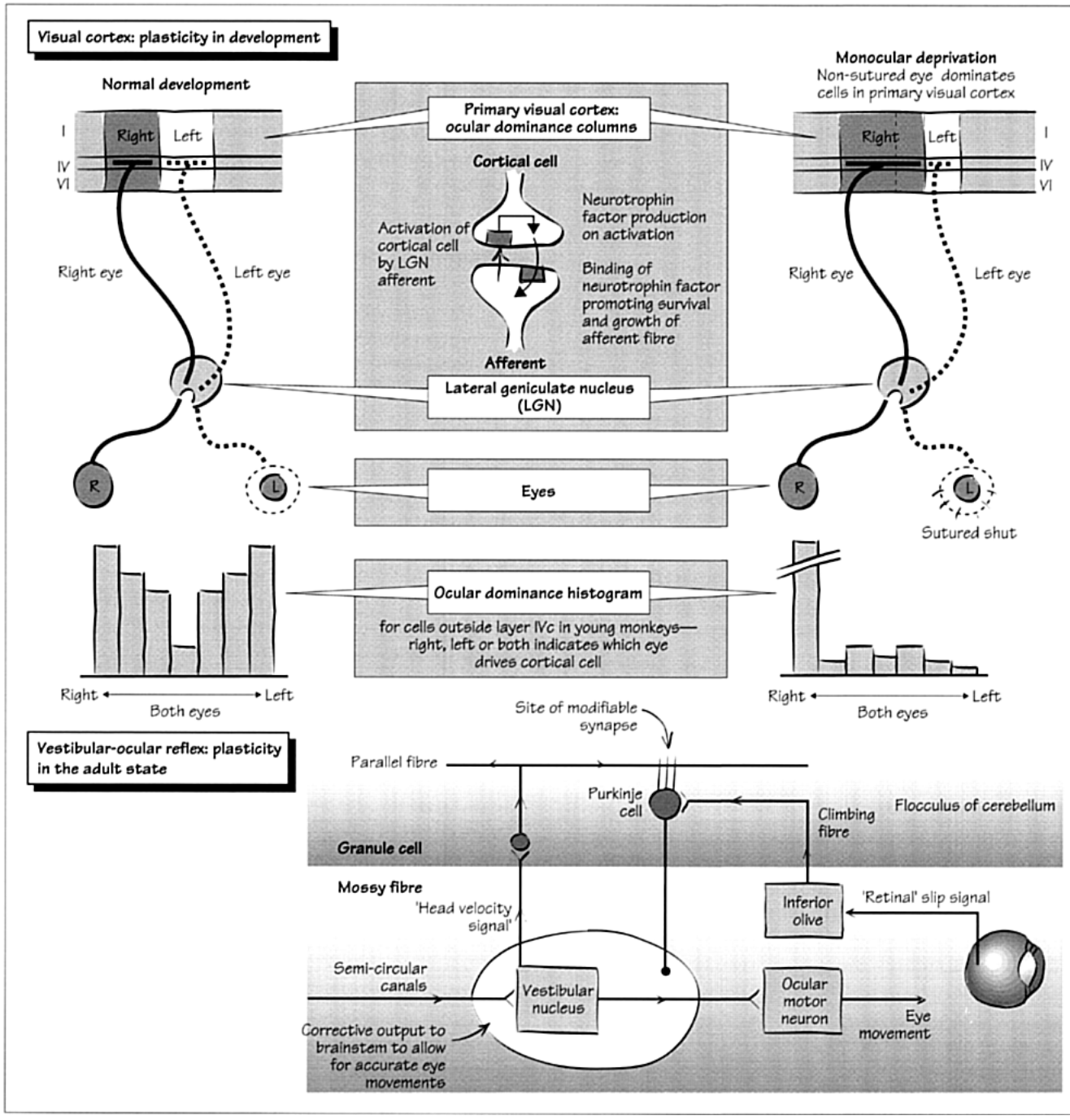
The number of neurotrophic factors has expanded greatly since the original description of the first of these, NGF. These factors, many of which are also found to influence non-neural populations of cells, form discrete families that act through specific types of receptors. Many of these receptors are composed of subunits, one or some of which form common binding domains for a family of neurotrophic factors. For example, the neurotrophin family of neurotrophic factors and the *trk* receptors use a range of cytoplasmic tyrosine kinases as part of their signalling mechanism.

Many populations of neurons respond to neurotrophic factors experimentally both *in vitro* and in the lesioned animal. However, despite these encouraging results, the administration of neurotrophic factors to patients in clinical trials of neurodegenerative disorders and neuropathies has met with only limited success. This argues against these disorders being the result of specific neurotrophic factor deficiencies (see Chapter 42).

Abbreviations

MN	motorneuron
MND	motorneuron disease
NGF	nerve growth factor

44 Neural plasticity and neurotrophic factors II: The central nervous system



There is now mounting evidence that regeneration and reorganisation can occur in the adult CNS. However, plasticity in the CNS is not caused by the production of new neurons, as these cells in the mature CNS are postmitotic, but to their ability to extend branching new axons. The time at which this is most florid is in the early postnatal period when the systems of the brain are developing, and it is during this time that major modifications can be made.

