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HUMAN AND ANIMAL SEROTONIN RECEPTORS: A SHORT REVIEW

RECEPTORII DE SEROTONINĂ LA OM ȘI ANIMALE: O SCURTĂ RECENZIE

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ABSTRACT | REZUMAT

Serotonin is an important neurotransmitter with many actions in the body, it is involved in generating emotions, is a natural stabilizer of mood, reduces depression, reduces anxiety modulates sleep, etc. The diversity of serotonin-induced effects on cognitive function and behavioral responses is related to its simultaneous effects on a multitude of neural targets and a large number of receptors. Due to these specificities, 5-HT systems can ensure fine-tuning of behaviors in various situations. Serotonin acts on a variety of receptors, in mammals, 5-HTRs are organized into seven families (5-HT1-7R) and more than 16 subtypes have been described. These have been characterized for several years in terms of cloning, pharmacology, and heterogeneous expression on the CNS. In contrast, 5-HTR physiology is less known in invertebrates, despite the assumption that they may have similar properties. This paper presents the results of nervous system research modern studies directly related to serotonin metabolism and receptors' function. Neuroanatomists have studied the shape of the brain, its cellular structure, and its circuits; neurochemists have studied the chemical composition of the brain, its lipids and proteins; neurophysiologists have studied the bioelectric properties of the brain; and psychologists and neuropsychologists have investigated the organization and neural substrates of behavior and cognition,from which only serotonin-related findings are presented in this bibliographic study. This paper summarizes the current understanding in each of the important areas that together define the full scope of serotonin transporter research.

Keywords: serotonin receptors, 5-HT system, neuromodulator

Serotonina este un neurotransmițător important cu numeroase efecte la nivelul organismului, este implicată în generarea emoțiilor, este un stabilizator natural al stării de spirit, reduce depresia, reduce anxietatea, modulează somnul etc. Diversitatea efectelor induse de serotonină asupra funcției cognitive și a răspunsurilor comportamentale este direct corelată cu efectele sale asupra unei multitudini de ținte neuronale și a numărului mare de receptori. Datorită acestor aspecte, sistemele 5-HT pot asigura reglarea fină a comportamentelor în diverse situații. Serotonina acționează asupra unei varietăți de receptori, la mamifere, cei de tip 5-HTR fiind organizați în șapte familii (5-HT1-7R), actualmente fiind descrise mai mult de 16 subtipuri. Recent, acestea au fost studiate și clasificate folosind criterii privind clonarea, farmacologia și expresia heterogenă la nivelul SNC. În schimb, fiziologia 5-HTR este mai puțin cunoscută la nevertebrate, în ciuda presupunerii că ar putea avea proprietăți similare cu cele descrise la vertebrate. Neuroanatomiștii au studiat forma creierului, structura sa celulară și legăturile neuronale; neurochimiștii au studiat compoziția chimică a creierului, lipidele și proteinele de la acest nivel; neurofiziologii au studiat proprietățile bioelectrice ale creierului; iar psihologii și neuropsihologii au investigat organizarea și substraturile neuronale ale comportamentului și cogniției, dintre toate acestea doar cele mai importante concluzii legate de serotonina sunt prezentate în acest studiu bibliografic. Această lucrare rezumă cunoștințele actuale în fiecare dintre domeniile importante, care definesc împreună întreaga sferă de cercetare a receptorilor de serotonină.

Cuvinte cheie: receptori de serotonină, sistem 5-HT, neuromodulator

Serotonin is a neuromodulator whose function is still poorly understood. Although it has been implicated in a wide range of physiological and behavioral processes in vertebrates, it does not appear to be essential for the performance of these processes. This definition of the role of a neuromodulator on central nervous system operations is well suited for 5-HT systems compared to other neuromodulatory systems, such as catecholamines, acetylcholine, histamine, and neuropeptides (2).

Serotonin is recognized as a major neuromodulator of the nervous system in both invertebrates and vertebrates, and is thought to have an impact on animal knowledge and behavior. It has been suggested that the animals' behavior varies along five different or continuous axes: boldness-shyness, avoidance-exploration, activity, sociability, and aggression.

