EROS & THE PINEAL

The Layman's Guide to Cerebral Solitaire, by Albert Most

Venom Press

Editor's note: Some have thought the title misleading, since there is not obviously much in this essay concerning sexual love. It is concerned with ways of influencing experience by influencing the metabolic activity of the pineal gland. Better than sex? Maybe that depends on how old you are.

IMPORTANT CONSIDERATIONS

Much of our current knowledge about biogenic amines stems from ongoing investigations into the biological basis of mental illness. Various disorders of amine metabolism have long been implicated in the etiology of schizophrenia. In your quest for a fuller understanding, be aware of the dangers associated with manipulations of amine metabolism. Realize that even a small dose of tryptophan — if added to an existing amine imbalance — could cause a serious disturbance of indole metabolism. Furthermore, realize that MAO inhibitors can evoke recurrences and exacerbations of the psychosis of schizophrenic persons.

On the other hand, notice that there is no substantial evidence that a combination of l-tryptophan and an MAO inhibitor can induce a permanent psychosis in normal, healthy, nonpsychotic humans. Yet.

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to a future generation of

Classic Textbook Cases

Neither the author, illustrator, nor publisher assumes any liability for the

application of the information contained in this pamphlet. It is presented solely to further the quest for a fuller understanding of the human experience.

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PART ONE

THE PINEAL

Located almost in the center of your brain is a small projection of tissue called the pineal gland. It is shaped like a tiny pine cone, roughly a quarter of an inch long, and weighs about a tenth of a gram. Despite its small size, the pineal gland contains enormous amounts of serotonin, a physiologically active biogenic amine and chemical neurotransmitter. But pineal cells are not neurons and do not use serotonin for neurotransmission. Instead, pineal serotonin functions as a substrate for the enzymatic production of other biologically active molecules.

Nevertheless, the pineal gland is intimately related to the broad network of neurons that do release serotonin as a chemical messenger, An estimated several thousand of these serotonergic neurons are in the human brain. Their cell bodies are located almost exclusively in the midbrain, the pons and the medula oblongata. Some of their axons descend to ennervate the gray matter of the spinal cord; others ascend to the brain and terminate in the thalamus, limbic forebrain, and hypothalamus. Related by a common biogenic amine, the pineal gland and the serotonergic neurons play an important role in the regulation of mood, behavior and consciousness.

EROS?

A unique biochemical mechanism exists within the human pineal gland. A pair of naturally occuring pineal enzymes, hydroxy-indole-O-methyl transferase (HIOMT) and indole-N-methyl transferase (INMT), are capable of converting serotonin into a number of potent hallucinogens. Regulated by a variety of

neuroendocrine mechanisms, these enzymes normally act on specific substrates and function as catalysts in the formation of biogenic amines. However, if they get out of phase with their normal substrates and act on pineal serotonin, they form potent psychoactive compounds within the human brain.

Interestingly enough, pineal catabolism can be intentionally shifted toward the production of these endogenous hallucinogens by a simple manipulation of amine metabolism. If you increase the concentration of pineal serotonin and block its normal enzymatic inactivation, it becomes a substrate for other pineal enzymes, like HIOMT and INMT. As their names imply, HIOMT and INMT are methyl transferase enzymes. They catalyze the transfer of a methyl group from one compound to another. As these enzymes add methyl groups to the indole-oxygen and amino-nitrogen positions, serotonin is converted into 5-methoxy-N,N-dimethyltryptamine, a relatively unknown but extremely potent hallucinogen.

PART TWO

THE BLOOD-BRAIN BARRIER

Before attempting any manipulation of biogenic amines in the human nervous system it is essential to have a thorough understanding of the blood-brain barrier (BBB). The BBB is a selective barrier, which isolates the brain from substances circulating in the bloodstream. When blood composition fluctuates, the BBB functions as a protective insulator and attempts to maintain a relatively constant internal environment for neural cells, The BBB is basically a barrier to the diffusion of molecules between the bloodstream and brain tissue. Existing at capillary levels this barrier can be understood by examining the capillary junctions and the nature of lipids and proteins within the cell membrane.

CELL MEMBRANE

Another important factor in the barrier to diffusion is the nature of the endothelial cell membrane. The membrane consists of phospholipid molecules (lipids) and specialized proteins. The lipids form the structural framework of the membrane and an anchoring structure for the various protein molecules.

LIPIDS

Each lipid molecule has a polar head and two non-polar tails. The polarity in the head results from the molecular interaction between the oppositely charged phosphate and nitrogen groups. The resulting dipole makes this part of of the molecule polar and, therefore, water soluble. It is called the hydrophilic, or water-loving, portion of the lipid molecule. In contrast, the two tails of each lipid

molecule are non-polar and water insoluble. They are composed of long-chain fatty acids which are hydrophobic, or water-hating, in nature. The tails are joined to a backbone molecule which, in turn, is attached to the polar head.

