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# Biogenic amines in the colon

## Aminy biogenne w jelicie grubym

**Miłosz Jastrzębski, Adam Przybyłkowski**

Department of Gastroenterology and Internal Medicine, Medical University of Warsaw, Poland

## Summary

The gastrointestinal (GI) tract contains the highest concentration of biogenic amines in the human body. Neurons located in the GI tract, modulated by biogenic amines and various peptide and non-peptide transmitters, are called Enteric Nervous System (ENS). That explains why many medications used in neurology and psychiatry present side effects from the gut. Serotonin (5-hyroxytrypatamine, 5-HT), 95% of which is synthesized in the gut, is the most important amine (beside epinephrine and norepinephrine) colon functionality but another substances such as histamine, dopamine and melatonin are also potent in modulating intestine's actions. Over 30 receptors for 5-HT were described in the human body, and 5-HT3, 5-HT4 and 5-HT7 are known to have the highest influence on motility and are a potent target for the drugs for treatment GI disorders, such as Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Diseases (IBD). Histamine is a key biogenic amine for pathogenesis of allergy also in the colon. Alteration in histaminergic system is found in patients with diarrhea and allergic enteropathy. Dopamine affects functions of the large intestine but its modulating actions are more presented in the upper part of GI tract. Melatonin is best known for regulating circadian circle, but may also be a potent anti-inflammatory agent within the gut. Despite many years of research, it seems that more studies are needed to fully understand human colon neurochemistry.

**Keywords:** **colon, gut, bowel, serotonin, dopamine, histamine, melatonin**

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**Author's address:** Miłosz Jastrzębski, Department of Gastroenterology and Internal Medicine, Medical University of Warsaw, S. Banacha 1A, 02-091 Waeszawa, Poland; e-mail: milosz.jastrzebski@gmail.com

### INTRODUCTION

The gastrointestinal (GI) tract contains the highest concentration of biogenic amines in the human body. Despite having different macroscopic structure and functions, the GI tract and the nervous system have many similarities on the cellular level. Although the GI tract is controlled by the autonomic nervous system, it has wide functional autonomy and its own automatisms. Neurons located in the GI tract, modulated by biogenic amines and various peptide and non-peptide transmitters, are called the Enteric Nervous System (ENS). ENS transmitters regulate peristalsis, secretion, absorption and visceral sensitivity. ENS works under the supervision of the central autonomic nervous system; therefore, the net of connections and their mutual influence is called brain-gut axis. ENS function is also modulated by microbiota. This may be one of potential reasons why ENS function has not been fully elucidated, despite years of research in this field. The proportion in density between spinal originated neurons and enteric neurons in innervation varies along segments of the GI tract, which influence the autonomy of a particular GI segment. For example, the esophagus is mostly controlled only by the vagal nerve, while the small

intestine may work automatically without any central orders. Moreover, vagotomy used as a treatment of a peptic ulcer does not cause the increase mortality in patients, while Hirschprung Disease (the lack of myenteric ganglia in the intestine) is a life-threatening condition. The different physiology of different parts of GI tube is being constantly investigated to understand the pathogenesis of many structural and non-structural (functional) disorders. Furthermore, the treatment used nowadays has not managed to modulate ENS without mild or severe side effects. With the growth of the mean age in society, physicians more often face problems connected to the functionality of the lower part of the GI. More and more drugs that modulate ENS are being registered in Europe and US; therefore, a better understanding of the effects of this agent is needed. That is why in this article we aim to present actual clinical findings on colon ENS with particular focus on biogenic amines.

## SEROTONIN

Serotonin (5-hydroxytryptamine, 5-HT) is one of the most important biogenic amines for the functionality of the gastrointestinal tract. It is not only crucial for gut motility and secretion, but also is an important neuromodulator and growth factor. Despite almost 80 years of experiments and studies, the role of serotonin in physiological conditions and pathogenesis of GI disorders is not fully understood. Although serotonin is known mostly for its essential role in the pathogenesis of disorders of the central nervous system (CNS), it is important to note that it was isolated for the first time by Erspamer in 1937 from a rabbit gastric mucosa. Over 20 years later, serotonin was established as a crucial enteroamine after a series of studies performed by Bulbring et al. [10, 11, 12] Over 95% of the body's serotonin is produced in the gut. Around 90% of this content is found in enterochromaffin cells (EC) in GI tract epithelium; the remaining 10% is stored within serotoninergic enteric neurons, which amounts to around 2% of ENS [72].