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Having a relatively fixed personality may seem nonadaptive compared to infinite behavioral plasticity, so the individual may respond adaptively to any changes in the environment. There may be physiological limitations to the phenotypic expressions of any trait, including behavior (5). The variation in neuroendocrinology may thus explain some of the most important behavioral manifestations. One neurotransmitter that closely influences and shapes the personality of the animal is serotonin. In the many realms of the serotonergic system, individual differences may arise that form a close basis for personality differences. Depending on the individual's motivational state, serotonin may decrease or increase the individual's aggression. Serotonin is negatively correlated with anxiety traits. (12).

SEROTONIN'S METABOLIC PATHWAYS

Serotonin metabolic pathways share similar characteristics between species. The amino acid precursor tryptophan is hydroxylated by tryptophan hydroxylase, which has two isoforms in different species. The product 5-hydroxytryptophan (5-HTP) is decarbo-xylated by L-amino acid aromatic decarboxylase (AADC) in 5-HT which can reach the vesicular com-partments through the vesicle transporter for mono-amines. 5-HT catabolism is complicated, not by recrui-ted enzymatic pathways involving monoamine oxi-dase A or B (MAOA, MAOB) and aldehyde dehydroge-nase to produce the final metabolite of 5-hydro-xyindole acetic acid (5-HIAA). Catabolism is compli-cated because it preferentially involves the MAOA enzyme in mammals, and this subtype, which differs from MAOB, is not usually located at the terminals of 5-HT neurons. It would imply that 5-HT catabolism is partly associated with other cells. In any case, 5-HT and its metabolite 5-HIAA (5-hydroxy-indoleacetic acid) which is the major metabolite of serotonin and is excreted in the urine. Carcinoid tumors of the diges-tive tract, along with other neuroendocrine tumors can cause excessive production of serotonin and thus 5-hydroxy-indoleacetic acid found in many different spe-cies. The amount of serotonin differs depending on the tissue, but generally follows the density of fibers and cell bodies. In crayfish, the highest amount is found in the cerebral ganglia (approximately 300 pg / mg), followed by the thoracic chain (120 pg / mg) and the abdominal chain (10 pg / mg). In mammals, the highest amounts of serotonin are found in the black matter (500-1000 pg / mg). In birds, the serotonin content is higher in the amygdala compared to the thalamus or striatum. Monoamine systems are strongly linked to stress resistance and mood disorders. As such, tricyclic antidepressants (acting by inhibiting serotonin and norepinephrine reuptake) and selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed medications to treat these disorders. To a limited extent, these agents also inhibit dopamine reuptake. Triple inhibition of monoamine reuptake corresponds to the function of cocaine, which is a powerful psychostimulant. In addition to monoamine reuptake inhibitors, drugs that inhibit the breakdown of monoamines are used to improve mood, especially monoamine oxidase A (MAO-A) inhibitors. However, these agents are also associated with substantial side effects. A major risk is serotonin syndrome, with too high serotonin levels being toxic. Therefore, while monoamine reuptake inhibitors and MAO-A inhibitors improve mood, especially in people with a low mood, their use is not without risks (9, 10).

STEROTONIN'S METABOLIC EFFECTS

High serotonergic tone favors obesity as evidenced by studies of rats with modified serotonin homeostasis (14). At the level of the brain, the biogenic serotonin exerts opposite effects on the regulation of body weight: the increase of the brain activity by 5HT is expected to decrease the body weight, while the increase of peripheral activity by 5HT will increase the body weight and adiposity. In a genetic model of rats with high or low constitutional homeostasis at 5HT (hyperserotonergic /hyposerotonergic rats), the study of how individual differences in endogenous 5HT levels modulate the body's net energy balance.

In animals in the 5HT and 5HT rats, the physiological characteristics associated with body weight homeostasis and the expression profile of a large scale of genes that regulate body weight in the hypothalamus, a major region of the brain that controls energy balance, were evaluated. The results showed that the animals underlined by rats with a high level of 5HT, compared to animals with a low level of 5HT, have an increased body weight throughout life (by 12%), a higher daily intake of food (by 9%) and a different distribution of fat type - higher amount of white adipose tissue and less amount of brown adipose tissue.