Because they each contain a hydrophilic and hydrophobic end, lipid molecules naturally form a bilayered membrane. The polar, water-soluble heads point toward the water on the inside and outside of the cell, while the non-polar, fatty-acid tails point away from water and toward the membrane interior. The resulting bilayer of lipid molecules contains an oily inner core, It functions as a selective barrier permeable to lipid-soluble substances and impermeable to polar, water-soluble substances.

CAPILLARY JUNCTIONS

One important factor in the BBB is the tightness of junctions between the cells of the brain capillaries. Throughout the body, capillaries are composed of endothelial cells — a single layer thick — which form a thin membrane between the bloodstream and the surrounding tissue. In the general capillaries of the body, the cells circle upon themselves but leave small gaps between adjacent cells. Water-soluble substances can easily diffuse through these gaps into the surrounding tissue.

In the brain capillaries, however, the endothelial cells circle upon themselves and form a barrier to diffusion. Adjoining edges are overlapped and fused, creating extremely tight junctions between cells. Substances that might easily diffuse through the gaps in general capillaries are blocked by the close connections between brain endothelial cells. The first factor, the tightness of these junctions, not only prevents intracellular diffusion but creates an extended cell membrane along the length of the brain capillaries.

PROTEINS

Various proteins are also associated with the membrane. They may support either the inner or the outer surface. They may be contained partially within one of the surfaces, or they may extend completely through the lipid bilayer. Some of these proteins are highly specialized molecules that capture specific substances from the bloodstream and transport them through the lipid barrier. Those proteins that extend through the membrane may actually transport substances through pores within themselves. Other proteins may combine with a substance at one membrane surface, diffuse across the lipid bilayer, and dissociate from the substance at the other surface.

AMINO ACID CARRIER PROTEINS

Different protein molecules transport different substances necessary for normal

brain function (amino acids, sugars, salts). Each of the amino acid carrier molecules has specificity for either basic, acidic, or neutral amino acids and is also selective toward the size of the molecule — clearly differentiating between large and small amino acids. For example, one type of carrier protein recognizes, captures and transports only the large neutral amino acids, tryptophan, leucine, isoleucine, valine, tyrosine, and phenylalanine — all large neutral amino acids — compete for this carrier. Transport is proportional to blood concentration. If one amino acid is proportionally higher in concentration it is preferentially transported through the membrane.

PART THREE

A SIMPLE MANIPULATION

Attempting to increase the amount of serotonin in the human nervous system might initially seem to require a supply of serotonin. How simple it would be if brain concentrations could be increased just by the ingestion of pharmaceutical serotonin or, for that matter, any of the many foods which contain serotonin. Unfortunately, this is not the case. Brain levels are not increased by dietary supplements; blood levels are elevated, but the BBB effectively blocks the diffusion of serotonin into brain tissue.

In the bloodstream, at physiological PHI the serotonin molecule exists in the ionized form. An electrical charge from the hydroxy group on the indole ring creates polarity in the molecule. As a result, serotonin has poor lipid solubility; it is more soluble in water than in oils or lipids. It can neither dissolve in nor diffuse through the lipid bilayer of the BBB and has no specific carrier molecule. Therefore, dietary serotonin can neither leave the bloodstream nor enter brain tissue.

TRYPTOPHAN

Cerebral serotonin is normally synthesized from l-tryptophan, its necessary precursor. Tryptophan is an essential amino acid. That is, it cannot be synthesized in the human body, it must be obtained from ingested protein or amino acid supplement. Unlike serotonin, dietary tryptophan can penetrate the BBB and enter brain tissue.

The process begins with digestion. Dietary tryptophan is absorbed into the bloodstream, where most of it circulates bound to albumin, a plasma protein. Tryptophan is unique; it is the only amino acid that binds to plasma proteins, The other large neutral amino acids are completely unbound.Valine, leucine, isoleucine, tyrosine, and phenylalanine all circulate in free form within the bloodstream. But most tryptophan is bound. Only 10 percent circulates unbound

in a free form and, naturally, only free, unbound tryptophan is able to leave the bloodstream. At the BBB the unbound tryptophan competes with the other large neutral amino acids for the specialized carrier molecules that transport these amino acids into the brain. Transport is proportional to blood concentration, Therefore, the amount of tryptophan that penetrates the BBB is ultimately determined by the ratio between free, unbound tryptophan and competing amino acids.

TRYPTOPHAN LOADING

The ratio between tryptophan and the other large neutral amino acids is easy to manipulate. Dietary supplements of l-tryptophan are available over the counter at any pharmacy. Ingestion of several grams increases the amount of bloodstream tryptophan without raising the levels of competing amino acids. However, most of this supplemented tryptophan binds to blood serum proteins. Only 20 percent circulates in the free, unbound form. And, since only the unbound form is able to penetrate the BBB, the proportion of free-to-bound tryptophan becomes quite important.

