15.6.1.2: Hormones of the Gut

Over two dozen hormones have been identified in various parts of the gastrointestinal system. Most of them are peptides and many of them are also found in other tissues, especially the brain. Many act in a paracrine manner as well as being carried in the blood as true hormones. Their importance to health is uncertain as no known deficiency disorders have been found for any of them. We shall look at 8 of them here:

1. gastrin
2. somatostatin
3. secretin
4. cholecystokinin (CCK)
5. fibroblast growth factor 19 (FGF19)
6. incretins
7. ghrelin
8. neuropeptide Y (NPY)
9. peptide YY3-36 (PYY3-36)

The endocrine cells of the small intestine also secrete serotonin and substance P.

Gastrin

Gastrin is a mixture of several peptides, of which the most active contains 14 amino acids. It is secreted by cells in the stomach and duodenum. It stimulates the exocrine cells of the stomach to secrete gastric juice, a mixture of hydrochloric acid and the proteolytic enzyme pepsin.
Somatostatin

This mixture of peptides is secreted by cells in the gastric glands of the stomach and acts on the stomach (thus a paracrine effect) where it inhibits the release of gastrin and hydrochloric acid, the duodenum where it inhibits the release of secretin and cholecystokinin and the pancreas where it inhibits the release of glucagon. Taken together, all of these actions lead to a reduction in the rate at which nutrients are absorbed from the contents of the intestine. Somatostatin is also secreted by the hypothalamus and the pancreas.

Secretin

It is a polypeptide of 27 amino acids and is secreted by cells in the duodenum when they are exposed to the acidic contents of the emptying stomach. It stimulates the exocrine portion of the pancreas to secrete bicarbonate into the pancreatic fluid (thus neutralizing the acidity of the intestinal contents).

Cholecystokinin (CCK)

A mixture of peptides, of which an octapeptide (8 amino acids) is the most active. It is secreted by cells in the duodenum and jejunum when they are exposed to food. It acts on the gall bladder stimulating it to contract and force its contents of bile into the intestine and on the pancreas stimulating the release of pancreatic digestive enzymes into the pancreatic fluid. CCK also acts on vagal neurons leading back to the medulla oblongata which give a satiety signal (i.e., "that's enough food for now").

Fibroblast Growth Factor 19 (FGF19)

A protein of 216 amino acids and is secreted by cells in the lower portion of the small intestine (the ileum). Travels in the hepatic portal system to the liver where it stimulates the synthesis of bile acids, uptake of glucose and its conversion into glycogen. It also travels to the gall bladder where it relaxes its smooth muscle wall allowing filling (in contrast to CCK which contracts the gall bladder).

Incretins

The release of insulin from the pancreas is much greater when glucose is ingested with food rather than injected intravenously. It is due to the fact that the arrival of food in the duodenum stimulates the release of polypeptides called incretins. The two most important are:

- glucagon-like peptide-1 (GLP-1) the most active version of which has 29 amino acids
- glucose-dependent insulinotropic polypeptide (GIP) of 42 amino acids.

Their effects:

- enhancing the ability of glucose to stimulate insulin secretion by the pancreas
- stimulating the ability of the tissues (e.g., liver and muscle) to take up glucose from the blood
• slowing the emptying of the stomach
• suppressing glucagon secretion
• suppressing appetite thus reducing food intake.

All the actions prevent a sharp rise in blood glucose when consuming a sugar-rich meal. Exenatide (Byetta®) and liraglutide (Victoza®) are synthetic peptides that mimic the action of GLP-1 but the effects are longer-lasting. They are being used to treat patients with type 2 diabetes.

Ghrelin

Ghrelin is a lipopeptide consisting of 28 amino acids with a covalently attached 8-carbon fatty acid. Ghrelin is secreted by endocrine cells in the stomach, especially when one is hungry and acts on the hypothalamus to stimulate feeding. This action counteracts the inhibition of feeding by leptin and PYY3-36. Ghrelin increases the deposition of adipose tissue in mice and rats and does not seem to increase their appetite (ghrelin knockout animals don’t eat any more food than normal animals).

Neuropeptide Y (NPY)

Neuropeptide Y contains 36 amino acids. It is a potent feeding stimulant and causes increased storage of ingested food as fat. Neuropeptide Y is also secreted by neurons in the hypothalamus where it blocks the transmission of pain signals to the brain and induces a calming effect in laboratory animals exposed to stressful situations. Velneperit is a drug that blocks the action of neuropeptide Y on its receptors. It is in clinical trials for the treatment of obesity.

PYY3-36

Peptide YY3-36 contains 34 amino acids, many of them in the same positions as those in neuropeptide Y. But the action of PYY3-36 is just the reverse of that of NPY, being a potent feeding inhibitor. It is released by cells in the intestine after meals. The amount secreted increases with the number of calories ingested and especially when these are derived from proteins rather than carbohydrates or fats. (This may explain the efficacy of the protein-rich, carbohydrate-poor Atkins diet.) PYY3-36 acts on the hypothalamus to suppress appetite, the pancreas to increase its exocrine secretion of digestive juices, and the gall bladder to stimulate the release of bile.

The appetite suppression mediated by PYY3-36 works more slowly than that of cholecystokinin and more rapidly than that of leptin. In a recent human study, volunteers given PYY3-36 were less hungry and ate less food over the next 12 hours than those who received saline. Neither group knew what they were getting, but one of the side-effects of injected PYY3-36 is a feeling of nausea and a bad taste to food which might account for these results!

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