



Serotonin: What is it Doing in My Gastrointestinal Tract?

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At a Glance

- Serotonin (5-HT) is a chemical that transmits signals to targets within the body.
- Serotonin is found in the central nervous system, GI tract, and blood.
- Most serotonin is in the GI tract.
- Serotonin can affect gut movement (motility) and sensitivity.
- Serotonin is a target for drug development to treat functional GI disorders.

Serotonin is an important *signaling molecule* in the gastrointestinal tract. It triggers reflexes that are crucial for the digestion of food and the elimination of waste products. It can initiate the transmission of signals related to gut pain and discomfort. Several lines of evidence indicate that serotonin signaling is altered in functional gastrointestinal disorders. Pharmacological treatment strategies have been developed for these disorders that target the serotonin signaling pathway, aiming to restore normal gastrointestinal function.

Serotonin was first discovered in the gut

Serotonin (5-HT) is well known as a *neurotransmitter* in the central nervous system (brain and spinal cord). Alterations in serotonin signaling in the brain have been implicated in a number of psychologic disorders. An interesting fact that most people are not aware of is that serotonin was first discovered in the gastrointestinal (GI) tract. An Italian physiologist named Vittorio Erspamer found that application of a compound he extracted from the

Words to Know

5-HT: Serotonin

Agonist: An agent that activates receptors

Antagonist: An agent that blocks receptors

Enterochromaffin (EC) Cells: Cells lining the gut that produce and store serotonin

Neuron: A nerve cell

Neurotransmitter: A chemical that carries messages to neurons

Receptor: A molecule on each cell that selectively receives and binds a specific substance including neurotransmitters

SERT: A protein that removes serotonin from nerve cell space

Signaling molecule: A chemical that transmits signals between cells

Synapse: The junction space between adjacent neurons

intestines causes the gut to contract. He called the compound “enteramine,” and in subsequent studies he demonstrated that the vast majority of the enteramine in our bodies (over 90%) is located in the GI tract. A few years later, investigators in Cleveland, Ohio searching for molecules contributing to high blood pressure found a chemical in serum that constricted blood vessels, and they called it “serotonin.” Subsequently, it was determined that enteramine and serotonin are actually the same chemical, 5-HT, but since the work on “serotonin” was much more active at the time, the name serotonin stuck.

Serotonin is an important signaling molecule in the gut

In the GI tract, 5-HT is used as a neurotransmitter by some gut nerve cells (*neurons*), but most of the 5-HT in the gut is synthesized and released by specialized cells in the GI lining called *enterochromaffin (EC) cells*. EC cells act like taste buds of the intestines, and release 5-HT in response to signals detected inside the gut interior (lumen) including certain chemicals and pressure. Once released 5-HT binds to *receptors* located on nearby nerve terminals and activates intestinal reflexes that promote the mixing and movement of the food and beverage that have been ingested. It increases secretion of fluids into the lumen to assist in the digestive process and enhance blood flow to the intestines. Serotonin released from EC cells also activates sensory nerve fibers that transmit signals to the central nervous system related to digestive reflexes, and gut pain and discomfort. In addition to serving as an important trigger of gut reflexes, 5-HT appears to play a role in promoting the survival and wellbeing of nerve cells, including cells involved in regulating movement (pacemaker cells) in the gut.

After serotonin signals nerves in the gut, it has to be removed. When serotonin sits around too long after release it can over-stimulate reflexes. It can also desensitize receptors so they stop responding. Changes in gut function may result.

An essential step that is involved in chemical signaling between cells by molecules such as 5-HT is the ability to stop the signaling once it has begun. Serotonin signaling in the intestine is stopped via reabsorption (reuptake) by a protein called the serotonin transporter (*SERT*). This is the same serotonin transporter that stops 5-HT signaling at *synapses* in the central nervous system. It also is the molecule whose function is inhibited by serotonin selective reuptake inhibitors (SSRIs), which are commonly prescribed for the treatment of depression and anxiety disorders. In the gut, SERT is located on essentially all of the cells that line the intestines. Therefore, it is as though the gut has a huge sponge responsible for regulating levels of 5-HT, and this is

further evidence of the importance of 5-HT signaling for gut function.

Intercellular signaling molecules, such as 5-HT, transmit messages to stimulate a response by activating receptors on nearby cells. This works sort of like a key selectively opening a certain lock. One of the notable aspects of 5-HT signaling is the large number of different types of 5-HT receptors that exist. A total of fourteen 5-HT receptor subtypes have been identified so far, and of these, ten have been found in the GI tract. (Serotonin receptors are identified by numbers following “5-HT”; e.g., 5-HT₁, 5-HT₂, etc.) In the gut, 5-HT receptors are located at specific sites along the neural circuitry within the wall of the stomach and intestines, as well as on smooth muscle cells and cells along the gut lining.

5-HT released in the gut by EC cells can also have actions at more distant sites. 5-HT that is not taken up by the serotonin transporter passes into the blood stream where it is taken up into specialized cells in the blood stream (platelets), which use 5-HT to help with blood clotting. Recent evidence suggests that 5-HT circulating in the blood stream influences bone density. 5-HT in the blood stream can stimulate the cells that are constantly forming bone (osteoblasts), through action on 5-HT_{1B} receptors. This can alter the normal development of these cells, and may lead to changes in bone density. Therefore, the amount of 5-HT released in the gut can have an impact on bones.

