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The importance of serotonin in the gastrointestinal tract

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SUMMARY

Introduction. Serotonin also called as 5-hydroxytryptamine (5-HT) is a very important neurotransmitter in the central nervous system, also plays an important role in the gastrointestinal tract. It is known that the basis of the peristaltic reflex in the gut is the result of serotonin release from enterochromaffin cells. The vast majority of serotonin in the human body is associated with the gastrointestinal tract. It is produced by enterochromaffin cells, the activation of which causes the serotonin secretion into the intercellular space and its active action through the receptors. There are seven main types of serotonin receptors and some of them have also subtypes.

Description of the current knowledge and conclusions. Serotonin is responsible for some symptoms of carcinoid syndrome. It is the result of higher 5-hydroxytryptamine content in the body. Moreover disrupted serotonin system is found in different gastrointestinal disorders e.g. in gastroesophageal reflux disease, functional heartburn, hypersensitive esophagus, functional dyspepsia, irritable bowel syndrome (both diarrhoea predominant and constipation predominant) as well as in inflammatory bowel diseases. Knowledge of changed mechanisms in particular diseases facilitates the optimal choice of treatment. Drugs affecting the serotonin system in gastroenterological clinical practice are useful especially in the case of abnormalities in the brain - gut axis.

Key words: serotonin, gastrointestinal tract

INTRODUCTION

Serotonin, colloquially called the happiness hormone, in the commonly everyday life as well as in the medical industry is usually associated with mood disorders. However, the human body system containing most of serotonin, is the digestive system [1]. The authors have analyzed the problem of assessing current knowledge concerning serotonin in the gastrointestinal tract. For this purpose, selected valuable literature were evaluated.

SEROTONIN BIOLOGY

Serotonin also currently known as 5-hydroxytryptamine (5-HT) was found in 1930's by Vittorio Erspamer. This substance was responsible for smooth muscle contraction, especially in rat uterus. Because it was isolated from gut, he had named it „enteramin". Regardless of this discovery in 1948, Page and Rapport isolated a vasocostrictive substance from the blood. Oblivious to the fact that they isolated "enteramine" gave it the name binding until today "serotonin". Soon after, the chemical structure of the substance was identified as 5-hydroxytryptamine [1, 2, 3].

It is estimated that the human body contains 10 mg of serotonin, 95% of which is located in the gastrointestinal tract. The rest of it remains mainly in the central nervous system. 90% of serotonin present in gastrointestinal tract is found in a series of enterochromaffin cells, and 10% is attributed to the fibers of the enteric nervous system (ENS). However serotoninergic fibers make up 1-2% of ENS fibers [4, 5]. In the intestinal mucosa, apart from the different epithelial, pluripotent and immunocompetent cells, enteroendocrine cells are also present, including enterochromaffin cells, which contain enzymes capable for synthesis serotonin from L-tryptophan. By means of the transformation from L-tryptophan in the first stage carried out by tryptophan hydroxylase 1 (TpH1), the hydroxyl group is added by enzymatic addition, thereby 5-hydroxytryptophan is produced. In a further stage, 5-hydroxytryptophan decarboxylase catalyzes the production of a native amine – serotonin [1, 6, 7, 8]. Afterwards, the 5-hydroxytryptamine is accumulated in secretory vesicles, found in the regions of both the apical and basolateral membranes of the cell just below the plasmatic membranes [8]. The mechanical stimulus acting on the gut from the mucosal side causes degranulation of serotonin from cells and its penetration into the lamina propria of the mucous membrane, where endings of nerve fibers are presented and some of them are equipped in 5-HT receptors [5, 7, 8, 9, 10]. In the reflex mechanism within enteric nervous system, serotonin interacts with 5-HT_3 receptors located on the nerve endings containing the calcitonin gene-related peptide (CGRP). These neurons have synaptic connections with both the ascending and descending interneurons. The stimulation of the ascending interneurons further activates excitatory motoneurons, which secrete acetylcholine, substance P and neurokinin A, causing smooth muscle contraction. In contrast, descending interneurons stimulate inhibitory motoneurones, cause relaxation of smooth muscle as a result of the secretion of nitric oxide (NO), vasoactive intestinal peptide (VIP) and peptide activating pituitary adenylate cyclase (PACAP) [6, 11]. Due to these mechanisms, local reflex neuronal activity at the ENS level causes contraction of smooth intestinal muscles in the proximal direction in relation to the activating stimulus and coordinated distal relaxation creating a force that moves the intestinal content in the caudal direction. Movements of the intestinal contents in the distal direction causes a mechanical interaction with the gut wall, which causes a domino effect - further release of serotonin, proximal contraction, distal relaxation and a consequent passage of gastrointestinal contents. At the same time, serotonin increases gut secretion of water and electrolytes, which may facilitate the movement of the gut contents, which is especially helpful in the distal parts of colon, where faeces are usually formed as solid mases [6, 11]. Secretory processes depend on acetylcholine and VIP, which, when interacting with intestinal epithelial cells, increase the activity of adenylate cyclase and intracellular calcium ion concentration, causing the activation of secretory processes [12]. The endings of nerve fibers originating from the central nervous system also reach in the gastrointestinal tract. In this way serotonin is responsible for the influence on the gut – brain axis. It plays the key role in visceral