In the GI tract serotonin is produced in EC, specialised enteroendocrine cells in the GI mucosa, and neurons of myenteric and submucosal plexuses. 5-HT is synthesized from an essential amino acid, L-Tryptophan, and this process is regulated by activity of rate-limiting enzyme tryptophan hydroxylase (TPH). Two isoforms of this enzyme were described within the GI tract, TPH-1 and TPH-2, in EC cells and neurons accordingly [75]. Enterochromaffin cells release 5-HT after biochemical, neuronal or mechanical stimuli of the mucous, such as colonic distention, ingestion of alimentation and after a contact with bacteria or cytokines [54].

Over 30 types of receptors for serotonin were described, cloned in the human body and grouped into 7 families (5HT1R to 5HT7R). Receptors 5HT3, 5HT4 and 5HT7 have the confirmed significant role in the motility, secretion, development and immunomodulation of the GI tract. Except for 5HT3, which is a ligand-gated ion channel, all serotonin receptors are G protein-coupled receptors. 5HT3R is expressed in the colon mainly on the endings of the myenteric neurons that stand for intrinsic primary afferent neurons (IPAN) in gut reflexes. 5HT3 is activated by increased intraluminal pressure and such a sensation of colonic distention may be then projected to both ENS by neuron bodies within submucosal plexus and, via vagal nerves, to the CNS [55]. Such activation of serotonic neurons may be then transduced as a first neuron in the motor reflex or unpleasant sensation from the bowel. 5HT4R is expressed mostly on presynaptic neurons of the ENS. Activation of 5HT4 on cholinergic nerves results in the release of acetylcholine from excitatory motor neurons into the synapsis that evokes peristalsis [48]. This phenomenon explains a key mechanism of action of 5HT4 agonists, a group of drugs used in constipated patients. However, stimulation of 5HT4R results in enhancing rather that initializing a motor response of the bowel [31]. 5HT4 receptors are also present on the gut's mucosa but their role in modulation of bowel's hypersensitivity is controversial [34]. The most recently described 5HT7 receptor is present mostly on the dendric cell (DC) within the gut. DCs are located close to the intestinal mucosa and play a significant role in initiating and modulating the process of colitis. Although the 5HT7 receptor mRNA is expressed also on mucosa and muscle layer of the gut, its role in motility is rather equivocal [35, 77].

Although many drugs affecting serotonin receptors were introduced to the market to treat bowel movement dysfunctions, an exact influence of serotonin on colonic motility is still a subject of discussion. Back in the 1960s it was stated that serotonin can definitely initiate peristaltic reflex, even after a removal of the mucosa and EC cells [65]. Modern studies are more conservative and re-introduce serotonin more as a modulator of cholinergic signaling during generation of colonic migrating motor complex (CMMC). Postprandial or neuronally induced degranulation of 5HT from EC cells changes gut movement patterns by affecting 5HT3 and 5HT4, but it is still unclear whether mucosal or neuronal receptors are more important for this process [37].

Degradation of released serotonin is not possible in the lumen of the colon, nor in an interstitial space. Serotonin is removed from that space via the serotonin-selective reuptake receptor (SERT), which is present in all epithelial cells within the gut [15] and then may be deactivated by intracellular monoaminooxdases (MAO). The rest of 5-HT that in not uptaken by the mucosa is reabsorbed by platelets circulating throughout the gut and then stands for the vast majority of serotonin circulating in the blood. It is due to ability of platelets to express SERT but no to synthesize serotonin. Changes in platelets count make it impossible to establish exact concentration of serotonin in the serum. A method to evaluate overproduction of 5-HT in the body (e.g. in patient with carcinoid syndrome) is to check urine concentration of 5-HT metabolite- 5-hydroxyindoleacetic acid (5-HIAA).