The mechanisms underlying this plasticity are not fully known, but the production and uptake of factors promoting neuronal growth and survival **(neurotrophic factors)** are important.

Plasticity in the developing visual system

In their pioneering studies Hubel and Wiesel demonstrated that at birth the input to laminae IV of the primary visual cortex (V1) is diffuse and that it is only during the **critical period** of development (in cats this is up to 3–14 weeks of postnatal life while in humans it may be several years) that these inputs segregate and form the basis of ocular dominance columns (see Chapter 23).

The segregation of input is dependent on the amount and type of activity within the afferent pathway from each eye; the greater this is, the more likely it is that the afferent input will gain control over those cortical neurons. Thus ocular dominance (OD) columns will form in the absence of competition between the input from the two eyes but will not develop when there is no afferent input from either eye.

Hubel and Wiesel experimentally manipulated the inputs by initially depriving one eye of an input by suturing it shut **(monocular deprivation)** and then in later experiments by reversing the procedure **('reverse suturing')**. Monocular deprivation created an expansion of the thalamic influence from the unsutured eye in layer IV with a subsequent shift in OD columns so that more cortical cells were under the control of the open eye. This pattern could be rapidly reversed by 'reverse suturing' during the critical period which implies that the initial shift in thalamic influence on cortical cells is caused by the activation of synapses that were present but functionally suppressed as there is not enough time for any axonal outgrowth. However, in time the initially suppressed synapses from the uncompetitive eye would be physically lost as the active thalamic input takes over the control of cortical cells.

The correct segregation of the ocular inputs into V1 as OD columns is important for the generation of many of the other visual functions in V1. However, once outside the critical period the ability to modify the visual cortex in such a fashion is reduced, but not lost.

Plasticity in the adult state

Somatosensory system and the vestibulo-ocular reflex

It is now known that the somatosensory system is capable of being remodelled in the face of alterations in the input from the peripheral receptors. Thus the loss of input from a digit (by amputation, for example) does not lead to a permanently silent area of cortex, but instead the adjacent cortical areas with sensory inputs from adjacent digits would sprout axons and exert influence over this initially silent cortical area.

Conversely, increased afferent information in a sensory pathway results in an expansion of the cortical area receiving that input. Simplistically, it can be imagined that the activity in a given afferent induces the production of a neurotrophic factor in the postsynaptic cell, which then binds to the appropriate receptor in the active presynaptic terminal promoting its growth and survival. In this way the CNS is constantly remodelling itself based on the amount and type of ongoing afferent information.

Subsequently it was discovered that major sensory deficits, such as the deafferentation of a whole limb, produced similar results which implied that the reclaiming of cortical areas by adjacent inputs was not solely achieved by the local sprouting of axons in the cortex.

A further example of the plasticity of the mature CNS is seen with the vestibulo-ocular reflex (see Chapter 26 and 33). The vestibular system provides a signal to the CNS on head velocity and this is relayed to the cerebellum via mossy fibres. The other input to the cerebellum, however — the climbing fibre can provide information on the degree to which the image is slipping across the retina (the degree to which eye movements are compensating for head movement). This input from the climbing fibre is not only important in providing a signal on the degree to which the reflex is working but provides a critical input to correct it. Thus if one alters the relationship between ocular and head movements by having the patient wear prisms, the reflex adapts with time to compensate for the new relationship and this adaptation is possible because the climbing fibre input can modify the parallel fibre (and so indirectly mossy fibre) input to the Purkinje cell (see Chapter 33). The basis for this latter modification at the level of the Purkinje cell, is an intracellular process and is termed **long-term depression** (**LTD**; see Chapter 33).

Limits on the regenerative capacity of the adult CNS

It must be realised that this regenerative capacity of the CNS is limited as:

1 all neurons are postmitotic in the mature CNS, and

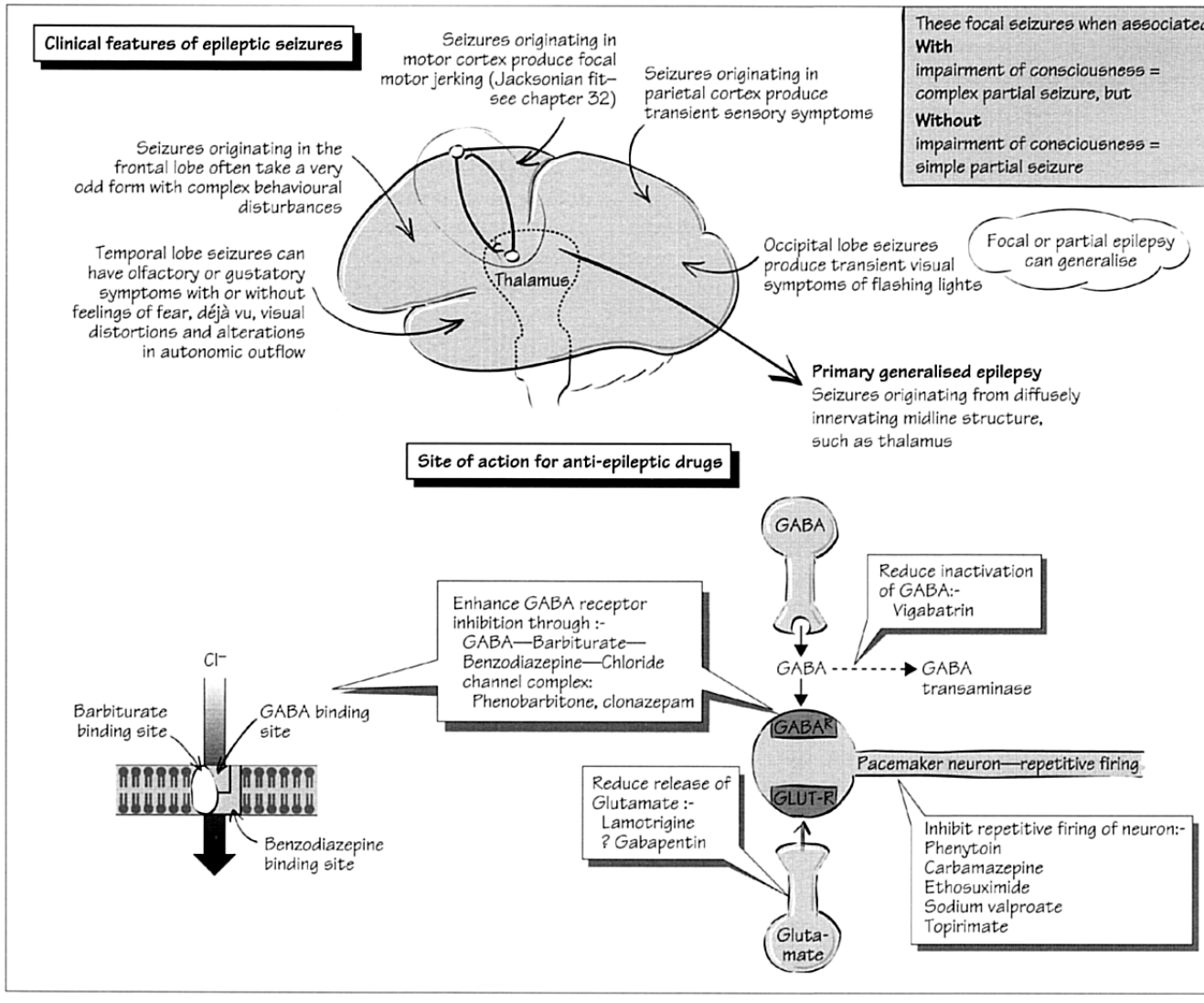
2 the glial cells in the CNS are generally inhibitory to axonal outgrowth (see Chapter 34).

Astrocytes produce signals that stop axons growing and oligodendrocytes produce a number of factors that repel axons or even cause the approaching axonal growth cone to collapse. This often becomes more apparent at the time of the CNS insult, when glial cells divide, become activated and form a glial scar.

Abbreviations

LGN	lateral geniculate nucleus of the thalamus
LTD	long-term depression
OD	ocular dominance column
V1	primary visual cortex

45 Neurophysiological disorders: epilepsy



Definition and classification of epilepsy

Epilepsy represents a transitory disturbance of the functions of the brain, that develops suddenly, ceases spontaneously and may be induced by a number of different provocations. It is the most prevalent serious neurological condition with a peak incidence in early childhood and in the elderly.

Patients with epileptic fits or seizures may be classified according to whether the fit is **generalised** or **partial (focal)** i.e. remains within one small CNS site, e.g. temporal lobe; whether there is an impairment of consciousness (if there is then it is termed **complex**) and whether the partial seizure causes secondary generalisation. Overall 60–70% of all epileptics have no obvious cause for their seizures, and about two-thirds of all patients stop having seizures within 2–5 years of their onset, usually in the context of taking medication.

Pathogenesis of epilepsy

The **aetiology of epilepsy** is largely unknown, but much of the therapy used to treat this condition works by modifying either the balance between the inhibitory γ-aminobutyric acid (GABA) and excitatory glutamatergic networks within the brain or the repetitive firing potential of neurons. The recording of the electroencephalograph (EEG; see Chapter 38) reveals that **epileptic fits** (so-called

ictal events) are associated with either generalised synchronous or focal spike and wave discharges, although abnormalities can be seen transiently at other times without overt evidence of a seizure **(interictal activity)**.

A generalised epileptic fit can take several forms but classically consists of a tonic (muscles go stiff)–clonic (jerking of limbs and body) phase followed by a period of unconsciousness. This used to be termed a grand mal seizure, but is now classified as a generalised tonic–clonic seizure. Petit mal epilepsy is now reclassified as a form of primary generalised epilepsy.

