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REVIEW

Pharmacodynamics of Serotonin. Emphasis on 5HT-3 Antagonists and SSRI Medication (I)

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Abstract

This paper presents a literature review of the pharmacology of serotonin. It focuses on the metabolism and transport of serotonin and on 5-HT receptors and their clinical significance. This report highlights the substances that affect serotonin signalling and body levels and may be employed in treating various disorders: either directly, by influencing the serotonin receptors or, indirectly, by inhibiting serotonin reuptake. The review will be published in two separate parts. The first part will contain a short introduction in the pharmacology of serotonin and it will emphasize the pharmacological properties of the first three of the 5-HT receptors (5-HT1, 5-HT2, 5-HT3). In the second part, the other four types of 5-HT receptors (5-HT4, 5-HT5, 5-HT6, 5-HT7) will be presented along with tendencies and prospects in influencing serotonin transporter (SERT) through selective serotonin reuptake inhibitors (SSRIs). Recent research involving serotonin aims to improve the safety and effectiveness of antidepressant therapy. In order to achieve this, scientists are developing drugs that not only target SERT, but can also act as a full or partial agonist or antagonist on certain serotonergic receptors.

Keywords: serotonin, 5- HT receptors, 5-HT_3 receptor antagonists, selective serotonin reuptake inhibitors (SSRI)

Rezumat

Acest articol prezintă o recenzie din literatura de specialitate privind farmacologia serotoninei. Este evidențiată sinteza, eliberarea, recaptarea și degradarea serotoninei, precum și diversitatea receptorilor serotoninergici. În acest sens sunt prezentate localizarea, tipurile de receptori și mijloacele farmacologice de influențare directă a receptorilor precum și modalități de influențare farmacologică prin inhibarea recaptării serotoninei. Lucrarea va fi publicată în 2 părți. În prima parte este prezentată o introducere în farmacologia serotoninei și o descriere detaliată a receptorilor serotoninergici 5-HT_1, 5-HT_2, 5-HT_3. Partea a doua va descrie celelalte patru tipuri de receptori serotoninergici 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7; posibilitățile actuale de influențare a transportorului pentru serotonină (SERT) în special prin inhibitorii selectivi ai recaptării serotoninei (SSRI) și perspectivele în acest domeniu. În concluzie, pentru îmbunătățirea siguranței și eficacității tratamentului antidepresiv, având ca referință tratamentul cu SSRI, se urmărește sinteza unor substanțe care, pe lângă influențarea SERT, să acționeze pe unele subtipuri de receptori serotoninergici fie ca agoniști deplini, fie ca agoniști parțiali, fie ca antagoniști.

Cuvinte cheie: serotonină, receptori 5-HT, antagoniști ai receptorilor 5-HT_3, inhibitori selectivi ai recaptării serotoninei

Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine neurotransmitter involved in regulating and modulating physiological and behavioral processes[1]. Serotonin also plays an important role in the functioning of enteric nervous system[2].

HISTORY

The substance was discovered in 1930s as italian scientist Vittorio Erspamer observed how an acetone isolate from enterochromaffin cells caused smooth muscle to contract[3]. After further testing, Erspamer established

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that the substance wasn't epinephrine and had an indole structure. He named the unknown compound enteramine[4]. In 1948, a research team from Cleveland Clinic, which then specialized in hypertension and arteriosclerosis, discovered a vasoconstrictor substance in blood serum and named it serotonin[5]. In 1952, Feldberg and Toh demonstrated that enteramine is the same substance as serotonin[6]. One year later, Betty Twarog and Irvine Page located serotonin in the central nervous system[7,8].

Starting in 1957, several types of 5-HT receptors were discovered. Picarelli and Gaddum were the first scientists to suggest that guinea pig ileum contains two distinct types of 5-HT receptors: D receptors (blocked by dibenzyline), located on smooth muscles, and M receptors (blocked by morphine), located on enteric cholinergic neurons[9]. The receptors, which were then named M, are now 5-HT_3[10].