During ontogenesis, neurons within the ENS develop in a specific order from the neuronal crest, and serotoninergic nerves are the ones that differentiate at the beginning

of this process. In mice lacking TpH-2 (TPH2KO mice), depletion in the number of dopaminergic and GABA-nergic nerves were observed and colonic motility was abnormally slow. Such an effect was not reached in TPH1KO mice, which suggests that mucosal serotonin has very little or no influence on the development and survival of enteric neurons [45]. The number of enteric neurons is significantly reduced in mice lacking 5-HT4R than in the wild types, suggesting the crucial role of this receptor in the enteric neurogenesis and establishing another potential positive actions of 5-HT4 agonist in the treatment of GI motility disorders. [49] The similar, negative effect on enteric and central neurons was reached in animals with overexpressed SERT activity. In such a condition, the number of neurons in the myenteric and submucosal plexus was decreased and this process was partially reversed by the admission of 5HT4R agonists [52]. Studies performed on SERTKO mice also indicated that enhanced 5-HT signaling in the bowel increases intestinal mucosal growth and glucose and peptide absorption [33].

## SEROTONIN AND GI DISORDERS

Serotonin plays a crucial role in the motility and secretion within the GI tract and alterations in serotoninergic system were studied as a hypothetical cause of various GI disorders, such as diverticular disease, irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD).

### Diverticular disease

In the study performed on patients with diverticular disease no differences in mucosal 5-HT level, EC cell numbers, TpH-1 expression and serotonin releases in basal condition or after stimulation were seen between studied and control groups. However, in patients with a recent history of diverticulitis, a significant decrease of SERT expression was observed. The authors suggest that lower 5-HT reuptake might be the cause of post-diverticulosis alternation in colon motility [21].

### Irritable Bowel Syndrome

Irritable bowel syndrome is a condition in which sensation, secretion and motility within the gut is altered.

According to predominant symptoms, ROME IV criteria divide patients into 3 main groups: diarrhoea dominant (IBS-D), constipation dominant (IBS-C) and mixed group (IBS-M) for patients that do not fulfill criteria for the first two groups. Pathogenesis of IBS is not fully understood, but abnormalities in colonic biochemistry and disruption in gut-brain axis are established as a main cause. Results of biochemical studies in patients with IBS are ambiguous. It seems that, in general, in both IBS-D and IBS-C patients EC cells count do not differ significantly from healthy individuals and in both groups, SERT expression was diminished. The only significant difference is that serotonin serum level was significantly increased in IBS-D and decreased in IBS-C [6, 19, 24, 56]. In patients who underwent GI infection, a postinfectious IBS may occur (usually diarrhoea dominant). In this type of disorder, an increased EC cells number occurs, resulting in hypersensitivity of the bowel [25, 68]. Drugs that affect serotoninergic system and are registered to treat IBS are 5-HT3 antagonist in IBS-D and 5-HT4 agonist in IBS-C. The first group seems to be efficient by modulating intrinsic sensory neurons and bringing relief to patients suffering from bloating and distention. The second group stimulates myenteric neurons enhancing motility.

### Inflammatory Bowel Disease

Inflammatory bowel diseases are the group of chronic gut disorders of an unknown origin. The most common forms of IBD are Ulcerative Colitis (UC) and Crohn's Disease (CD). Intestinal serotonergic signalling plays a multi-faceted role in IBD pathogenesis. However, results of many performed studies have shown inconclusive results [20]. In the classic study performed by Magro et al. on mucosal speciments taken from the humans suffering from IBD, significant reduction of NE, DA and 5HT concentration was observed. Authors assumed such results due to impairment of amine synthesis in both damaged mucosal tissue and submucosal neurons [51]. Few years later, the proinflammatory role of serotonin seemed to be well established [32]. As mentioned before, especially 5HT7 receptor is now intensively studied due to initiating the immune response via interaction with DC and potent ameliorating properties of 5HT7 antagonist in IBD [40, 43]. Anti-inflammatory properties were also confirmed in rat model colitis for 5-HT3 antagonists – Tropisetron and Granisteron [29, 57]. Gershon in 2013 suggested that the influence of serotonin on colon inflammation varies not only with which receptor is activated but even where 5-HT was synthesized. The authors claimed that serotonin secreted from EC is pro-inflammatory, in contrast to "neuronal" serotonin, which is anti-inflammatory [53]. A recent study performed on patients with Crohn's Disease showed upregulation of 5HT3, 5HT4, 5HT7 and downregulation of SERT expression in changed mucosa, suggesting a clear pro-inflammatory role of 5HT in this condition [62]. Another paper published by Salaga et al. suggested another proinflammatory pathway of 5HT via reducing endocannabinoid signalling in the rat model of colitis [60]. Although serotoninergic nerves cannot create a regular synapsis with cells of immune system, there is strong evidence that they are in close functional connection.

