Effect of galanin and its analogues, M15, M35 and C7 and somatostatin immunoneutralization on the gastrointestinal tract in human and animal models

Ph.D. thesis

István Kisfalvi M.D.

Semmelweis University
School of Ph.D. Studies

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István Kisfalvi M.D.

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Program Leader:  Prof. Dr. Tulassay Zsolt M.D., D.Sc.

Consultant:  Prof. Dr. Varga Gábor D.Sc.

Opponents:  Prof. Dr. Mózsik Gyula M.D., D.Sc.
Dr. Herszényi László M.D., Ph.D

Committee:  Prof. Dr. Regőly-Mérei János M.D., Ph.D.
Prof. Dr. Banai János M.D., Ph.D.
Prof. Dr. Takács Tamás M.D., D.Sc.

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The complex mechanism of digestive, secretory, motility and excretory functions in the gastrointestinal tract requires a very elaborated regulation involving neuropeptides, the central nervous system and enteric neuronal system. So far over 50 gastrointestinal peptides have been described, some of them are well characterized, like somatostatin. In case of some recently discovered neuropeptides, like galanin, we are still in the process of collecting data about their effects and importance.

Recently developed techniques in immunology and pharmacology provide effective tools to describe the presence and localization of specific peptides in certain tissues, and to characterize their physiological and pathophysiological roles in vivo and in vitro, both in humans and animal models. Furthermore, production of new selective antagonists and specific monoclonal antibodies leads to a specific approach in understanding the role of endogenous bioactive peptides in physiological actions and certain diseases.

By using some of these modern techniques I studied the effect of galanin and somatostatin in details on gastric acid and pancreatic enzyme secretion in vivo. I described the effect of galanin and its newly developed potent antagonists on gastrointestinal motility (in the stomach and small intestine). My data provide evidence, for the first time, about the presence and effect of galanin in the human jejunum.

Galanin is a 29-amino-acid neuropeptide originally isolated from porcine intestine and subsequently found to be widely distributed in the central nervous system and most parts of the gastrointestinal tract. Galanin has been suggested to have a wide range of biological functions in the central nervous system (CNS) and in the gastrointestinal tract. The importance
of galanin in food intake, cognition, pain perception, aging and Alzheimer-disease stimulated a broad array of investigation focusing on the brain and the central nervous system, but little is known about its effect on the regulation of gastrointestinal functions. The most potent galanin antagonists in the CNS are the chimeric peptide analogues M15, M35 and C7. I was the first to study and publish the effect of these antagonists on physiological gastrointestinal actions.

Aims

I studied the effect of galanin, the putative analogues and somatostatin in the following gastrointestinal functions:

- the effect of galanin, M15, M35 and C7 on gastric acid secretion in conscious rats
- the effect of galanin, M35 and C7 on pancreatic amylase secretion in vivo, in rats
- the effect of galanin, M15, M35 and C7 on gastric emptying in conscious rats
- the effect of galanin, M15, M35 and C7 on the contractions of isolated rat jejunal smooth muscle
- the effect of galanin, M15, M35 and C7 on the contractions of isolated human jejunal smooth muscle
- the presence of galanin immunoreactive nerve fibers in the human jejunum
- using somatostatin immunoneutralization I studied the involvement of endogenous somatostatin in the regulation of basal and stimulated gastric acid and pancreatic enzyme secretion in vivo, in anaesthetized rats
Results

- Galanin inhibited pentagastrin-stimulated gastric acid secretion, the effect was dose dependent and reversible. M15, M35 and C7 analogues functioned as agonists, mimicking the effect of galanin on gastric acid secretion.

- Galanin inhibited CCK8-stimulated pancreatic amylase secretion in a dose-dependent and reversible manner. The galanin analogue M35 and C7 behaved as galanin antagonists on inhibiting the amylase output.

- In conscious rats neither galanin nor its chimeric analogues M15, M35 or C7 affected the gastric emptying of non-caloric liquids, indicating that galanin does not play a role in the regulation of gastric emptying.

- Galanin and acetylcholine were equally effective in stimulated the contractions of the isolated rat jejunal muscle. The effect of galanin was dose-dependent. M15 and M35 did not antagonize it, moreover, they acted as galanin agonists.

- The stimulatory effect of galanin on isolated jejunal smooth muscle contractions was not inhibited by either atropine or tetrodotoxin indicating a direct effect on the smooth muscle cells.

- Galanin stimulated the contractions of isolated human jejunal muscle in a dose-dependent manner. The effect of galanin was equal to that of acetylcholine, suggesting a physiological role of galanin in the
regulation of the motility in small intestine, in humans.

- The effect of galanin on isolated human jejunal smooth muscle was not inhibited by either atropine or tetrodotoxin indicating that galanin may have a direct effect on human intestinal smooth muscle.

- Our morphological studies (with immunohistology) served as the first demonstration of galanin immunoreactive neurons being present in the human jejunum. Galanin immunoreactive nerve fibers were found in all layers of the small intestine, with their density more pronounced in the inner circular muscle layer. Galanin immunoreactive fibers were found in close proximity to the muscle cells.

- Immunoneutralization of somatostatin with a monoclonal antibody resulted in a considerable increase in basal acid secretion and this effect did not depend on the type of anesthetics. Somatostatin immunoneutralization, however, did not affect basal pancreatic amylase secretion but significantly increased the previously stimulated (CCK-8 induced) amylase secretion.
Conclusions

- Galanin may have a physiological role in the regulation of gastric acid secretion and pancreatic enzyme secretion.

- The peripheral galanin receptors that are involved in the regulation of gastrointestinal secretory functions are distinct from those originally found in the brain and spinal cord.

- Galanin is a potent physiological regulator of jejunal muscle contractions both in rats and humans.

- The widely distributed galanin immunoreactivity in the human jejunum wall suggests the involvement of galanin in the regulation of human intestinal functions (including motility).

- The galanin-stimulated contractions in the human jejunum are results of direct effects of galanin on the smooth muscle cells.

- The opposite effects of the galanin analogues in the gastrointestinal tract and in the central nervous system (agonist versus antagonist effects) requires more attention and careful administration of pharmacological agents affecting galanin responses, in the future.

- Endogenous somatostatin mediates suppression of basal gastric acid secretion but not of basal pancreatic amylase secretion. However, the stimulatory effect of somatostatin immunoneutralization on CCK-stimulated pancreatic enzyme secretion suggests that endogenous somatostatin may be a physiological regulator of stimulated pancreatic enzyme secretion.
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