A large number of hypothalamic genes may explain 22% of the occurrence of obesity, mutations in the MC4-R - melanocortin-4 receptor gene, in heterozygous form, in the β3-adrenergic receptor gene or PPARy2 - Peroxisome- proliferator-activated receptor, a nuclear transcription factor with a key role in adipocyte differentiation, are other examples of genes involved in simple obesity that regulate body weight that were analyzed for their mRNA expression: 24 genes by reverse transcription - reaction quantitative chain of polymerase (n = 9-10 rats / sublines), including neuropeptides and their receptors, growth factors, transcription factors and peripheral signaling receptors

Table 1

Serotonin 5-HT receptor families and their mechanisms of action

	Tipes	Mechanism	Action
5 – HT1	G – protein coupled	Decreasing cellular levels of cAMP	Inhibitory
5 – HT2	G – protein coupled	Increasing cellular levels of IP3 and DAG	Ecitatory
5 – HT3	Ligand- grated Na and K cation channel	Depolarizing plasma membrane	Ecitatory
5 – HT4	G – protein coupled	Increasing cellular levels of cAMP	Ecitatory
5 – HT5	G – protein coupled	Depolarizing plasma membrane	Inhibitory
5 – HT6	G – protein coupled	Increasing cellular levels of cAMP	Ecitatory
5 – HT7	G – protein coupled	Increasing cellular levels of cAMP	Ecitatory

and a total of 84 genes of different classes by chain reaction matrix polymerase (groups of six rats / sublines). Only a few genes showed significant differences in mRNA expression levels between 5HT subtypes (e.g., neuropeptide receptor Y, fibroblast growth factor), but animals with high 5HT showed a clear tendency to upregulate mRNA for a number of orexigenic signaling peptides, their receptors and other molecules with orexigenic activity. The receptors for peripheral signals (leptin, insulin) and their downstream signaling molecules have not been altered, indicating no change in central insulin / leptin resistance (6).

SEROTONIN RECEPTORS

The diversity of serotonin-induced effects on cognitive function and behavioral responses is related to its simultaneous effects on a multitude of neural targets and a large number of receptors. Due to these specificities, 5-HT systems can ensure fine-tuning of behaviors in various situations. The organization of 5-HT systems is completely different between species ranging from a limited number of Drosophila cells (100 5-HT immunoreactive cells) to several thousand neurons in vertebrates (2).

Serotonin acts on a variety of receptors (Table 1). In mammals, 5-HTRs are organized into seven families (5-HT1-7R) and more than 16 subtypes have been described. These have been characterized for several years in terms of cloning, pharmacology, and heterogeneous expression of the CNS. In contrast, 5-HTRs are less well known in invertebrates, despite the assumption that they may be almost similar. In short, four 5-HTRs called 5-HT1Adro (or d5-HT1A), 5-HT1 Bdro, 5-HT2dro, and 5-HT7droR were discovered in Drosophila and three in crustaceans (5-HT1 Acrust, 5-HT2 Bcrust, and 5HT7 Cost).

In molluscs, two 5-HTRs were cloned into Lymnaea stagnalis belonging to the 5-HT1R and 5-HT2R families, while five were cloned into Aplysia: 5-HTap1 and 5-HTap2 inhibited adenylate cyclase activity and 5-HTapAC1 stimulated -a. In a pond snail (*Helisoma trivolvis*), two types of receptors (5-HT1Hel and 5-HT7 Hel) were cloned and characterized. In crayfish, 5-HTRs are widely distributed in different nerve structures with a specific location in each. For example, 5-HT1 is located in the thoracic lymph nodes surrounding the axonal branches that project into the second nerve of each lymph node and more specifically near the neuropil part of the motoneurons. These receptors can be located in the same area where 5-HT fibers form many close appositions with motoneurons and are involved in classical inhibitory synaptic responses. In contrast, 5-HT2 is located more centrally in the cancerous ganglia of cancer, where 5-HT fibers are not colocalized with the axon of some motor neurons and may be involved in a more global excitatory paracrine response. These receptors would modulate the potential action of the membrane through an action involving K+ channels (2). The effects of food compounds on the serotonin receptor are also considered a stress factor that activates the sympathetic nervous system (SNS), represented by the sympathomoadrenal-adrenal system (8).