## HISTAMINE

Histamine (2-(imidazo-4-yl) ethylaminie) is a bioamine that has multiple effects on the human body. Its name refers to the Greek histos due to a wide activity in various tissues in the mammal's body, including immune response, wound healing, cell differentiation, regulation of nervous, cardiovascular and gastrointestinal system. It was primarily synthesized in 1907 and characterized in 1910, but their connection to the mast cells was not well established until 1952 [5, 58]. Histamine is synthesized from the amino-acid histidine by the histidine decarboxylase, an enzyme that is expressed in various tissues including GI mucosa,

central and peripheral nervous system, parietal cells, EC cells, platelets, mast cells and basophils. However, only the last two are able to store the amine in specific granules. Histaminergic neurons of ENS are present mostly in submucosal plexus and they expressed all four types of receptors [8].

Histamine exerts its action by binding to four different receptors (H1–H4), numbered according to the order by which they were cloned and described. All receptors are a G-coupled protein widely spread in the whole body. They are present throughout the whole GI tract with some differences of distribution between regions and intestine wall layers [39, 69]. H1 receptor plays a pivotal role in the inflammatory and allergic response to histamine release in the whole body, but its role in the GI tract is much more diverse. In the intestine Histamine via H1 receptor causes a smooth muscle contraction and affects enteral mucosal, fluid secretion by chloride efflux and sodium absorption [1, 36]. This fact explains more specifically the pathogenesis of diarrhoea and allergic enteropathy and shows H1 antagonist as a potential solution in such disorders. Moreover, microscopic studies also revealed a close neighbouring of mast cells to enteric neurons. Mast cells overgrow, degranulation and activation of H1 and H4 receptor within the ENS play a significant role in transducing nociception from the intestine. All these facts present alteration in histamine signalling as an important part of pathogenesis of such condition as IBS and postinflammatory hypersensitivity [4, 23]. The second receptor for histamine (H2R) is well known as a target of anti-acid drugs. It is expressed on almost every layer of the intestine and the main action of its activation is gastric acid secretion, degranulation of mast cells and lymphocytes proliferation. H2 agonist does not significantly affect contraction of longitudinal smooth muscle or may even have an opposite effect [39]. The presence of H3 receptor in the human GI tract is still under discussion [8, 39, 61]. Its action refers to presynaptic, inhibitory response within histaminergic neurons in the CNS. Its alteration may influence a circadian circle and may cause cognitive impairment and metabolic syndrome [41]. Currently, H3 receptor is not taken under consideration as a target for drugs modulating intestine functions.

Described in 2000, H4 receptor was a subject of intense studies in the past 20 years. H4 receptor can be found in GI mucosa, smooth muscles and lymphoid tissue, but it is present in much lower concentrations than H1 and H2 receptors. Its stimulation causes mainly immune response within the gut, but muscle contraction was also reported [22, 39, 61].

### Histamine and colon disorders

Histamine is best known as a proinflammatory agent and it was studied as a mediator in immunological response in the GI tract. Studies about the induced colitis in various species confirmed increased mast cell degranulation within the affected large intestine and overexpression of H1 and H2 receptors in the mucosa [39]. Moreover, similar results were revealed during studies performed on the animal models of IBS. That would be in accordance to lower urine histamine concentration in individuals who follow FODMAP diet that is recommended for patients suffering from IBS [28]. Taking everything into consideration, histamine antagonist and mast cell stabilizers are interesting potential agents in treating both IBS and IBD.