Interestingly enough, both the ratio of tryptophan to competing amino acids and the proportion of free-to-bound tryptophan can be manipulated by the ingestion of a candy bar. Carbohydrate consumption stimulates the release of insulin from the pancreas. Insulin, in turn, lowers the plasma concentration of glucose and simultaneously enhances the uptake of branched-chain amino acids into muscle. These are the same amino acids which normally compete with tryptophan for transport through the BBB. As their blood concentration decreases, tryptophan continues to circulate in both the free and bound form. But insulin affects this equilibrium as well and releases tryptophan from its binding sites and the albumin molecules. Free, unbound tryptophan increases in concentration, achieves the competitive advantage at the BBB, and is preferentially transported through the endothelial cell membrane by carrier proteins.

SYNTHESIS OF SEROTONIN

After penetrating the BBB, tryptophan is taken up by the paraneuron cells of the pineal as well as the neurons of the serotoneoic pathway. Once inside, tryptophan diffuses to intracellular sites rich in the metabolic enzymes which convert it into serotonin.

The conversion is a two step process. In the first step, an enzyme called tryptophan-5-hydroxylase adds a hydroxyl group to the 5 position on the indole ring. Then a second enzyme called aromatic amino acid decarboxylase removes the carboxyl group from the amino acid side chain. The product, 5-hydroxytryptamine, is commonly called serotonin.

Increased amounts of serotonin are noticeable in brain tissue within two to three hours after the ingestion of a candy bar and a couple of grams of l-tryptophan. Employing a simple manipulation of blood chemistry, this method circumvents the BBB and increases the concentration of serotonin in the human nervous system.

MONOAMINE OXIDASE (MAO)

Normally the major pathway in the catabolism of serotonin involves inactivation by the mitochondrial enzyme monoamine oxidase (MAO). In a process called oxidative deamination, MAO converts as much as 80 percent of the body's serotonin into a physiologically inactive metabolite. As serotonin binds to the enzyme's active sites MAO removes the amine function and renders the molecule harmless and ineffective.

MAO is an important catabolic enzyme in the human body. It is the major enzyme involved in the breakdown and inactivation of serotonin. Any drug that interferes with the function of this enzyme is, by definition, an MAO inhibitor.

MAO INHIBITORS

MAO inhibitors can be classified by long-term or short-term inhibition. The long-term MAO inhibitors bind irreversibly to the enzyme and therefore, exert their effects long after the drug is cleared from the body. New MAO protein must be synthesized in the cell body in order to terminate the inhibition. This usually requires a period of ten to twenty days. [This irreversible MAO inhibition was presumably the biochemical basis of the McKenna brothers' 3-week psychedelic voyage in the Amazon in 1971, as described in *True Hallucinations*. — Ed.] In contrast, a short-term MAO inhibitor is reversible on the order of three to six hours. The harmala alkaloids, harmine and harmaline, for example, are especially potent, short-term MAO inhibitors. A small oral dose (25-50 milligrams) temporarily prevents physiologically active amines, like serotonin, from binding to the active site of the MAO molecule and undergoing deamination. For three to six hours, the harmala alkaloids interfere with the function of MAO before their action is reversed and MAO activity restored.

ENDOGENOUS HALLUCINOGENS

A combination of l-tryptophan and a short-term MAO inhibitor creates a favorable condition for the formation of psychoactive tryptamines within the human pineal gland. Tryptophan loading produces a significant increase in brain tryptophan levels and a subsequent increase in serotonin levels. When its major inactivation pathway is blocked by MAO inhibition, serotonin becomes a substrate for other pineal enzymes. Two methyltransferase enzymes, HIOMT and INMT, are capable of converting excess serotonin into a number of psychoactive

derivatives.

HIOMT, localized exclusively within the pineal gland, specifically catalyses the transfer of a methyl group to the oxygen located at the five position an the indole ring. In other words, HIOMT converts a 5-hydroxy-indole into a 5-methoxy-indole. This enzyme converts serotonin, 5-hydroxytryptamine, into a psychoactive compound called 5-methoxytryptamine. In turn, this compound becomes a substrate for INMT, another pineal methyltransferase enzyme.

INMT specifically catalyses the transfer of methyl groups (one at a time) to the amine nitrogen on an indole side chain. The resulting monomethyl intermediate, 5-methoxy-N-methyltryptamine, is also psychoactive, but it is quickly converted to the dimethyl derivative by INMT. The final molecule — endogenously produced in the human pineal gland — is 5-methoxy-N,N-dimethyltryptamine, a relatively unknown but extremely potent hallucinogen.

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