REVIEW ARTICLE

Serotonin: A review

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Serotonin is an almost ubiquitous substance in the animal and plant kingdom. It has such widely different sources as pineapples, bananas and plums; stings and venoms of wasps, scorpions and the common stinging nettle; and tissue cells of fish, amphibians, reptiles and man.

The discovery of this biogenic amine was made independently by two different groups of investigators. In Italy, in the 1930's, Ersparmer[1] observed that extracts of the gastric and intestinal mucosa which contained the so-called enterochromaffin cells, caused contraction of the smooth musculature of the gut and uterus. They named the active principle of the extracts enteramine, and gradually accumulated a great deal of information about its distribution and pharmacological activity. Almost at the same time, at the Cleveland Clinic, Rapport, Green and Page[2] isolated a vasoconstrictor substance which appears in serum after blood has clotted. They coined the name serotonin for this vasoconstrictor and subsequently showed that chemically it is an indolalkylamine, 5-hydroxytryptamine. In 1951 the synthesis of serotonin was successfully accomplished, and a year later it was established that enteramine and serotonin have an identical chemical structure. As soon as the new substance became available, diverse types of research began and the two original notions of Ersparmer and Page, that 5-hydroxytryptamine is concerned with contraction of the intestine and peristalsis, with coagulation and vasoconstriction, became gradually extended over an unexpectedly wide area.

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Origin and distribution in the body

The distribution and content of serotonin in the body varies in different species. The amount in the body of an adult man is about 10 mg., found mainly in the enterochromaffin cells of the intestinal mucosa. Large amounts are contained in the blood platelets and in certain areas of the brain. In rats and mice there are additional stores of serotonin in mast cells, but in man, mast cells neither synthesize nor store serotonin.

In the living body the precursor of serotonin is tryptophan. Tryptophan is an essential amino acid; i.e., its omission from the diet of man or animals is promptly followed by tissue wasting. The body needs from 6 to 9 mg. of tryptophan per kilogram body weight to prevent negative nitrogen balance. Not all of the ingested tryptophan required for maintenance is utilized; half of the ingested amount may be found excreted in the urine. A normal person converts about 1% of the metabolized tryptophan into serotonin. This conversion is accomplished in two steps. The enzyme hydroxylase adds a hydroxyl group to the tryptophan in position 5, and 5-hydroxytryptophan is formed. In the next step the enzyme decarboxylase removes a carboxyl group, and the end result is 5-hydroxytryptamine, or serotonin. Cells of the living body either themselves synthesize serotonin or take it up from the blood stream. Some cells do both.

The distribution of serotonin synthesized *in vivo* can be followed if one injects the precursor, 5-hydroxytryptophan, tagged with a radioactive label. The uptake of serotonin by various tissues of the body can be determined if one injects radioactive serotonin. Within a few minutes about half of the injected amount is metabolized and the rest is taken up by various tissues of the body, such as the reticulo-endothelial cells of the spleen and liver, the septal cells of the lung, and the platelets. The most important removal sites of serotonin are the lungs. This property of the lungs was shown for the first time about 50 years ago, when Starling and Verney caused the vasoconstrictor activity of blood to disappear by perfusing it through the lungs of a dog.

Serotonin is taken up into cells from the extracellular fluid by an active transport mechanism called the "amino pump". This pump can be blocked by reserpine, following which the tissues become depleted of their serotonin content. Inside the cells and platelets, serotonin is contained in cytoplasmic granules. In cells of the central nervous system serotonin is locally synthesized and becomes contained in synaptic vesicles of the axon terminals of serotonergic nerves. Exogenous serotonin, in order to reach the brain tissue, must be injected directly into the cerebral ventricles, since, except for very small amounts, it does not pass the blood-brain barrier. Many tissues, such as lung, spleen, liver, brain and the enterochromaffin cells of the gut, take up serotonin from the circulation or extracellular fluid even though they contain locally produced endogenous serotonin. Platelets are an exception—they acquire the amine solely from the

blood. They are unable to synthesize serotonin because they lack the necessary decarboxylase.

The concentration of serotonin in tissues can be determined from bioassays or by spectrophotofluorometry. Bioassays are based on the contracting effect of serotonin on smooth muscle. They employ a variety of biological materials like rat stomach strip, colon or uterus, the heart of the mollusc *Venus mercenaria* and others. Spectrophotofluorometry utilizes the intense fluorescence exhibited by serotonin. The concentration of serotonin in normal human blood is 0.05 to 0.5 μg. per ml.; it is contained almost exclusively in the platelets.

The degradation of serotonin is effected by the enzyme monoamine oxidase, which removes the amine group and converts serotonin into its urinary excretion product, 5-hydroxyindole acetic acid (5-HIAA). Very small amounts are excreted as conjugates of glucuronic acid and as ethereal sulfates. The amount of 5-HIAA excreted daily by a normal adult person is 1 to 10 mg. The excretion of the chief metabolite is increased when large quantities of bananas, pineapples or nuts containing serotonin are ingested. If the excretion exceeds 25 mg. in 24 hours, the presence of a malignant carcinoid, a tumour of enterochromaffin cells, is to be suspected.