## DOPAMINE

Dopamine (DA) is a crucial neurotransmitter for functionality of the central and peripheral nervous system. It is synthesized from aminoacid alanine. The influence of DA on the GI motility and its functions have been studied since the late 1970s [42]. For many years, DA was believed to be produced only in the neurons. Early 1990s findings revealed that DA may also be synthetized in non-neuronal cell bodies of mesenteric tissue, such as the pancreas, intestine and spleen, creating another peripheral amine system. The same study proved that 43% of GI dopamine pool is the final product of synthesis, not converted further into noradrenaline (NA). This explains why the concentration of DA, which is an intermediate product in synthesis pathway of NA, is altered during stress [26, 79]. Further studies revealed that dopamine modulates GI motility, blood flow, fluid absorption and intestinal secretion in various species. Dopamine may be synthesized within every part of the GI tube [73]. It is also one of the substances crucial for the development of the ENS and neuronal crest [46]. Similarly to serotonin, dopamine is re-uptaken from the neuronal junction by the specific transporter called dopamine amine transporter (DAT).

Dopamine affects the GI tract via five receptors divided into two families: D1-like-D1 (D1a) and D5 (D1b) receptors, and D2-like- D2,D3,D4 receptors [7]. They present a certain specificity in distribution among tissues. It is still unclear what the exact location of the receptors is in the intestinal wall layers, especially submucosal and myenteric plexuses. D5 receptors are widely distributed on the colonic goblet cells and stimulation of these receptors results in increased mucus production in the colon [44]. Li et al. suggested that the D2 receptor is exclusively expressed within neurons, while the other dopamine receptors are detected in mucosa and neurons in the gut [46]. The importance of D2 receptor role in GI motility is confirmed by clinical observation in psychiatric patients. Patients treated with neuroleptics, which are mainly D2-antagonist, present constipation as a common side-effect in this population.

Dopamine is well established as an inhibitory modulator of the GI movement. In the study performed by Walker et al., the blockade of D1 and D2 receptors increased significantly the basic tone and spontaneous phasic contractions of smooth muscles. Inhibitory effect was pronounced even better in DAT knock-out mice [74]. The authors suggest that dopamine connects with D2R on both the pre- and postsynaptic level of the junction and D1R only on the postsynaptic one. On the contrary, Auteri et al. found D2R only on the postsynaptic level and D1R on the presynaptic side of the gap. In their study, D1R activation reduced acetylcholine release within the ENS and increased concentration

of inhibitory neurotransmitters, such as nitric oxide and purines in the examined tissue [3]. As noted above, Zizzo et al. recently confirmed direct action of DA within muscle layer of the intestine. They claimed that D1 receptor activation causes a contraction of circular muscle layer and D2R activation results in the relaxation of the longitudinal muscle layer [81]. Zhang et al. distinguished the role of D1 and D2 receptor in a different way, suggesting that direct inhibition of the muscle layer resulted via D1R (especially in distal colon) without involving the ENS, and D2R is only a weak modulator of the whole process. Author introduces dopamine mainly as a precursor of noradrenaline [79]. Liu et al. treated rats with inhibitors of monoamine oxidase A (MAO-A, an enzyme that degrades dopamine), which resulted in a reduction of colonic motility. They did not settle whether neuronal or muscular modulation of DA receptors is crucial for this process [47]. Some authors establish dopamine as a neuronal modulator only within ENS plexuses [46]. The results of recent studies suggested that dopamine has a direct influence on the muscle layers of the gut without involving neuronal DA receptors [79, 81].

Similarly to CNS, dopamine synthesis in Parkinson's disease patients is also decreased in ENS. Surprisingly, constipation is a common complaint in this population, and treatment with L-DOPA alleviates those symptoms [64]. Impairment in dopaminergic system was also stated as a part of pathogenesis of IBD. A few animal model treatments with D2R antagonist decreased the severity of colitis and size of mucosal lesions. It was achieved by decreasing inflammatory mediators, reducing activation of myeloperoxidase, limiting vascular permeability and excessive vascular leakage of the inflamed mucosa [38, 71, 78].