Serotonin signaling in the gut is altered in functional GI disorders

A number of recent studies have reported that gastrointestinal disorders, including functional disorders, may be associated with alterations in various aspects of 5-HT signaling. Examples of the types of changes that have been detected in intestinal tissue samples from individuals with irritable bowel syndrome (IBS) include changes in the amount of 5-HT, changes in the number of EC cells, and changes in the amount of SERT. Any one or combination of these changes could alter normal gut reflexes and sensation.

Genetics related to 5-HT signaling may also be involved in the development of functional GI disorders. Certain sections, or “regions,” of the gene for SERT can exist in different forms in different individuals. These regions of the gene are thought to affect the amount of SERT that is made by the cells that do make this transporter molecule. Investigations are under way to determine whether individuals with certain forms of the SERT gene are more or less likely to develop functional GI disorders.

At this point, a consensus pattern of alterations has not emerged, but enough studies have reported changes that suggest 5-HT signaling is altered in functional GI disorders. However, this still leads to questions regarding the cause and effect relationship. In other words, do changes in 5-HT signaling contribute to abnormal bowel habits and sensation, or do abnormal bowel habits and sensation lead to compensatory changes in 5-HT signaling in an effort by the body to restore normal function? Future studies are required to address these issues.

Many therapies for functional GI disorders involve serotonergic targets in the gut

Given the importance of 5-HT as a signaling molecule for gut function and sensation, it is not surprising that pharmacological strategies targeting 5-HT signaling have been developed to improve bowel function and ease pain and discomfort. The existence of so many 5-HT receptors that serve various functions in the gut provides the opportunity to increase or decrease gastrointestinal functions such as motility and secretion through selectively blocking or activating certain subtypes of 5-HT receptors.

Two 5-HT receptor subtypes in particular, the 5-HT₃ and 5-HT₄ receptors, have been exploited as targets for the development of medications to treat functional GI disorders. For example, blockers of 5-HT₃ receptors (5-HT₃ *antagonists*) have been used to treat IBS with diarrhea. These compounds are thought to act by blocking the stimulation of nerves near the intestinal lining when 5-HT is released from EC cells. This would inhibit local reflexes controlling motility and secretion, and decrease the frequency and

strength of painful signals passing to the central nervous system.

Drugs that stimulate 5-HT₄ receptors (5-HT₄ *agonists*) have been used to promote gastric emptying in cases of gastroparesis, a disorder when the stomach takes too long to empty its contents. These drugs have also been used to treat IBS with constipation, and chronic constipation. 5-HT₄ agonists are thought to act by increasing the release of another neurotransmitter, acetylcholine, from nerves in the gut. Acetylcholine enhances gastrointestinal motility and secretion.

Unfortunately, drugs acting at 5-HT receptors have had a turbulent history. Cisapride (Propulsid), a 5-HT₄ agonist, was removed from the market when it was determined that, in addition to stimulating 5-HT₄ receptors, it blocks a cellular passageway (potassium channel) that is important to heart function. This is an example of a situation in which it took a long time to completely understand the mechanism of action and the adverse side effects of a very effective medication. Cisapride was originally classed as a cholinergic compound because it was known to increase acetylcholine release, and acetylcholine stimulates gut reflexes. Subsequently, the 5-HT₄ receptor was discovered, and it was determined that cisapride acts by stimulating this 5-HT receptor subtype. Years later, a type of potassium channel was discovered called the ERG channel that is important in regulating the rhythm of the heart, and mutations of this channel's gene cause irregularities in the electrocardiogram (ECG). Regrettably, this is the same potassium channel that is blocked by cisapride, and individuals with the mutation in this gene are susceptible to heart failure when they take the drug. Initially, the manufacturer of cisapride considered recommending that patients undergo an ECG test before going on the drug, but ultimately it was removed from the market.

Tegaserod (Zelnorm) was available for five years before it was removed from the market. Tegaserod is a 5-HT₄ agonist that was prescribed for the treatment of IBS with constipation. Analysis of collective data

from a number of studies suggested that the risk of heart attacks and strokes was greater for individuals taking tegaserod than those on placebo. It is worth noting that the placebo group from these studies had an incidence of cardiovascular disease that was lower than the general population, and some of the individuals who were taking tegaserod in these studies had preexisting conditions. The drug was withdrawn from the U.S. market in 2007.

Alosetron (Lotronex) is a 5-HT₃ antagonist that has been used for the treatment of IBS with diarrhea. After it was released, alosetron was temporarily withdrawn from the market because a number of individuals experienced severe constipation and ischemic colitis, which is an inflammation of the colon caused by decreased blood flow. It is not completely clear whether the drug caused these conditions, if individuals with constipation were inappropriately prescribed the drug, and/or if it was associated with the increased incidence of ischemic colitis that occurs in IBS. In the U.S., physicians who have enrolled in a program mandated by the Food and Drug Administration (FDA) for registered prescribers can now prescribe alosetron. This program involves measures to assure that the patient understands the potential adverse effects of the drug and can recognize them at an early stage if they do occur.

Conclusion

In conclusion, many individuals have benefited greatly by treatments involving 5-HT₃ antagonists or 5-HT₄ agonists, and the adverse effects associated with their use are not completely understood. Hopefully, future research into the development of selective drugs and delivery strategies will enable the safe use of drugs targeting these receptors and allow for the effective management of symptoms in functional GI disorders.

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