The enzymes hydroxylase, decarboxylase and monoamine oxidase are present in most tissues of the body. There is a striking similarity between the enzymes responsible for the synthesis and degradation of serotonin and epinephrine: the rate-limiting step for synthesis is at the level of hydroxylation in position 5. The particular amino acid is tryptophan for serotonin and phenylalanine for epinephrine. Oral administration of p-chlorophenylalanine, the tryptophan hydroxylase inhibitor, causes selective depletion of brain serotonin. The destruction of either serotonin or epinephrine can be delayed by monoamine oxidase inhibitors.

Physiological effects

As far as physiological activities are concerned, it is characteristic of serotonin that its actions tend to be variable. The variability is of such a degree that responses differ not only from species to species, but also between animals of the same species, and even in successive tests in the same individual. This variability obviously leads to much controversy, since many discrepant reports exist.

The effect on the cardiovascular system exemplifies uniquely the complexity of responses one can obtain with serotonin. The direct effect on the smooth muscle of blood vessels can lead to either vasoconstriction or vasodilatation, depending on the particular vessels influenced. Moreover, many of the effects of serotonin are reflexly mediated, and since it affects sensory nerve endings, additional pressor or depressor reflexes can be evoked. If one excludes nervous control of blood vessels by denervation, serotonin leads to powerful vasoconstriction. Renal, placental and umbilical vessels also respond with vasoconstriction, whereas coronary vessels and vessels of the skeletal muscle respond with vasodilatation. The effect of serotonin on the blood pressure of man consists of three phases: first there is a brief *early depressor phase* following immediately after the injection; then comes *the pressor phase,* as serotonin increases the total peripheral resistance; and finally, when serotonin dilates the vessels of the skeletal muscles, a *late depressor phase* is observed.

Serotonin influences respiration by stimulating the carotid and aortic chemoreceptors. This results in a short-lasting increase in respiratory minute volume. Also, serotonin stimulates directly the smooth muscle of the bronchi, leading to bronchoconstriction. The alimentary tract is stimulated to greater motility by serotonin. Doses of different magnitude cause increased tone or intense spastic contractions, colic and evacuation of the bowels. In addition to causing contractions of the smooth muscle of the intestine, bronchi and blood vessels, serotonin stimulates the smooth muscle of the isolated uterus, urethra and nictitating membrane. An injection of a small dose of serotonin causes an intense stimulation of sensory nerves: in man there is a pain at the site of injection, followed by gasping, hyperventilation, substernal pressure, coughing, "tingling and pricking all over" and nausea.

In addition to all of its effects on smooth musculature, serotonin acts as a neurohumoral transmitter in certain areas of the central nervous system. Large stores of serotonin are contained in synaptic vesicles of the long descending nerve fibres in the mesencephalon, diencephalon and spinal cord. The brain possesses all the enzymes necessary for synthesis as well as for destruction of serotonin. The turnover is fast; the half-life is only a few minutes. Nerves liberating serotonin as their neurohumor have been identified by histochemical fluorescent techniques. They are called serotonergic or 5-hydroxytryptaminergic nerves; their function is so far not clearly understood.

A number of drugs, such as ergot alkaloids and derivatives of lysergic acid, are chemically related to serotonin. These drugs inhibit the primary action of serotonin on smooth muscle or nerve elements and are therefore called serotonin antagonists. Most of these drugs are at the same time active upon the central nervous system as potent hallucinogens. The latter observation prompted an almost immediate speculation about a possible involvement of serotonin in mental disorders. One thought that if serotonin antagonists caused hallucinations, derangements in serotonin metabolism could cause mental disorders like schizophrenia. The latter hypothesis was considerably weakened when a potent serotonin antagonist, d-bromlysergic acid diethylamide (BOL-148), turned out to be non-hallucinogenic.

Another quite different field in which serotonin was proved to be deeply involved is carbohydrate metabolism. In the liver fluke *Fasciola hepatica,* as well as in the isolated rat liver, serotonin increases the formation of adenosine 3′-5′-monophosphate, which activates phosphorylase and leads to glycogenolysis. In other words, *in vitro,* serotonin acts very similar to adrenaline. There are conflicting reports about the effect of serotonin on the blood sugar level of

the intact animal. However, if the appropriate dose is given, or if the counterbalancing effect of insulin is removed, hyperglycemia is observed.