A model for the generation of an epileptic discharge is that the interictal activity corresponds to a depolarising shift with superimposed action potentials from an assembly of neurons. There follows a period of hyperpolarisation as these same neurons activate local inhibitory interneurons while becoming inactivated themselves.

With repeated interictal spikes the period of hyperpolarisation shortens and this activates a range of normally quiescent ion channels in the neuron as well as raising extracellular K^+ concentrations, all of which further depolarises the neurons. If sufficient neurons are activated (and the inhibition of local GABA interneurons overcome) then synchronous discharges are produced across populations of neurons which can lead on to a seizure. The seizure or synchronous discharge is then terminated by active processes of inhibition both within the neuron (through ion channels) and within the neuronal network by GABAergic interneuronal activity.

Although this model is useful as a means of understanding the cellular physiology of epilepsy irrespective of cause, it is clear that different forms of epilepsy have different underlying abnormalities. **Primary generalised epilepsy**, which is associated with diffuse EEG changes, is thought to result from abnormalities in specific calcium channels in the thalamus.

Whilst patients with ***complex partial seizures of temporal lobe origin***, may have a small scar in the mesial temporal lobe corresponding to neuronal loss and gliosis within the hippocampus, secondary to hypoxic or ischaemic events early in life.

Treatment of epilepsy

The treatment of epilepsy involves drug therapy or a surgical approach if an underlying structural lesion is identified and/or drug therapy is ineffective. Drug therapy is useful in all forms of epilepsy. Administration of a single drug will control the fits in 70–80% of patients with tonic–clonic seizures. Those poorly controlled patients may benefit from the addition of a second drug.

Mechanisms of action of antiepileptic drugs

These are not well understood. Some drugs (e.g. benzodiazepines, vigabatrin, phenobarbitone) enhance GABA-mediated inhibition, whilst others are Na^+-channel blockers (phenytoin, carbamazepine, valproate, lamotrigine). Ethosuximide, which is effective only in absences, inhibits the spike-generating Ca^{2+} current in thalamic neurones. Valproate also has this action on Ca^{2+} channels in addition to its effects on Na^+ channels, explaining its wide-spectrum of anticonvulsant action.

Carbamazepine and valproate are widely used because they have relatively few unwanted side-effects.