Involvement in physiological functions

Most of the human body's total serotonin is found in the gastrointestinal tract[11]. There, serotonin is secreted by enterochromaffin cells, which contain more than 90% of the total 5-hydroxytryptamine (5-HT) within the human body[12]. Serotonin is released from the enterochromaffin cells into the lamina propria mainly in response to mechanical pressure[13]. Other stimuli for releasing 5-HT are low pH, amino acids, hyper- and hypotonic solutions, caffeine, tyramine and nutrients[14]. One major action of serotonin in the digestive tract is the contraction of gastrointestinal smooth muscle, action which plays a role in the peristaltic reflex, making the intestine contract prior food bolus (orally) and relax aborally[15]. Serotonin has numerous other effects on the gastrointestinal tract. It is also involved in irritable bowel syndrome, chemotherapy-induced vomiting and carcinoid syndrome. It appears that platelet-derived serotonin plays an important role in liver regeneration after partial hepatectomy. Additionally, it may determine the progression of hepatic fibrosis and steatohepatitis[16].

Platelets from the veins draining the gastrointestinal tract collect serotonin and store it[17]. 5-hydroxytryptamine is released when the thrombocytes adhere to a clot or a damaged tissue. 5-HT acts as a vasoconstrictor contributing to hemostasis, but also induces extracellular matrix synthesis in interstitial fibroblasts via activation of 5-HT_{2B} receptors, leading to fibrosis[18].

A small faction of serotonin is synthesized in serotonergic neurons of the central nervous system (CNS), particularly in the neurons of the raphe nuclei[19]. The axons of the neurons in the higher raphe nuclei are distributed to the entire brain, while the axons of the neurons from the lower raphe nuclei go to the cerebellum and spinal cord[20]. In CNS, serotonin has various functions. It regulates the mood, perception, reward, anger, aggression, appetite, memory, sexual behavior and attention. It has also been involved in the pathogenesis of several conditions like anxiety and panic disorders, depression, migraine, schizophrenia, hypertension, eating disorders, vomiting, etc[1].

Serotonin levels and signalling also appear to be influencing bone mass. Higher serotonin levels in the blood may be associated with increased bone turnover[21]. 5-HT_{2B} receptor is a mediator of serotonin in bone formation (encourages osteoblast recruitment and proliferation) and its absence or disruption leads to osteopenia and osteoporosis[22].

Synthesis, transportation and metabolism

Like other biogenic amines, serotonin is synthesized from an amino acid precursor. To obtain serotonin, the amino acid tryptophan undergoes an enzymatic process catalyzed by two enzymes. The first enzyme is tryptophan hydroxylase which creates 5-hydroxytryptophan later converted into serotonin by the second enzyme, 5-hydroxytryptophan decarboxylase[23]. Serotonin is released into the synaptic gap when an action potential triggers a calcium-dependent exocytosis of the neurotransmitter from the presynaptic vesicles[24]. Then, serotonin diffuses over in order to activate 5-HT receptors situated on the cell bodies, dendrites and presynaptic terminals of nearby neurons.

Unlike other neurotransmitters, serotonin is not usually degraded after its action. The 5-HT is carried back into the neurons by a specific serotonin transporter (SERT) which allows functional recycling of the neurotransmitter[25,26]. Specifically, SERT is a symporter that transports simultaneously Na^+, Cl^-, K^+ and 5-HT^+[27].

Some substances like selective serotonin reuptake inhibitors (SSRIs, used as antidepressants), cocaine, dextromethorphan (used as antitussive) or tricyclic antidepressants can inhibit serotonin reabsorption through SERT[28-30].

Also, there is considerable evidence indicating that increased serotonergic neurotransmission because of a short allele *(s)* in the SERT gene (which lowers transcriptional efficiency and therefore lowers serotonin transporter expression, thus decreasing cellular uptake of serotonin) is anxiogenic in animal as well as in humans[31]. The long allele *(l)* in the SERT gene has been linked to irritable bowel syndrome with predominantly constipation and decreased response to tegaserod (a 5-HT_4 receptor agonist)[32].

Furthermore, SERT knockout mice showed anxiety-like behaviour, reduced aggression and exaggerated stress responses[33].