Clinical considerations

There are several disease states in which serotonin is or may be involved. The most dramatic symptoms are presented by the malignant carcinoid. This is a metastasizing tumour of enterochromaffin cells of the gut, and is characterized by an excessive synthesis, storage and release of serotonin. Blood levels of serotonin become elevated about 100 times above the normal, and the excretion of 5-hydroxyindole acetic acid is also considerably increased. The symptoms of the disease include intermittent attacks of colic, watery diarrhea, bronchoconstriction, tachypnea, tachycardia, hypotension and intense flushing. The flushes always appear at the same site and are of many peculiar pinkish and bluish shades. In advanced cases they can be evoked by massaging the liver. The flushes are due to venous constriction, and the pooling of blood in passively dilated capillaries of the skin. As the hemoglobin is gradually reduced within the stagnant blood of the capillaries, the initial red flush changes to a blue cyanotic hue. The tumour forms metastases mainly in the liver. These contain very high concentrations of serotonin, and hence the level of serotonin in blood reaching the right heart is also excessively elevated. As a result, endomyocardial fibrosis of the right heart develops. Even though the carcinoid syndrome had been described in the medical literature as late as 1953, the clinicians became so impressed by its signs that soon it was immortalized in the following limerick by Bean and Funk:[3]

> This man was addicted to moanin',
> Confusion, edema and groanin',
> Intestinal rushes,
> Great tricoloured blushes,
> And died from too much serotonin.

Serotonin, however, is not the sole cause of the manifold symptoms of carcinoid; substances like histamine, bradykinin, kallikrein, and possibly others released by the tumours also contribute to the signs.

There are several other disease states in which serotonin seems to be involved. However, our knowledge of the activity of serotonin in health and disease is merely fragmentary, and we are unable to interpret or fully to integrate all the observations that have been made. For example, it is interesting that endomyocardial fibrosis is quite frequent in populations whose diets contain large amounts of serotonin. Natives of Africa, eating large quantities of bananas and plantain, seem to detoxify and excrete serotonin much less efficiently than do people in general. The condition is aggravated if the natives suffer from protein malnutrition. Serotonin seems to be involved somehow in active rheumatic arthritis: an injection of serotonin causes pain, erythema and severe cyanosis. The symptoms cannot be evoked by injecting histamine, epinephrine, norepinephrine or acetylcholine; they can be blocked immediately by the serotonin antagonist BOL-148. Serotonin is implicated in anaphylactic reactions in certain animal species, and in endotoxin shock in the dog. It stimulates fibrinolytic activity, especially following circulatory arrest and release. The concentration of serotonin is decreased in the plasma of children with phenylketonuria. Injections of serotonin can cause renal cortical necrosis from excessive vasoconstriction. Pregnant rats react to an intraperitoneal injection of serotonin by abortion, preceded by hypoxic and degenerative lesions of the placenta. Serotonin has an anti-mouse tumour effect: when injected directly into the tumour, it destroys metastases of sarcoma growing in lymph nodes of mice. Drinking alcohol has a profound effect on serotonin metabolism: the amount excreted as 5-HIAA is decreased and, instead, large amounts are excreted as glucuronide and sulfate conjugates of 5-hydroxytryptophol. The dumping syndrome which occurs after gastrectomy in some patients is also characterized by flushing, tachycardia, palpitation, epigastric discomfort, explosive diarrhea and elevated urinary excretion of 5-HIAA; serotonin and bradykinin are probably the causative agents. Lack of serotonin plays a role in migraine headaches. Serotonin has a strong tonic constrictor effect on scalp arteries, and if this humoral stimulation ceases, the arteries dilate and migraine headache develops. In susceptible subjects one can elicit typical migraine headache by a dose of reserpine, which depletes the stores of serotonin, and conversely the headache can be ameliorated by a dose of serotonin. Serotonin is involved in the response of the body to injury. It is an important amine in inflammation, since it stimulates phagocytosis. Wound healing in rats subjected to injury is greatly delayed if the skin has been depleted of serotonin. Serotonin protects the body against the lethal effects of total body irradiation.

Pharmacological aspects

Serotonin belongs to the group of autacoids, i.e. substances of intense pharmacological activity that are normally present in the body and that cannot be classed with hormones or neurohumors. Other representatives of the autacoid group are histamine, angiotensin, bradykinin and kallidin. All of these substances have a very wide range of pharmacological activities, even though they exert their effect in minute amounts. Their physiological role in the body cannot be exactly defined, and the value and place of these drugs in therapeutics are not precisely stated. There is, however, general agreement that autacoids are important in the body's overall regulation and economy, employed as they are in the execution of various functions in health and disease. Serotonin, viewed from this point of view, is a regulatory humor which aids the organism to adapt to its changing environment. It is present in great abundance earlier in the phylogenetic scale; later, in more advanced forms, it is associated with the catecholamines in the fulfilment of similar but not identical functions.

Conclusion

Serotonin's low grade of specificity is that property which enables it to serve its many diverse functions, although it is present in vanishingly small amounts in the body. Serotonin, however, is not used therapeutically. Drugs that

antagonize its action or interfere with its metabolism have been tried in the therapy of disease states in which serotonin plays a part. It seems that the involvement of serotonin in the metabolic activities of the body is so manifold[4] that each new scientific observation in the field discloses still newer and wider horizons. As Page and McCubbin[5] prophesied in 1956, serotonin has truly become a "tenure for the pharmacologist", and is becoming one for the physiologist and the clinician as well.

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