sensation and that makes it possible to feel discomfort and pain coming from the viscera by interacting with the nerve fibers of the spinal cord ganglia [3]. This interaction is often the subject of hypotheses on the pathogenesis of irritable bowel syndrome and functional dyspepsia [3, 5, 13]. Moreover increased serotonin secretion from enterochromaffin cells, e.g. after cancer chemotherapy, induces nausea and vomiting by the influence on nerve fibers as well as straightway on the central nervous system [14, 15, 16].

Serotonin is biologically active until it remains in the intercellular space, because there are no extracellular mechanisms for 5-HT biodegradation. Significant amount of 5-HT is absorbed by the re-uptake transporters to neurons, epithelial and enterochromaffin cells. The residue passes into blood vessels where it is bound by platelets [1, 3, 5]. For thrombocytes, the gastrointestinal tract plays a leading role in the absorption of serotonin. They are not able to produce 5-HT independently. Thus the gastrointestinal tract can be considered as a system participating in the haemostasis process [5].

In the intercellular spaces in which serotonin is found after its release from enterochromaffin cells, due to the anatomical structure of the intestinal wall, there is a relatively large mechanical obstacle to its access to the neurons of the muscular plexus which controls the motility of the gastrointestinal tract. This protects the body against an incommensurable increase of gastrointestinal motility after every serotonin-releasing stimulus (e.g., caused by the moving gut content) [5]. Beside mechanical stimulation, other agents that are able to release serotonin from enterochromaffin cells are also known and in the small intestine they include vagus nerve stimulation, low pH, amino acids, hypotonic and hypertonic solutions, caffeine, tyramine. In the large intestine, short-chain fatty acids have a stimulating effect on serotonin release [5, 7, 8].
Because serotonin is constantly synthesized in the living body, there are also biodegradation mechanisms for this substance. After reabsorbing into the cells, the serotonin metabolism pathway begins with oxidative deamination catalysed by monoamine oxidase. Product of biochemical reactions, the 5-hydroxyindoleacetic acid is excreted from the body by the urinary system [3, 17, 18].