Another transporter accumulates serotonin into synaptic and secretory vesicles by exchange of protons[34]. Recently, it has been suggested that not only SERT, but also another monoamine transporter known as PMAT (*Plasma Membrane monoAmine Transporter*) or hENT4 (human equilibrative nucleoside transporter-4) may account for a significant part of serotonin's clearance[35].

Serotonin that is not stored in vesicles is degraded by monoamine oxidase A (MAO-A) to 5-hydroxyindoleacetic acid (5-HIAA)[36]. 5-HIAA is used to diagnose and monitor carcinoid tumors[37].

Serotonergic receptors and their implications in therapy

A number of structurally and pharmacologically distinct mammalian receptors that respond to serotonin was described. These receptors are categorized into seven families[38]. Six out of the seven categories of 5-HT receptors are G-protein-coupled receptors that activate an intracellular second messenger system[10]. One class of receptors (5-HT_3) contains ligand-gated ion channels[39]. In Table I we present a succinct classification of 5-HT receptors and their major signalling pathway. However, some 5-HT receptors also have others signalling pathways. For example, 5-HT_{1A} modulates small-conductance $Ca2^+$- K^+ activated channels[40].

The 5-HT_1 family of serotonin receptors has five receptor subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E} and 5-HT_{1F}) and is usually coupled with $G_{i/0}$ proteins which inhibit the intracellular formation of cAMP[42,43].

5-HT_{1A} receptors have been involved in the regulation of adrenocorticotropic hormone (ACTH)[44] and in decreasing the blood pressure and heart rate[45].

Also, low levels of 5-HT_{1A} receptors have been frequently found in mood and anxiety disorders. In 5-HT_{1A} receptor knockout mice it have been observed anxiety-like behaviour[46]. Buspirone and other 5-HT_{1A} receptor partial agonists are being used for the treatment of anxiety and depression[47]. More, pindolol, a 5-HT_{1A} receptor antagonist and adrenoceptor antagonist was demonstrated to enhance the therapeutic efficacy of antidepressive medication in patients with clinical depression when was coadministered with SSRI[48]. It has also been showed that selective 5-HT_{1A} receptor agonist, F13640, produces powerful analgesia in rat models of chronic pain[49].

5-HT_{1B} receptors and 5-HT_{1D} receptors are similar in sequence although they are encoded by two different genes. The pharmacological interest for these two receptors began with the discovery of sumatriptan, a 5-HT_{1B} receptor agonist, with antimigraine properties. Other agonists (elitriptan, donitriptan, zolmitriptan, almotriptan) have been developed for the treatment of migraines[50].

Additional effects of the 5-HT_{1B} receptor activation seem to be penile erection, hypothermia, hypophagia and modulatory functions in the immune system[51-53].

5-ht_{1E} receptors are distributed especially in the frontal cortex, hippocampus and olfactory bulb. Its role remain unknown, although it is hypothesized that 5-ht_{1E} regulates memory mainly because of the receptors' localization and their lack of significant mutations of the 5-ht_{1E} receptor protein, which suggest an important biological role[54,55].

5-HT_{1F} receptors are structurally similar to 5-ht_{1E}. Some agonists of 5-HT_{1F} have antimigraine properties[56,57].

The 5-HT_2 family of serotonin receptors consists of three subtypes 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. These receptors are coupled preferentially with Gq-protein and, upon activation, stimulates phospholipase C (PLC) that releases diacylglycerol (DAG) and inositol triphosphates (IP3) which elevate cytosolic $Ca2^+$.

5-HT_{2A} receptor is found in the central nervous system, in the neocortex, but also in periphery in neurons, platelets or monocytes[58,59]. 5-HT_{2A} receptors may modulate cognitive processes, attention and memory[60]. A mutation in the gene that codes for the 5-HT_{2A} receptor may increase risk of suicide[61].