Conveyor and receptor effects in neuronal diseases

Structural changes in different regions of the brain have become clinically relevant and have been considered clear signs of neurological diseases. Morphological changes in the brain are also associated with neuronal and neurochemical changes. Studies have shown that minor changes in neurochemical levels can have a significant impact on the subject's psychobehavior. Several profiles of neurological diseases with such specific psycho-behavioral expression have been reported. However, the application of behavioral abnormalities as possible markers of disease progression has not been widely considered and emphasized.

Reports suggested that subjects, who had already entered the terminal stage of the disease, used to

show cardinal behavioral signs for a specific profile of the disease. Because most neurodegenerative disorders are unidirectional and progressive in nature, therapeutic intervention at the right time is essential to achieve the desired result. Moreover, early diagnosis can also help manage the progression of the disease. The psycho-behavioral analysis could meet the expected result of the diagnosis of the disease if it is implemented properly and in a timely manner. In the present analysis, we amalgamated the behavioral anomalies related to the background of support on a neurochemical basis. In addition, we concluded that behavioral studies could be a potential diagnostic tool for the early diagnosis of major neurological diseases, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), bipolar disorder, schizophrenia, Pulse Control (ICD) and Obsessive-Compulsive Disorder (OCD).

Neurotransmitters are chemical messengers released by neurons that regulate neuronal function by mediating appropriate receptor-ligand interactions. Subtle changes in the quality and quantity of neurotransmitters can cause severe behavioral changes. Such changes may occur as a result of genetic mutation or toxicity. Moreover, research is being conducted to investigate such anomalies for the effective design and formulation of new therapies. A wealth of experimental evidence has shown that the distribution and function of neurotransmitters are positively correlated with psychological events. Molecular mechanisms associated with electrical gradients have been reported to alter neurophysiology affecting patient psychometry. It is noteworthy that, functionally, not all neurotransmitters are uniform in nature; the abundance of the neurotransmitter also depends on the location in the brain. Among the neurotransmitters, dopamine, serotonin, norepinephrine, and acetylcholine contribute profoundly to psycho-behavioral events in humans. Each of these entities plays a selective role in maintaining proper brain function, such as feedback mechanisms for the synthesis of certain neurotransmitters (3).

Among the main neurotransmitters, serotonin is responsible for movement, memory, knowledge, attention, pleasure, reward, motivation, sleep regulation, creativity, and personality determination. In people with Parkinson's, serotonin production remains constant but dopamine levels are unstable.

SEROTONIN'S EFFECT ON NEURONAL DISEASES

The mammalian genome encodes 28 distinct members of the potential transient receptor (TRP) superfamily of cationic channels, which exhibit varying degrees of selectivity for different ionic species. Several TRP channels are present in all cells and are involved in various aspects of cellular function, including sensory perception and signal transduction. In particular, TRP channels are involved in the regulation of vascular function and pathophysiology, the focus of this review. TRP channels in vascular smooth muscle cells help regulate contractility and proliferation, while endothelial TRP channel activity is an important contributor to endothelium-dependent vasodilation, vascular wall permeability, and angiogenesis. TRP (transient receptor potential) channels are expressed either in the peripheral nervous system or in skin cells (keratinocytes). Almost all of these functions are mediated by changes in global intracellular Ca^{2+} levels or subcellular Ca^{2+} signaling events. In addition to direct mediation of Ca^{2+} input, TRP channels influence the intracellular dynamics of Ca^{2+} by depolarizing the membrane-associated with cation inflow or by receptor or storage mechanisms. TRP channel disorder is associated with vascular pathologies, including high blood pressure, ischemia-reperfusion injury, pulmonary edema, and neurogenic inflammation. In this review, we briefly consider the general aspects of TRP channel biology and provide an in-depth discussion of the functions of TRP channels in vascular smooth muscle cells, endothelial cells, and perivascular cells under normal and pathophysiological conditions (13).