GENERAL CHARACTERISTICS OF SEROTONIN RECEPTORS
Seven types of receptors for serotonin have been identified and classified so far: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5HT_5, 5HT_6, 5-HT_7. Some of them also have subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C} [1, 19].
However, molecular mechanisms of receptor functioning are different. The 5-HT_3 receptor is conjugated to the Na / K membrane cation channel, thereby it is an ionotropic receptor. The others belong to the metabotropic receptors. The 5-HT_1 and 5-HT_5 types reduce the activity of adenylate cyclase. The 5-HT_4, 5HT_6 and 5-HT_7 act on the contrary way leading to an increase cAMP. The 5-HT_2 receptor activates phospholipase C [7, 19, 20].
In the gastrointestinal tract, the following 5-HT receptor subtypes, have been found and functionally characterized (by Hasler 2009) [7]:

1. The 5-HT_{1A} subtype, which is present in motor neurons of the enteric nervous system and on enterocytes. A reduction in motor activity of ileum and pyloric antrum in stomach is attributed to this receptor as well as a reduction of gastric funding tone. 5-HT_{1A} receptor plays also the regulatory role in visceral sensation processes.

2. Subtypes 5-HT_{1B} and 5-HT_{1D}, which occur in smooth muscle, neurons belonging to the central and enteric nervous system. They are responsible for the reduction of contractility and for delaying gastric emptying.

3. The 5-HT_{2A} subtype, which has been found in ENS, smooth muscles and enterocytes.

Serotoninergic stimulation of this receptor enhances antral and colonic contractions, reductes fundic tone and stimulates epithelial secretion.

4. The 5-HT_{2B} subtype receptor subtype whose presence has been confirmed in enteric neurons, smooth muscle, interstitial Cajal cells and in connective tissue. This receptor is responsible for fundic, ileal, and colonic contractions. Moreover, some regulatory functions of this receptor in visceral sensation and enteric nerve growth has been also proved.

5. The 5-HT_3 type, which occurs in enteric neurons, interstitial Cajal cells, enterocytes, extrinsic nerves and enterochromaffin cells. Activation of this receptor increases frequency of small bowel motor complexes, regulates visceral sensations and stimulates gut epithelial cells to secretion.

6. The 5-HT_4 receptor, the presence of which has been confirmed in the ENS neurons, gut smooth muscles, interstitial cells of Cajal, enterocytes and in enterochromaffin cells. The 5-HT_4 receptor intensifies gut peristalsis and smooth muscle relaxation (depending on the receptor location), but it is also suspected that this receptor can control functions in visceral sensation, stimulate to epithelial secretion and enhance of neuronal survival in the gastrointestinal tract.

7. The 5-HT_7 receptor, which is present in the neurons of enteric nervous system and in the gut smooth muscles. Its excitation causes relaxation of smooth muscle and plays a role in the regulation of the visceral sensation.

In the stomach, the 5-HT_{1A} and 5-HT_{2B} receptors predominates [7]. Whilst in the gut, 5-HT_3 and 5-HT_4 the types are definitely more numerous [7, 21], and their functions in this part of gastrointestinal tract is best known [1].

SEROTONIN IN PATHOLOGY OF GASTROINTESTINAL DISORDERS

Carcinoid syndrome

Carcinoid syndrome is a clinical manifestation of neuroendocrine tumours, which secrete biogenic amines, including serotonin. Tumours secreting serotonin are most often located in the gastrointestinal tract. The second place of frequency is respiratory tracts, whilst other locations are sporadically described. The symptoms of carcinoid syndrome result primarily from the biological active substances and one of the most important of them is serotonin. The most common clinical complaint reported by patients with carcinoid syndrome is flushing. This phenomenon is a result of vasodilatory effects of biologically active amines, peptides and prostaglandins. Character of flushing is paroxysmal and is described as reddish discoloration of the skin of upper body, mainly on the face, but also neck, and upper part of the trunk. Often, this attack is accompanied by palpitations and wheezing. The second clinical manifestation of carcinoid syndrome is diarrhoea. It is the result of excess serotonin, which intensifies the motility and intestinal secretion. Typically the symptoms of carcinoid syndrome appear in advanced forms of serotonin-secreting tumours, usually with the presence of liver metastases. In this disease, there is an obvious relationship between the increased amount of serotonin and clinical symptoms [22, 23, 24, 25].
The clinical data confirmed efficacy of ondansetrone (5-HT3) against carcinoid - related diarrhoea, thus the participation of 5HT_3 receptor in this symptom is very likely [26].

