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THE CONCENTRATION OF SEROTONIN IN THE BRAIN IS DETERMINANT FOR ITS BIOLOGICAL RESPONSE

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ABSTRACT

Serotonin (5-HT) is a neurotransmitter that acts both in the central nervous system (CNS) and peripherally, and affects cell proliferation and migration. 5-HT plays a role in psychiatric diseases where it is deficient. 5-HT acts on smooth muscles where it can cause contraction or dilation and can also act on sensory nerve endings, causing pressor or depressor reflexes. 5-HT can cause contrasting biological effects. For example, 5-HT causes strong vasoconstriction in blood vessels, while in skeletal muscle vessels, it causes vasodilation. In the CNS, 5-HT participates in numerous functions such as the regulation of mood and sleep, the modulation of body temperature, sexuality, cognitive functions, and appetite. There are 4 classes of 5-HT receptors: slow-acting 5-HT2R which releases calcium ions (Ca^{++}), 5-HT4R, 5, 6, and 7, which increase cAMP, 5-HT1/5R which decreases cAMP, and fast-acting 5-HT3R that promotes the flow of Na^{+} or K^{++}. The 5-HT1AR receptor binds the 5-HT and is involved in the regulation of stress and tissue defence, while the 5-HT2AR receptor is a mediator of stress in the active phase. A more in-depth study on 5-HT and its reuptake, could lead to the discovery of new drugs for treating depression and neuropsychiatric diseases. Pharmacological treatment of neurological disorders due to changes in 5-HT levels can certainly improve the patient's quality of life.

KEYWORDS: *serotonin, 5-HT, neurotransmitter, psychiatric disease, CNS, 5-HT receptor*

INTRODUCTION

Serotonin is a biogenic amine that is produced by both the plant and animal kingdoms, including humans (1). In 1930, the Italian researcher Erspamer reported that tissue extracts from the gastrointestinal system contained particular cells called enterochromaffin, which caused the contraction of smooth muscles (2). The substance responsible for these biological effects was first called enteramine (3). Subsequently, Rapport, Green, and Page isolated a vasoconstrictor molecule similar to enteramine which they gave the name ‘serotonin’ or 5-hydroxytryptamine (5-HT) (4).

The biosynthesis of endogenous 5-HT derives from tryptophan, an essential amino acid that is introduced into the body through the diet and excreted in the urine. Tryptophan is converted into 5-hydroxytryptophan thanks to the action of tryptophan hydroxylase. Only 1% of introduced tryptophan is converted to 5-HT through a hydroxylase enzyme that adds a hydroxyl group to tryptophan at position 5 to form 5-hydroxytryptophan (5). Subsequently, the decarboxylase enzyme removes the carboxyl group to form 5-HT (6). The synthesis of 5-HT varies by species and tissue type, and in humans, 5-HT is mostly concentrated in platelets and brain and intestinal mucosa (7). Human immune cells, such as mast cells (MCs), do not contain 5-HT, while those of rodents, such as rats and mice, do contain it and it is stored in granules (8).

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5-HT is ubiquitous in the organism and is a neurotransmitter peptide along with other hormones such as substance P, somatostatin, and vasoactive intestinal polypeptide. Platelets in human blood contain the majority of 5-HT, which is degraded by the tissue enzyme monoamine oxidase (MAO) by removing the amino group and converting 5-HT into 5HIAA excreted in the urine (9). 5-HT mediates intestinal tissue contraction and peristalsis, coagulation, vasoconstriction, and many neurological functions (10). Macrophages treated *in vitro* with 5-HT are stimulated to phagocytosis, an important effect in the inflammatory process that could also be extended to brain microglial cells.

DISCUSSION

5-HT is a neurotransmitter implicated in psychiatric diseases. Most studies on this topic indicate that there is decreased availability of the 5-HT transporter in patients with psychiatric disorders (11). These studies suggest new avenues for anti-depressant treatment to elucidate response mechanisms to selective 5-HT reuptake inhibitors (SSRIs) and provide a basis for pharmacological treatment (12).

5-HT is stored in neurons, platelets, enterochromaffin cells, and MCs of rodents. The cytoplasmic granules of platelets contain 5-HT, whereas in neurons, 5-HT is synthesized locally in the synaptic vesicles of serotonergic nerves (13). When injected experimentally into the bloodstream, 5-HT does not reach the CNS because it is blocked by the blood-brain barrier (BBB) (14). However, when the BBB is disrupted, the brain, and other organs of the body, absorb 5-HT from the bloodstream and body fluids, while platelets, which do not synthesize 5-HT, only take it from the blood. The effectiveness of the biological contractive effect of 5-HT is verified *ex-vivo* through the contraction of strips of stomach or heart tissue of experimental animals (15). However, this effect depends on 5-HT concentrations.