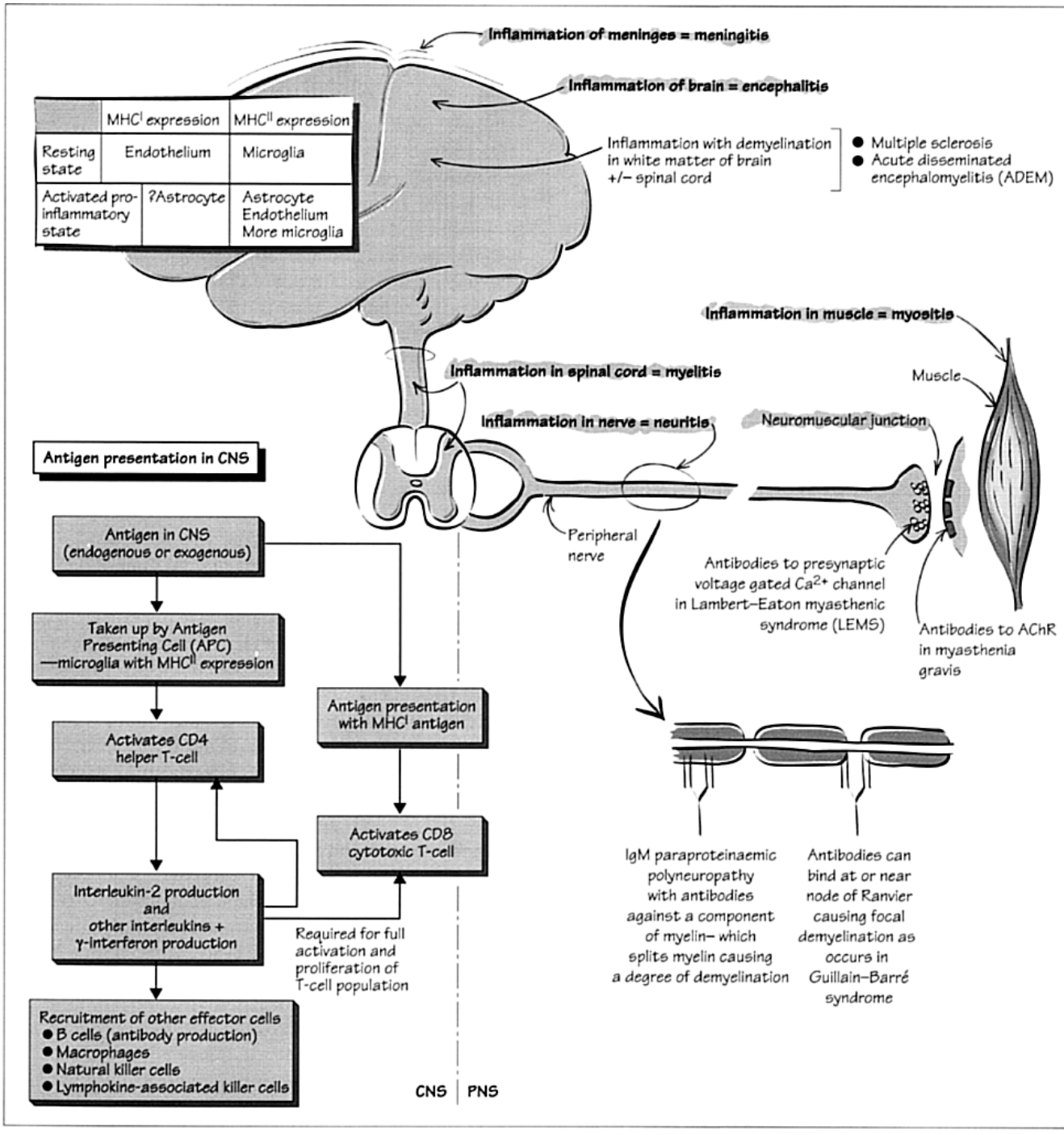
The advantages of **sodium valproate** are its relative lack of sedative effects, its wide spectrum of activity and the mild nature of its adverse effects (nausea, weight gain, bleeding tendencies and transient hair loss). The main disadvantage is that occasional idiosyncratic responses cause severe or fatal hepatic toxicity. For this reason **carbamazepine** is often preferred. Carbamazepine is metabolised in the liver to carbamazepine-10,11-epoxide, an active metabolite that partly contributes to both its anticonvulsant action and neurotoxicity. Mild neurotoxic effects are common (nausea, headache, drowsiness, diplopia and ataxia) and often determine the limit of dosage. Agranulocytosis is a rare idiosyncratic reaction to carbamazepine. **Phenytoin** is a difficult drug to use because of its complex metabolism such that it may take up to 20 days for the serum level to stabilise after changing the dose. Therefore, the dose must be increased gradually until fits are prevented, or until signs of *cerebellar disturbance* occur (nystagmus, ataxia, dysarthia). Other unpleasant side-effects including gum hypertrophy, acne, greasy skin, coarsening of the facial features and hirsuitism make the drug unpopular with patients, especially women. **Lamotrigine** is a newer drug. It seems to be similar to phenytoin but with fewer side-effects. **Phenobarbitone** is effective in tonic–clonic and partial seizures but is very sedative. Tolerance occurs and sudden withdrawal may precipitate status epilepticus. Side-effects include *cerebellar symptoms*, drowsiness in adults and hyperkinesia in children. **Vigabatrin, gabapentrin** and **topirimate** are newer agents introduced as 'add-on' drugs in patients where epilepsy is not satisfactorily controlled by other antiepileptics. **Ethosuximide** is only effective in the treatment of absences and myoclonic seizures (brief jerky movements without loss of consciousness). **Clonazepam** is a potent benzodiazepine anticonvulsant that is effective in absences, tonic–clonic seizures and myoclonic seizures. It is very sedative and tolerance occurs with prolonged oral administration.

Anticonvulsant therapy in pregnancy should be done cautiously because of the teratogenic potential of many of these drugs.

Abbreviations

EEG	electroencephalograph
GABA	γ-aminobutyric acid
GABA-R	GABA receptor
Glut-R	glutamate receptor

46 Neuroimmunological disorders



CNS immunological network

The CNS has relative **immunological privilege** compared with the PNS and most other parts of the body. The reason for this is that the **blood–brain barrier (BBB)** normally prevents lymphocytes, macrophages and antibodies from entering the CNS (see Chapters 4, 15). This, coupled to the very poorly developed lymphatic drainage system of the CNS, and the low level of expression of major histocompatibility complex (MHC) antigens means that antigen presentation is poor. However, breakdown of

the BBB can greatly alter this situation (e.g. ***multiple sclerosis (MS)***).

In the resting state some activated T-lymphocytes are able to cross the BBB and circulate within the CNS. In addition **MHC expression** is confined to only a few cells although the situation is different in the inflamed state. Thus once triggered an immune response can be amplified and propagated by the elaboration of cytokines and induced MHC expression with the opening up of the BBB.

In these circumstances the **microglia** are thought to be important as the **antigen presenting cells** and their interaction with T-helper lymphocytes is then pivotal in generating a full-blown immunological reaction.

Clinical disorders of the CNS with an immunological basis

Multiple sclerosis (MS)

MS is a common neurological disorder in which the patient characteristically presents with episodes of neurological dysfunction secondary to the inflammatory lesions within the CNS. Pathologically these lesions represent small areas of demyelination secondary to an underlying inflammatory mainly T-cell infiltrate—the trigger and target for which is not clear. The lesions often resolve with remyelination and clinical recovery, although with time a permanent loss of myelin ensues with secondary axonal loss and the development of fixed disabilities.