Calcium ions play a central role in many cellular processes including muscle contraction, transmitter release, cell proliferation, gene transcription, and cell death. TRP channels contribute to changes in the free Ca^{2+} concentration, either by acting as Ca^{2+} entry pathways in the membrane or by changes in membrane polarization, modulating the driving force for Ca^{2+} entry mediated by alternative pathways. Probably intracellular TRP channels are also formed for the release of Ca^{2+} from several organs. Given the unique importance of Ca^{2+} signaling in all cell types, it is not surprising that dysfunctions in Ca^{2+} channels are causal or at least involved in the pathogenesis of several diseases, in which serotonin plays a central role (4).

Neurodegenerative diseases are a large group of neurological disorders with various etiological and pathological phenomena. However, current therapies are mainly based on symptomatic relief, while failing to address the pathobiology of the underlying disease.

G protein-coupled receptors (GPCRs) are one of the most commonly targeted receptors for the development of new therapies for central nervous system (CNS) disorders. Many currently available antipsychotic drugs also act as antagonists or agonists of various GPCRs. Therefore, the development of GPCR-based drugs is expanding widely to regulate neurodegeneration and associated cognitive deficits by modulating canonical and non-canonical signals. Here, the role of GPCRs in the pathophysiology of various neurodege-

nerative disease progressions and cognitive deficits was highlighted and the current pharmacological developments with GPCRs were emphasized to provide a perspective on a potential therapeutic target in the treatment of neurodegeneration.

G protein-coupled receptors (GPCRs) are the largest family of membrane receptors in humans, and approximately 34% of marketed drugs target this family. Since their discovery, this family of receptors has been both pharmacologically and biologically important in the treatment of various pathological conditions. GPCRs contain a common pattern in their basic structures. They consist of seven domain structures that stretch across the membrane, which they use to sense various signals and stimuli, including light, stress, hormones, peptides, and so on.

Neurodegenerative diseases (NDD) are the most common and prevalent in the elderly around the world and cause progressive neuronal dysfunction and death. These diseases lead to an irreversible weakening of all brain functions. About 30 million people world-ide are affected by NDD. Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia (FTD), Parkinson's disease (PD), and Huntington's disease (HD) are prevalent NDDs commonly diagnosed in the elderly.

Of the various NDDs, AD, which causes impaired cognitive function and memory loss, is the most widely discussed and researched. Amyloid β (Aβ) plaque formation and hyperphosphorylation of proteins in neurofibrillary tangles of the frontal and temporal lobe and other regions of the neocortex are observed during AD progression (1).

SEROTONIN RECEPTORS' EFFECTS ON NEURONAL DISEASES

Platelet serotonin transporter (SERT) is a primary mechanism for the absorption of serotonin (5HT) from blood plasma. Changes in plasma levels of 5HT are associated with a number of cardiovascular diseases and disorders. Therefore, the regulation of carrier activity is a key mechanism for stabilizing the 5HT plasma concentration.

There is a biphasic relationship between 5HT plasma increase, surface SERT loss, and platelet depletion (11).Specifically,in platelets, plasma membrane SERT levels and 5HT platelet uptake increase initially as 5HT plasma levels increase but then fall below normal as 5HT plasma levels continue to increase. Therefore, we propose that increased plasma 5HT limits its uptake into platelets by down-regulation of SERT, as well as by modifying the characteristics of SERT partners in membrane traffic.

This review will summarize current findings on the biochemical mechanisms by which increased 5HT down-regulates SERT expression on the platelet membrane.

Interesting aspects of this regulation include the intracellular interaction of SERT with G protein and 5HT-mediated concerted phosphorylation. G protein plays a central role in signaling. It amplifies the responses of the receivers and influences the amplitude and latency of the signals. The receptors ensure the activation of G proteins by GTP (guanosine triphosphate), a group of proteins that bind many neurotransmitters. G protein exists in two conformational states, one active linked to GTP and the other inactive, linked to GDP (7).