5-HT_{2B} receptor is present both in CNS and in periphery. It has behavioural effects[62], vascular effects (is involved in the pathogenesis of pulmonary hypertension and valvular disease[63,64]) and controls serotonin rele-

Table 1. Classification of 5-HT receptor and their major signalling pathway (after reference 41, 42)

	5-HT_1	5-HT_2	5-HT_3	5-HT_4	5-ht_5	5-HT_6	5-HT_7
Subtypes	5-HT_{1A} 5-HT_{1B} 5-HT_{1D} 5-ht_{1E} 5-HT_{1F}	5-HT_{2A} 5-HT_{2B} 5-HT_{2C}	5-HT_{3A} 5-HT_{3B}		5-ht_{5A} 5-ht_{5B}		
Major signalling pathway	cAMP↓	IP3↑	Ion channel	cAMP↑	cAMP?	cAMP↑	cAMP↑

ase via SERT[65]. Activation of this receptor was also involved in the drug-induced valvular cardiac disease because of the proliferation of cardiac valves fibroblasts[66].

Some anti-Parkinsonian dopaminergic agonists, which stimulate serotonergic 5-HT_{2B} receptors (pergolide, cabergoline) have been withdrawn from the market, as a result of several reports that patients taking this medication showed a statistical increase of cardiac fibrosis and valvular disease[64].

5-HT_{2B} receptor selective agonists also seem to have antidepressant-like properties. The 5-HT_{2B} receptor appears to positively modulate serotonergic activity and may be employed for the therapeutic actions of SSRIs[67]. Given the role of 5-HT_{2B} receptors in the central actions of serotonin, potential new antidepressants are now targeting 5-HT_{2B} receptors[68].

5-HT_{2C} receptor is involved in the pathophysiology and treatment of anxiety disorders[69]. Preclinical data show that 5-HT_{2C} antagonists enhance the neurochemical and behavioural effects of SSRIs. Furthermore, desensitisation of 5-HT_{2C} receptors is reported after chronic SSRI treatment[68].

The 5-HT3 serotonin receptors are cation-selective ion channels that are part of the Cys-loop superfamily, which also includes nicotinic, glycine, GABAA[70,71].

Each receptor from the 5-HT_3 serotonin family has five subunits encircling a central ion-conducting pore. The 5-HT_3 receptor binding site is composed of six loops from two adjacent subunits. Three of these loops (from A to C) come from the principal subunit and three (from D to F) from the complementary subunit[72]. There is an important interindividual diversity of human 5HT-3 serotonin receptors with distinct signaling properties. Due to this particularity, further developments in the clinical use of 5 HT-3 receptors are expected[73].

The 5-HT_3 serotonin receptors are present in both CNS and in the peripheral nervous system. In the CNS, receptors are located especially in the brain stem, in the area postrema and nucleus tractus solitarius, brain structures involved in the vomiting reflex. 5-HT_3 receptors are also present in hippocampus, nucleus accumbens, ventral tegmental area, substantia nigra and cortex[74]. These receptors may be involved in anxiety and cognition[75].

5-HT_3 receptors are also found in the enteric nervous system of the gastrointestinal tract where they regulate intestinal motility and peristalsis[76]. They may also play an important role in the urinary tract. A hypersensitive serotonin 5-HT_3 receptor in a mutant mice lead to excitotoxic neuronal cell death and, consequently, bladder hyperdistension, urinary retention, and overflow incontinence[77].

Activation of 5-HT_3 receptor modulates the release of several neurotransmitters, including dopamine, GABA and cholecystokinin. 5-HT_3 serotonin receptors have been found in both pre and postsynaptic nerve terminals[78].

5-HT_3 receptors are established drug targets. Its antagonists are used in medical treatments more than 5-HT_3 agonists (e.g. varenicline[79]) who have nowadays little clinical use because of their adverse effects like anxiety, nausea and vomiting[80].

Drugs that selectively antagonize 5-HT_3 receptors are generically called setrons. Setrons are used in the clinical treatment of postoperative or chemotherapy-induced nausea and/or emesis. 5-HT_3 antagonists have also proved to be efficient and they are used in the treatment of irritable bowel syndrome.

Furthermore, central 5-HT_3 receptors have been proposed as potential pharmaceutical targets for the treatment of fibromyalgia, pruritus, migraine, rheumatic diseases, various psychiatric disorders, nociception, cognitive dysfunctions and drug abuse and withdrawal[73].Their side effects include constipation, headache and dizziness. All of these are reversible after interrupting the treatment[81].