To date the most successful therapies are high-dose intravenous methylprednisolone that hastens recovery from acute relapses but does not alter the long-term disease process, and β-interferon that reduces the relapse rate but again has, as yet, an unproven role in modifying the long-term prognosis.

Acute disseminated encephalomyelitis (ADEM)

This is a rare inflammatory demyelinating disease of the CNS that occurs as a complication of a number of infections and vaccinations (e.g. measles and rabies vaccination). It is a monophasic illness (unlike MS) characterised by widespread disseminated lesions throughout the CNS which pathologically consist of an intense perivascular infiltrate of lymphocytes and macrophages with demyelination. This condition resembles **experimental allergic encephalomyelitis (EAE)** which is a well-characterised T-cell mediated disorder against a component of myelin (probably myelin basic protein; MBP) induced by inoculating animals with a combination of sterile brain tissue and adjuvants.

Other immunological diseases

A number of other diseases with an immunological basis can affect the CNS and these include those diseases that primarily affect blood vessels (the ***vasculitides***).

In addition, there is a rare group of disorders in which there is CNS dysfunction as a remote effect of a cancer; the so-called ***paraneoplastic syndromes***. In these conditions antibodies to components of the CNS are generated, presumably triggered by the tumour, which then lead to neuronal cell death and the development of a neurological syndrome, e.g. anti-Purkinje cell antibodies cause a profound cerebellar syndrome by the immunological removal of this cell type in the cerebellum. The exact mechanism by which these antibodies exert their effect is not known as antibodies normally do not cross the BBB, but pathologically there is often evidence of a lymphocytic infiltrate in the affected structure which implies that the antibody is capable of inducing an immune mediated process of neuronal loss.

Clinical disorders of the PNS with an immunological basis

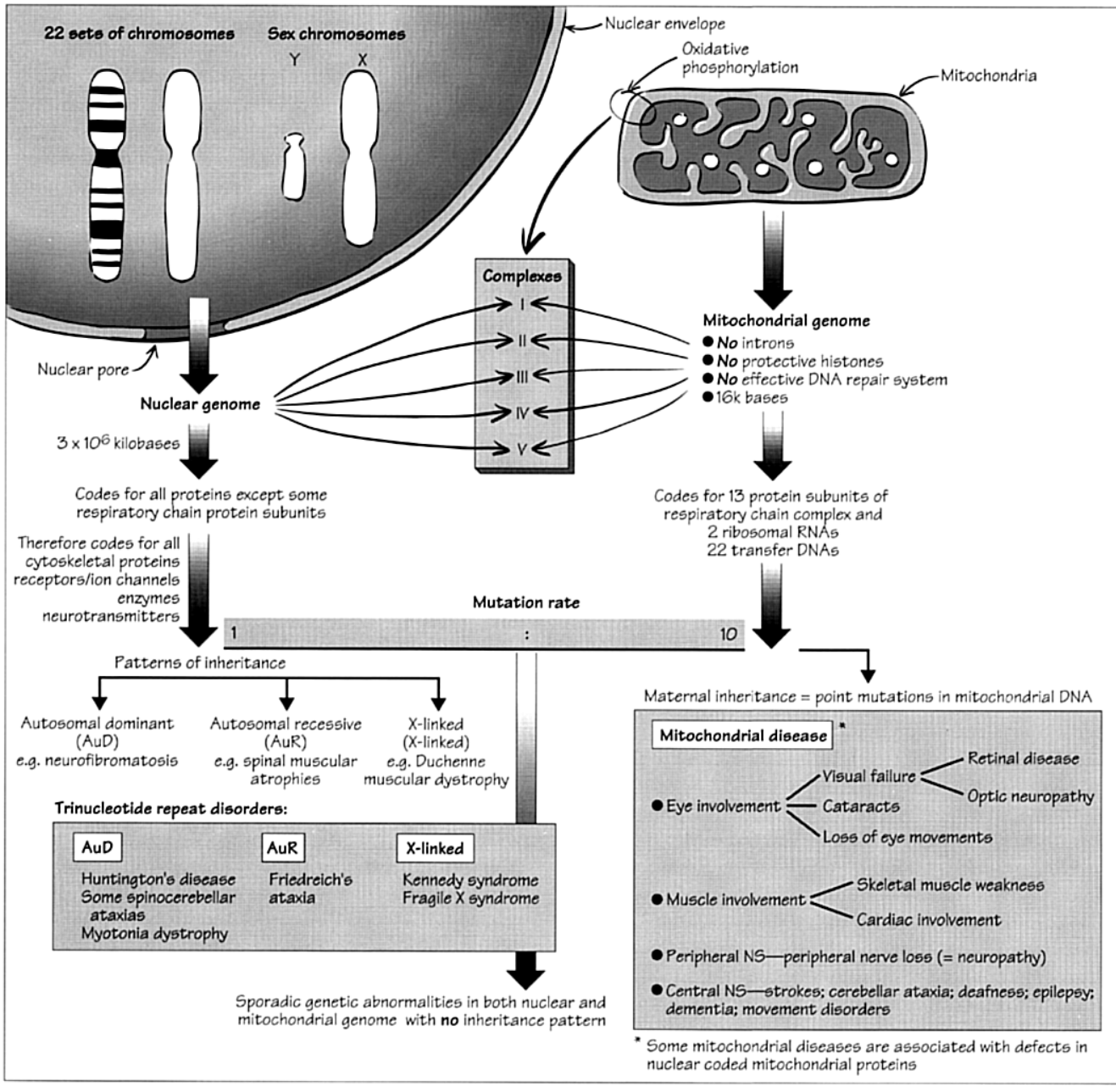
The PNS has fewer of the protective features of the CNS, so is more susceptible to more conventional immune mediated diseases:

- The **peripheral nerve** is affected by a number of immunological processes, including the ***Guillain–Barré syndrome***. In this condition there is often a preceding illness (e.g. *Campylobacter jejuni* or cytomegalovirus infection) that induces an immune response which then cross-reacts with components in the peripheral nerve (e.g. certain gangliosides). This then induces focal demyelination in the peripheral nerve, which prevents it from conducting action potentials normally (see Chapter 5). In time the patient usually recovers although he/she may require immunotherapy with either plasma exchange or intravenous immunoglobulin. A similar condition is seen in some diseases where excessive amounts of abnormal antibody are produced (the ***paraproteinaemias***).
- The **neuromuscular junction (NMJ)** can be affected by immunological processes as occurs in ***myasthenia gravis*** and the ***Lambert–Eaton myasthenic syndrome*** **(LEMS)** (see Chapter 7).
- **Muscles** can be involved in inflammatory processes. The commonest form of this is ***polymyositis*** which is a T-cell mediated condition associated with proximal weakness and pain. In contrast, ***dermatomyositis*** is a B-cell mediated disease centred on blood vessels that causes a painful proximal muscle weakness in association with a florid skin rash. This latter condition can represent a paraneoplastic syndrome in more elderly patients with tumours in the lung, breast, colon or ovary.

Abbreviations

AChR	acetylcholine receptor
ADEM	acute disseminated encephalomyelitis
BBB	blood–brain barrier
EAE	experimental allergic encephalomyelitis
LEMS	Lambert–Eaton myasthenic syndrome
MBP	myelin basic protein
MHC	major histocompatibility complex
MS	multiple sclerosis
NMJ	neuromuscular junction

47 Neurogenetic disorders



A large number of genetic disorders involve the nervous system, and some of these have pathology confined solely to this structure. The recent advances in molecular genetics have meant that many diseases of the nervous system are being redefined by their underlying genetic defect.

Two major new developments have revolutionised the role of genetic factors in the evolution of neurological disease. First, genes encoded in the maternally inherited **mitochondrial genome** can cause neurological disorders and, secondly, a number of inherited neurological disorders have as their basis an expanded trinucleotide repeat (so-called **triplet repeat disorders**).

Disorders with gene deletions

Many different disorders within the nervous system result from the loss of a single gene or part thereof. For example,

hereditary neuropathy with a liability to pressure palsies, in which the patient has a tendency to develop recurrent focal entrapment neuropathies in association with a large deletion on chromosome 17 which includes the gene coding for the peripheral myelin protein 22 (PMP 22).

Disorders with gene duplications

The duplication of a gene can, under some circumstances, cause disease. An example of this is in certain types of ***hereditary motor and sensory neuropathy***, where the patient develops distal weakness, wasting and sensory loss in the first decades of life. In some of these cases there is duplication of part of chromosome 17 including the gene coding for PMP 22.

Disorders with gene mutations

This is the most common form of genetic defect and in these diseases there is a mutation in the gene coding for a specific enzyme or protein which results in that product failing to work normally.

An example of such a situation is found in some familial forms of ***motorneuron disease*** (see Chapter 42) as well as ***myotonic syndromes*** (see Chapter 5).

Disorders showing genetic imprinting

Genetic imprinting is the differential expression of autosomal genes depending upon their parental origin. Thus disruption of the maternal gene(s) on a certain part of chromosome 15 (15q11-q13) causes the ***Prader–Willi syndrome*** (mental retardation with obesity, hypogenitalism, and short stature) while disruption of the same genes from the father causes ***Angelman's syndrome*** (a condition of severe mental retardation, cerebellar ataxia, epilepsy and craniofacial abnormalities).

Mitochondrial disorders

Mitochondria contain their own DNA and synthesize a number of the proteins in the respiratory chain responsible for oxidative phosphorylation (see Chapter 42), although the vast majority of mitochondrial proteins are encoded by nuclear DNA. Thus mitochondrial disorders (deletions, duplication or point mutations) can result from defects in either these nuclear coded genes, or the mitochondria genome. However, mitochondrial DNA mutates more than 10 times as frequently as nuclear DNA and has no introns (non-coding parts of the genome), so that a random mutation will usually strike a coding DNA sequence. As mitochondria are inherited from the fertilised oocyte, disorders with point mutations in the mitochondrially coded DNA show maternal inheritance (always inherited from the mother). However, within each cell there are many mitochondria and so a given cell can contain both normal and mutant mitochondrial DNA, a situation known as **heteroplasmy** and it is only when a given threshold is reached that disease results.