Functional dyspepsia

In people with functional dyspepsia, serotonin homeostasis is impaired [3]. Higher concentration of 5-HT was confirmed in the group of patients with epigastric pain syndrome than in healthy population, whereas in patients with postprandial pain syndrome serotonin concentration was slightly lower than in healthy subjects [18]. This fact is reflected in the treatment e.g. drugs

affecting the motility of the gastrointestinal tract by the activity to 5-HT receptors such as cisapride are helpful in reliving the symptoms of functional dyspepsia [27, 28].

Gastroesophageal reflux disease

Serotonin attenuates the esophageal squamous epithelial barrier function by the influence on the tight junction proteins [29]. Thus it can be more susceptible for the development of gastroesophageal reflux complications like esophagitis and Barrett esophagus. Definitely more evidences are for the disorders in the serotonergic system is case of functional heartburn and hypersensitive esophagus. Thus patients with heartburn and nonconfirmed pathological acid reflux are good candidates to selective serotonin reuptake inhibitors (SSRI). In this group of patients SSRIs are helpful in controlling symptoms [30, 31].

Irritable bowel syndrome

Many evidences of intestinal disorders associated with abnormal 5-HT signalling are reported but the irritable bowel syndrome (IBS) is one of the most common. Both irritable bowel syndrome with constipation predominance (IBS-C) and irritable bowel syndrome with diarrhoea predominance (IBS-D) are characterized by the disrupted serotonin signalling. Abnormalities of brain – gut axis are the first of them. Serotonin plays the important role in abnormalities in IBS, especially when visceral sensitivity is occurred. Then the changes in number and proportions of serotonin receptor as well as in number of enterochromaffin cells had been found in IBS patients [3, 17, 32, 33, 34]. In clinical practice drugs influencing the serotonin system are used in IBS therapy [33, 35].

Selective serotonin reuptake inhibitors as well as serotonin-norepinephrine reuptake inhibitors are helpful in IBS treatment, especially when patients complaint is abdominal pain. In clinical trials, the efficacy of IBS treatment with fluoxetine, paroxetine and citalopram has been demonstrated [35]. Cisapride is an agent with mixed pharmacologic actions on 5-HT receptors. It both antagonizes the 5-HT_3 receptor and agonizes the 5-HT_4, whilst the action on 5-HT_4 receptors is much stronger, so clinical effects are rather the result of the excitating abilities. This substance was used as a prokinetic drug. Thus its pharmacological properties were helpful in IBS-C treatment [33, 36]. But due to the side effects this drug had been withdrawn from the common usage. Uncommon but fatal arrhythmias depending on QT prolongation have led to discontinuation of the usage the product in many countries [37, 38, 39]. Whereas by antagonizing the 5 HT_3 receptors, a significant improvement in the course of IBS-D is obtained [40, 41].

Inflammatory bowel diseases

Disorders in the serotonin system associated with inflammatory bowel diseases have been shown [32, 42]. Serotonin is a signaling molecule in triggering, enhancing, and countering inflammation in the gut. The proinflammatory effect of serotonin has been proven as well as inflammation itself promotes increased serotonin activity. Inflammation leads to decrease in the activity of serotonin reuptake proteins. This makes serotonin longer biologically active in the extracellular space. Inflammation also leads to increase the number of enterochromaffin cells. This is the reason for even greater secretion of serotonin. These factors contribute to the severity of the symptoms in inflammatory disease through the intensification of gastrointestinal motility and increased intestinal secretion [43].

RECAPITULATION

Although in over a dozen years we will celebrate the centenary of the serotonin discovery, this substance and its effect on many pathophysiological processes in the body remains undiscovered. The basic physiological functions of serotonin were quite well understood. However, the role of 5-hydroxytryptamine in disease processes, especially those associated with inflammation, remains very poorly known. A wider examination of the issue in the future can enable finding an effective and safe grip point for drug action.

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