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### “Little brain” in the gastrointestinal (GI) tract

The *enteric nervous system*, or the “little brain” in the gut, refers to the nerves in the wall of the intestines that control how the gut reacts to food. It regulates digestion, nutrient absorption, and waste elimination. When the digestive system is not working properly, symptoms like diarrhea, constipation, vomiting, and abdominal pain can occur. These responses all involve the actions of the enteric nervous system.

**Gastrointestinal (GI) tract** is the system of connected digestive organs starting with the mouth, proceeding through the esophagus, stomach, intestines and anus.

**Enteric nervous system** is the system of nerves in the gastrointestinal (GI) tract.

### Function

In the gastrointestinal (GI) tract, chains of nerves called neural circuits are in the wall of the intestine. They can regulate various features of GI function such as *motility* and *secretion*.

While these neural circuits can be controlled by the brain, they can also function independently. The enteric nervous system has many special features, including:

- 1. Sensitivity:** The enteric nervous system can sense invasive organisms like bacteria and viruses. This activates a protective response like vomiting or diarrhea. It can also sense nutrients and activate digestion.
- 2. Intestinal motility:** The enteric nervous system processes information about nutrients and invading pathogens. This activates the appropriate gut behaviors, like mixing contents around for digestion or propelling them along the gut for elimination.

**Motility** is movement in the body (in this context, usually movement of food through the GI tract).

**Secretion** is the act of releasing a substance within the body, usually by a gland.

- 3. Secretion:** This system also can activate or suppress the activities of muscles or glands in the gut.

The nerve cells of the intestines regulate all these functions. In patients with gastrointestinal illnesses with *inflammation*, like Crohn’s disease or ulcerative colitis, activities like sensitivity, motility and secretion are altered, and the individuals suffer from a range of symptoms.

Recent discoveries have shown that inflammation leads to changes in the response of nerves. This can disturb GI motility and sensitivity and might be involved in *functional GI disorders*. These changes to the GI function can be long-lasting. They can also continue even after the inflammation has been cleared up.

**Inflammation** is a reaction that happens in tissues, which includes redness, swelling, tenderness, pain, and heat.

**Functional GI disorders** are disorders that occur because of abnormal functioning of the GI tract, which can affect motility, sensation, and brain–gut communication.

### Serotonin Signaling in the GI Tract

Serotonin (also called 5-HT) is a signaling molecule, or neurotransmitter, in the brain that influences one’s state of mind. It may be surprising that most of the body’s serotonin is in the GI tract. Here it is made by specialized cells in the intestine called enterochromaffin (EC) cells as well as neurons. Serotonin is absorbed in the intestine by a protein called the serotonin selective reuptake transporter (SERT; the target of SSRIs), located

**Serotonin** is a neurotransmitter, also called 5-HT, whose activity is impaired in inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS).

**Enterochromaffin (EC) cells** are specialized cells in the lining of the intestine that produce and secrete serotonin/5-HT.

on cells in the inner lining of the intestines. Serotonin signaling can be affected by some anti-depressants and is impaired in people with inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS).

### **Current Research**

Regulating serotonin selective reuptake transporter (SERT) activity is a major research focus. Scientists are studying how nerve cells control muscles in the GI tract under normal and diseased conditions. Also, scientists are interested in better understanding how serotonin is involved in digestion and what changes it causes in IBD and IBS.

A better understanding of how serotonin works in the gut could be useful for developing safe and effective treatments for functional GI disorders.

### **5-HT<sub>4</sub> Receptor as a Potential Target for Treatment**

A type of serotonin receptor (the 5-HT<sub>4</sub> receptor) has been identified as a potential target for new medications. Drugs that activate this receptor are called as 5-HT<sub>4</sub> agonists. Examples include cisapride, tegaserod, prucalopride, and mosapride. These have been approved to treat constipation but there are concerns about cardiovascular side effects.

One potential site of action of these drugs is on nerve terminals of the enteric nervous system, where their stimulation increases neurotransmitter release. Recent research has shown that essentially all the cells in the inner lining of the colon have the 5-HT<sub>4</sub> receptor. Studies showed that using 5-HT<sub>4</sub> agonists led to secretion of fluids, mucus, and serotonin. These actions may help reduce constipation and pain in the colon. It may be possible to create 5-HT<sub>4</sub> agonists that act only in the gut, which may help avoid side effects in the rest of the body.

### **Conclusions**

Each meal triggers a highly choreographed series of reflexes along the GI tract that allow absorption of nutrients and elimination of waste. Ongoing research is aiming to identify the key elements of these reflexes at the molecular, cellular, and tissue levels, to figure out the implications for gut function and sensitivity. Collectively, this research is revealing new targets for the treatment of inflammatory and functional GI disorders.

### **Key Points**

- The nerves in the wall of the intestines control how the gut reacts to an ingested meal.
- These neural circuits regulate the sensitivity, intestinal motility and secretions of the gut.
- Inflammation in the gut, due to GI disorders, disrupts the normal neural functioning in the gut.
- Studying the electrical properties of single neurons can detect changes potentially responsible for altered gut function and sensitivity.
- Serotonin (5-HT) is a signaling molecule synthesized by enterochromaffin (EC) cells in the intestine. The 5-HT signaling is compromised in people with inflammatory bowel disease (IBD) and in irritable bowel syndrome (IBS).
- Medications that act on the 5-HT<sub>4</sub> serotonin receptor may be potential treatment.

### **Related Fact Sheets from IFFGD**

- 121: Gut Motility in Health and Irritable Bowel Syndrome
- 161: Antidepressants and Functional GI Disorders
- 243: Serotonin: What Is it Doing in My GI Tract?

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