The clinical disorders associated with different defects in the mitochondrial genome are legion, and the reason why some areas are targeted in some conditions and not others is not clear.

Trinucleotide repeat disorders

A number of different disorders have now been identified that have as their major genetic defect an expanded triplet repeat, i.e. there is a large and abnormal expansion of three bases in the genome. In normal individuals triplet repeat sequences are not uncommon but once the number of repeats exceeds a certain number, the disease will definitely appear.

This pathological triplet (or trinucleotide) repeat either occurs in the coding part of a gene (e.g. ***Huntington's disease*** **(HD)**; see Chapter 34) or in a non-coding part of the genome (e.g. ***Friedreich's ataxia***). The resulting expansion either causes a loss of function (e.g. frataxin in ***Friedreich's ataxia***) or a new gain of function in that gene product (e.g. huntingtin in **HD**). This latter aspect is of interest as the new protein appears to have a function that is unique to it and which is critical to the evolution of the neurodegenerative process. However, the mechanism by which this protein produces selective neuronal death in specific CNS sites is not known as many of the mutant gene products are widely expressed throughout the brain and body.

The consequence of a large unstable DNA sequence as occurs in these disorders is that the triplet repeat can increase during mitosis and meiosis, resulting in longer triplet repeat sequences (so called **dynamic mutations**). This means that the most likely time for triplet expansion is during spermatogenesis and subsequent fertilisation/embryogenesis, and has two major implications. First, longer repeats tend to occur in the offspring of affected men and, secondly, longer repeats tend to occur in subsequent generations. This results in patients of subsequent generations presenting with earlier onset and more severe forms of the disorder—a phenomenon known as **genetic anticipation** as longer repeat sequences are associated with younger onset and more severe forms of the disease.

Abbreviations

AuD	autosomal dominant
AuR	autosomal recessive
HD	Huntington's disease
PMP 22	peripheral myelin protein 22

Appendix 1: Major neurotransmitter types

Neurotransmitter	Distribution	Receptor types	Associated disorders
Amino acids			
Excitatory			
Glutamate	Widespread throughout CNS	1. Ionotropic: Non-NMDA (AMPA kainate; quisqualate receptors) NMDA 2. Metabotropic	Epilepsy (Ch.45) Excitotoxic cell death (Ch.42)
Inhibitory			
GABA	Widespread throughout CNS	$GABA_A$ $GABA_B$	Spinal cord motor disorders (Ch.31) Epilepsy (Ch.45) Anxiety (Ch.41)
Glycine	Spinal cord	Glycine	Startle syndromes (Ch.31)
Monoamines*			
Noradrenaline (norepinephrine)	Locus coeruleus to whole CNS (Ch.11) Postganglionic sympathetic nervous system (Ch.36)	α1; α2 β1; β2	Depression (Ch.40) Autonomic failure (Ch.36)
Serotonin (5-hydroxytryptamine)	Raphé nucleus in brainstem to whole CNS (Ch.11)	$5HT_1$ (A–F) $5HT_2$ (A–C) $5HT_3$–$5HT_7$	Depression (Ch.40) Anxiety (Ch.41) Migraine
Dopamine	Nigrostriatal pathway in basal ganglia (Ch.34) Mesolimbic and mesocortical pathways (Ch.40) Retina (Ch.21) Hypothalamic–pituitary projection (Ch.37)	D1/D5 receptors on activation cause an increase in intracellular cAMP D2 receptors cause a decrease in intracellular cAMP on activation D3/D4 are independent of cAMP signalling system	Parkinson's disease (Ch.34) Schizophrenia (Ch.40) Control of pituitary hormone secretion (Ch.37) Control of vomiting
Acetylcholine	Neuromuscular junction (Ch.6) Autonomic nervous system (Ch.36) Basal forebrain to cerebral cortex and limbic system (Chs 39 & 42) Interneurons in many CNS structures including striatum (Ch.34)	Nicotinic Muscarinic (M1–M3 subtypes)	Disorders of the neuromuscular junction (Ch.6) Autonomic failure (Ch.36) Dementia of the Alzheimer type (Ch.42) Parkinson's disease (Ch.34) Epilepsy (Ch.45) Sleep-wake cycle (Ch.38)
Neuropeptides	Widespread distribution in CNS but especially are found in: dorsal horn of spinal cord (Ch.20) basal ganglia (Ch.34) autonomic nervous system (Ch.36)	Various	See: Pain systems (Ch.20) Basal ganglia (Ch.34) Autonomic nervous system (Ch.36) Neural plasticity (Ch.43) Anxiety (Ch.41)
Others			
Purinergic			
ATP			
Endozapines			

*Histamine and adrenaline are monoamines that are found primarily in the hypothalamus and adrenal medulla respectively.

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