## MELATONIN

Melatonin (N-acetyl-5-methoxytryptamine) is a close derivative of serotonin and was primarily identified in the pineal gland. It is commonly introduced as a hormone responsible for circadian cycle, but, what is not widely known, the majority of melatonin in mammals' circulation originates in the GI tract. In some GI tissues their concentration level is over 400 times higher than pineal gland and 10–100 fold greater that in the serum [14]. Melatonin synthesis occurs, similarly to serotonin, in mucosal EC cells and is attenuated by food intake. Unlike the pineal melatonin, GI hormone blood concentration is not affected by the day-night circle. Melatonin is hypothesized to be a natural antagonist of serotonin in the GI tract and they may work as counterbalancing systems [70]. Melatonin inhibits the contraction of the muscular layer in the stomach, ileum and colon, reduces basal electric activity of the GI tract, increases GI transit time, increases mucous production and has a protective role in the pathogenesis of stress induced ulcerations, inflammatory bowel disease and colorectal cancer [9, 76]. Postprandial mucosal synthesis of melatonin and its increased intraluminal concentration was confirmed in a few studies, however, other origins of gut's melatonin are also taken under consideration, such as the pineal gland, alimentation or microbiota. Paradoxically, long fasting also increases plasma and tissue level of melatonin in the animal models.

Two melatonin receptors were described, type 1A (MT1) and 1B (MT2), which are both G-coupled receptors. In the study performed by Soderquist et al. on human tissue from resected intestine, MT1 receptors were likely to be found in the colonic mucosa and submucosal plexus in the colon. They were not present in the smooth muscles. MT2 receptors were present in all studied tissues in the all GI levels (stomach, small intestine, colon) with an especially high concentration in enterocytes, EC cells, submucosal and myenteric plexuses [66].

With its modulatory effect on GI motility, circadian cycles and abdominal pain, melatonin is described as a potential agent for the treatment of IBS and a few clinical trials on this group of patients were performed. Improvement of symptoms, especially in individuals with sleep deprivation, with no major side effects were observed. However, dosage and treatment period varied among tested groups, and is not yet established [17, 50, 59, 67].

Melatonin is also well known as an anti-inflammatory and anti-oxidant agent that reduces synthesis of cytokines, proteases and Th2, Th13 and Th17 lymphocytes, thus alleviating colitis and reducing oxidative stress in the tissue. However, the mechanism of melatonin's action is still unclear. Currently, NK-kB/TLR4 pathways seem to be the most crucial for the process [13]. Studies performed with specific agonists negated the direct involvement of MT receptors in healing colitis [80]. This amine was intensively tested on IBD model rodents with promising results in alleviating the symptoms, protecting enteric neuronal tissue and facilitating healing of the mucosa [13, 16, 27, 63]. In a small trial on humans, melatonin was tested as an adjuvant treatment to mesalazine, resulting in a lower risk of recurrence of the disease during a 12-month observation [18]. Results are promising, especially in patients with anxiety and sleep disturbances, but more clinical studies on humans are needed. In rodent models, melatonin also improved intestine healing after radiotherapy-induced damage and reduced the negative histopatological effect of chemotherapy in post-operative intestine [2, 30].

## CONCLUSIONS

Biogenic amin signalling in the colon is a very complex and still not well-understood system. It is a very potent target for drugs that may modulate the outcome of GI functional disorders and inflammatory bowel diseases. The vast majority of noted studies were performed *in vivo* on rodents, animals with drug-induced disorders or human colonic tissue taken during the oncological surgical resections. Very little is known about neuronal physiology and *in vivo* changes in pathologically changed colonic mucosa in humans. It is also important to note that cited authors usually limited

their investigation to the one amine system at a time and such an approach can result in overestimating the role of certain, isolated parts of this complicated net of connections. Furthermore, the high availability of endoscopic procedure facilitates obtaining intestinal samples. In an aging society, where GI disorders have a strong impact on quality of life and in the presence of potential drugs tested or those already registered on the market, further studies on the biochemical background of human colon functions should be performed.

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The authors have no potential conflicts of interest to declare.