The biological effects of 5-HT are variable and differ between animal species, between human individuals, and in different tissues. For example, 5-HT can cause vasoconstriction or vessel dilation on the smooth muscle of the cardiac vessels depending on the type of vessel on which it acts (16). At a cerebral level, 5-HT acts on nerve sensory endings where it can cause pressor or depressor reflexes (17). 5-HT causes strong vasoconstriction on denervated blood vessels (an effect which is not dependent on the CNS), while on skeletal muscle vessels, including cardiac ones, it causes vasodilation (18).

The intravenous effects of 5-HT on blood pressure initially show a short phase of vasodepression, and subsequently, a phase with increased pressure, and finally, there is a depressive phase with vasodilation. An increase in 5-HT can cause flushes on the skin due to venous constriction and blood deposited in dilated capillaries, while the lack of 5-HT can be the cause of headaches (19). 5-HT injected subcutaneously causes pain, erythema, and cyanosis, effects which are not caused by histamine, and which can be inhibited with a 5-HT antagonist (20). 5-HT mediates anaphylactic reactions, renal necrosis through vasoconstriction, and in some animals, shock caused by bacterial endotoxins (21). In rodents, 5-HT causes placental degeneration and abortion, and tissue destruction when injected into a tumor site (22). In addition, it can also cause tachycardia, palpitation, epigastric discomfort, and diarrhea.

5-HT plays a protective role for the human body against radiation and has a positive effect on wound healing. In fact, experiments on tissue lesions in rats have shown that 5-HT deficiency delays skin healing (23). Histamine, bradykinin, and angiotensin also belong to the 5-HT family. These substances, like 5-HT, have broad-spectrum biological activities with different functions at both a physiological and pathological level.

In the mouse, 5-HT binds to various receptors consisting of 7 gene families, with approximately 14 distinct subtypes participating in various transduction pathways (24). The 5-HT receptor 5-HT1AR is implicated in moderating stress and defending the brain against insults, while the 5-HT2AR receptor mediates active stress. In fact, antidepressants could improve the biological activity of 5-HT1AR by blocking the reuptake of 5-HT, while 5-HT2AR is increased by agonist substances (25).

5-HT that is released by the brain activates neurons through a complex process, which is dependent on an increase in 5-HT receptors. Most research regarding the involvement of 5-HT in psychiatric diseases suggests there is decreased availability of the 5-HT transporter in patients. 5-HT concentrations are important because at different concentrations neurons can respond differently, even in opposite ways. For example, at low to moderate concentrations, 5-HT can inhibit pyramidal neurons, while at higher concentrations, 5-HT enhances the effects on the firing of pyramidal neurons (26). Therefore, 5HT requires high concentrations to perform its biological effect on 5-HT1AR, while on 5-HT2AR, it requires lower concentrations. In the brain, 5-HT receptors are divided into four classes: a) slow-acting 5-HT2R which releases calcium ions (Ca^{++}), b) 5-HT4R, 5, 6, and 7, which increase cAMP, c) 5-HT1/5R which decreases cAMP, and d) fast-acting 5-HT3R that promote the flow of Na^{+} or K^{++}. Thus, at low or moderate concentrations, 5-HT reduces the pyramidal activity of neurons, while at higher concentrations, there may be a recruitment of fast-acting, disinhibitory 5-HT3Rs that are expressed on γ-Aminobutyric acid (GABA)ergic neurons in the cerebral cortex.

CONCLUSIONS

5-HT is an important neurotransmitter that can act on both migration and cell proliferation. This neurotransmitter is ubiquitous in the human body and is stored by neurons, platelets, and enterochromaffin cells. 5-HT can cause both the contraction and release of smooth muscles, depending on the type of target tissue and its concentration. 5-HT, which is degraded by MAO, by binding its receptors 5-HT1AR or 5-HT2AR, can be a mediator of stress and psychiatric disorders. Depression can be treated pharmacologically with serotonergic drugs that improve the patient's cognitive phase and quality of life. However, future studies are necessary to illuminate more precisely the true biological role of 5-HT.

Conflict of interest

The author declares that they have no conflict of interest.

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