In Europe, there is a wide use of 5-HT_3 antagonists tropisetron, ondansetron, granisetron, dolasetron and palonosetron. Other 5-HT_3 antagonists like alosetron have been approved by the FDA (*Food and drug Administrations*) in United States for treating irritable bowel syndrome. Also, azasetron and ramosetron are available in the Far East[72].

Palonosetron has improved the treatment of nausea and emesis and, in combination with corticosteroids, has been shown to have an improved long-term benefit compared with some other compounds like ondansetron[82].

However, 5-HT_3 receptor antagonists are restricted to the treatment of nausea and vomiting induced by chemotherapy, radiation treatment or surgery. They have little or no efficacy in treating other causes of emesis (e.g. motion sickness)[84,85].

5-HT3 receptor antagonists may also be useful in preventing pain during the injection of anaesthetics. For example, dolasetron proved to be as effective as the local anaesthetic lidocaine at preventing pain86. Furthermore, an injection with tropisetron has shown to reduce pain in chronic back pain and arthritis, and reduce the symptoms of fibromyalgia[87-89]. Anti-inflammatory and immunomodulatory properties have been observed for 5-HT3-receptor antagonists which might explain promising findings in systemic sclerosis and other immunological conditions[80].

5-HT_3 serotonin receptor are also involved in the treatment of **irritable bowel syndrome (IBS)**. IBS is a complex gastrointestinal disorder that has a higher incidence amongst women[90]. IBS is associated with altered gastrointestinal motility, secretion and abdominal pain. Irritable bowel syndrome can be categorized into three main types: IBS-C (with mostly constipation), IBS-D (with mostly diarrhea) and mixed or alternating IBS. Around 25% of patients with IBS have predominantly diarrhoea (IBS-D). IBS-D is associated with an increase in gastrointestinal serotonin and a decrease in the serotonin transporter (SERT)[91]. The causes of IBS are not entirely clear. However, patients with this disorder have obvious serotonin signalling anomalies.

Psychiatric conditions like depression, anxiety and chronic fatigue are commonly found in people with IBS. Also, people with IBS seem to also have comorbidities such as fibromyalgia, temporomandibular joint disorder and chronic pelvic pain[92]. Studies have shown abnormalities in enterochromaffin cell numbers, serotonin content, serum serotonin levels, tryptophan hydroxylase message levels, 5-hydroxyindoleacetic acid levels, and expression of the serotonin-selective reuptake transporter (SERT)[93].

In order to treat this disorder, the clinical studies have been focused on $5HT_{1B}$, 5-HT_3 and 5-HT_4 serotonin receptors from the gastrointestinal tract. There was an interest for beta3-adrenoceptor agonists[94], but none of drugs in the pipeline was authorised.

5-HT_3 receptor antagonists have proved efficacious in treating symptoms of IBS-D. Alosetron, a 5-HT_3 receptor antagonist, decreases gut transit[95], increases the compliance of the colon to distension[96] and reduces pain[97,98].

However, in phase IV studies, alosetron was shown adverse reactions like severe constipation, ischemic colitis and even death. Ischemic colitis occurs at a rate of 1 of 1000 patient per year[72,99]. Other 5-HT_3 antagonists such as ramosetron and ondansetron have not been associated with ischemic colitis. In order to prevent some of the side effects, the recent studies focus on agents with partial agonist activity on the 5-HT_3 receptors. Decreasing the activity of the ion channel without blocking its function may prevent severe constipation and normalize bowel function[100].

Promising data on the therapeutic potential of 5-HT_3 antagonists have been reported for treatment of psychiatric disorders such as anxiety and depression[101] or schizophrenia, when added to standard antipsychotic medication[102]. Also, several other studies have found that 5-HT_3 receptor antagonists can induce a statistically significantly improvement in cognitive dysfunction (in Alzheimer's, stroke, multiple sclerosis)[103], substance abuse and addiction (ethanol)[104].

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