TREATMENTS THAT REGULATE SEROTONIN LEVELS IN HUMANS AND ANIMALS

The pharmacology of 5-HT receptors is complex and it is now clear that responses to 5-HT drugs differ between invertebrate and vertebrate receptors. Furthermore, the pharmacological responses of a 5-HT receptor within the same phylum may be different. For example, 5-methoxy-tryptamine, a 5-HT1R agonist in vertebrates, has variable effects on invertebrate receptors, triggering some 5-HT1R activity in bees and beetles, but little or no activity in *Manduca sexta*. The combination of all these factors implies that the 5-HT system exerts complex regulations at the cellular level, especially by controlling cellular and neural excitability for the whole organism (2).

The most commonly used drugs in the treatment of mood disorders are selective serotonin reuptake and monoamine oxidase inhibitors (MAOs), increasing the level of serotonin in the brain. However, side effects have been reported for these medicines.

Because serotonin levels in the brain depend on the availability of the food-derived tryptophan precursor, foods such as chicken, soy, cereals, tuna, nuts, and bananas can serve as an alternative to improving mood and cognition.

Here we discuss the effects of foods with high or low tryptophan content, as well as plant extracts with modest monoamine reuptake and functional MAO-A inhibition profile, on mood and knowledge in rodents and healthy human subjects. Current studies suggest that there is an inverse U-shaped curve for tryptophan plasma levels, with low and too high tryptophan levels affecting cognition and moderate to high levels of tryptophan enhancing cognition.This relationship may also exist for mood, the inverted U-shaped curve for tryptophan plasma levels, and mood may be based on different tryptophan concentrations in healthy versus vulnerable individuals.

Animal studies allow further understanding of the effects and action of food-derived serotonergic components on mood, knowledge, and mechanisms.

CONCLUSIONS

As research progressed, it became clear that neural functions could best be incorporated into the nervous system, considering their operations at four fundamental hierarchical levels: molecular, cellular, systemic, and behavioral. These levels are based on the fundamental principle that neurons communicate through chemical signals, through the activity-dependent secretion of neurotransmitters, at specialized contact points called synapses. At the molecular level, the emphasis is on the interaction of molecules, usually the protein that regulates gene transcription, their translation into proteins, and their posttranslational processing. The proteins that mediate this intracellular process of synthesis, storage, and release of emissions or the intracellular consequences of intercellular synaptic signaling are essential neuronal molecular functions. Such a molecular transducer mechanism includes neutron-transmitting receptors, as well as auxiliary molecules that allow these receptors to influence the short-term biology of receptive neurons by regulating ion channels and their long-term regulation, through changes in gene expression. The completion of the human, chimpanzee, rat, and mouse genomes can be seen as an extensive inventory of this molecular element, more than half of which is thought to be either much richer in the brain or even expressed exclusively in the blood. At the cellular level, the focus is on the interactions between neurons through their synaptic transactions and between neurons and glial cells. Much research presented at the cellular level focuses on the biochemical systems of specific cells that mediate phenomena that may explain the body's dependent adaptation to various activities related to the environment, food, disease, or drugs. Cellular research in this branch of neuroscience investigating neurotransmitters is working to determine which specific neurons and which of their closest synaptic connections may mediate a behavior or behavioral effects of a given ex-perimental disorder. This transport of serotonin by the SERT protein terminates the action of serotonin and recycles it in a sodium-dependent manner. This protein is the target of many antidepressant drugs in the SSRI classes and tricyclic antidepressants, being a neuro-transmitter. Repeated length polymorphism in the pro-moter of this gene has been shown to affect serotonin uptake rate and may play a role in sudden infant death syndrome, aggressive behavior in Alzheimer's patients, post-traumatic stress disorder, and sensitivity to depression. people who suffer emotional trauma. Some of the safest antidepressant drugs are considered to be selective serotonin reuptake inhibitors (SSRIS), which are why they are also the most prescribed antidepressants. The most important risks related to the use of selective inhibitory antidepressants serotonin reuptake (SSRI) are due to the influence of the serotonergic system mainly in the so-called "enteric brain" represented by the Meissner and Auerbach plexuses of the intestine. In serotonergic synapses, a larger amount of serotonin in the body is found in the gut. By influencing the enteric serotonergic system, these antidepressants can mainly cause nausea, vomiting, sometimes affecting the intestinal transit. Serotonin transporter (SERT) is a key molecule for the control of synaptic serotonin levels that hasn't been fully investigated.

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