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# THE HISTORY OF GASTROINTESTINAL HORMONES AND THE POLISH CONTRIBUTION TO ELUCIDATION OF THEIR BIOLOGY AND RELATION TO NERVOUS SYSTEM

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At the turn of XIX and XX century, the principal concept explaining the mechanism of secretory activity of the digestive glands was *nervism* proposed by I. P. Pavlov at Russian physiological school in St Petersburg, and this dogma was widely recognized for several years in other countries. The discovery of secretin in 1902 by W.B. Bayliss and E.H. Starling, and then of gastrin in 1906 by J.S. Edkins, emphasized the hormonal regulation of pancreatic and gastric secretion, respectively. In 1943, A.C. Ivy and E. Olberg discovered a hormone, which contracts the gallbladder - cholecystokinin (CCK), while A. Harper and H.S. Raper described another hormone, pancreozymin, which stimulated pancreatic enzymes. It required over twenty years, however, for these and many other hormones to be identified, purified and synthesized due to the extensive work of several teams including R. Gregory, G. Dockray and Kenner of the UK; J. Rehfeld of Denmark and E. Wunsch of Germany for their work on gastrin; E. Jorpes and V. Mutt of Sweden and N. Yahaihara of Japan for their work on secretin and other GI hormones including, CCK, vasoactive intestinal peptide (VIP), gastric inhibitory peptide (GIP), motilin, gastrin-releasing peptide (GRP) and others peptides. CCK and pancreaozymin were found by E. Jorpes and V. Mutt to represent structurally a common messenger for pancreatico-biliary secretion. This rapid development of GI endocrinology in the 1960s and 1970s could be attributed to the application of peptide biochemistry in characterizing various peptide hormones. The technique of radioimmunoassay by S.A. Berson and R.S. Yalow in 1959 measured minute amounts of hormones in the circulation and tissue, and the technique of immunocytochemistry detected the cellular origin of these hormones. Further progress in molecular biology led to sequencing GI hormones and their prohormones, and opened a new area of investigation for the physiological role of these hormones in the mechanism of digestive gland secretion, motility of gastrointestinal tract, visceral blood flow, tissue growth and integrity in health, as well as in various digestive diseases. Overall, apparent divergent concepts, the nervous control (Pavlov) and hormonal control (Bayliss and Starling), greatly facilitated the elucidation of the interacting neuro-hormones during the cephalic, gastric, and intestinal phases of gastric and pancreatic

secretion in health and digestive diseases. Although Polish contributions in the early phase of GI endocrinology concerned mostly gastric inhibitory hormones such as enterogastrone and urogastrone, major Polish traces can be detected in the elucidation of origin and physiological role and pathological involvement of gastrin, CCK, secretin, motilin, gastric inhibitory peptide and the most recent additions of enterohormones such as epidermal growth factor, somatostatin, leptin or ghrelin. Major achievements have been obtained in gastric and colorectal cancerogenesis involving gastrin and its precursor, progastrin.

Key words: *gastrointestinal hormones, Edkins, Bayliss and Starling, Gregory, gastrin, cholecystokinin, secretin, motilin, gastrin-releasing hormone, somatostatin*

## INTRODUCTION

### *Historical background*

The process of digestion called from Hippocrates "pepsis" has been closely related to various gastrointestinal diseases and regarded since antiquity to involve "cocation" or fermentation of food (1). This process was believed to transform the food in different portions of the gut into vital forces released to the vessels and distributed to various organs to maintain their activity. Chemical composition of chyme in the stomach was suspected since its first dissection by A. Vesalius in the XVI century (2). Bitter-sour liquid in the stomach was proposed by H. Berhaave (1668-1738) to be some kind of acid that Paracelsus, an alchemist physician in the XVI century, thought to originate from drinking of acidic spare water (1). The great authority in medicine and physiology in the XVIII century, Albrecht von Haller, in his famous *Elementa Physiologiae Corporis Humani*, proclaimed that acid in the gastric contents originated from the degradation of food, while bile comes from liver, being necessary for digestion of fat. L.S. Spallanzani of Padua could not find any evidence of fermentation in the stomach and suggested the process of digestion or putrefaction as a first step of assimilation of ingested food. The final identification of hydrochloric acid in gastric juice has to be ascribed to W. Prout in 1823 (3) and it was confirmed by W.W. Beaumont in 1829 in his book "*Physiology of Digestion*" (4) describing how gastric acid secretion follows ingestion of a meal, as observed on his patient with a gastric fistula.

Following the identification of hydrochloric acid as a product of the stomach, the debate focused on the mechanism of its secretion and its regulation. The late XIXth century was dominated by the concept of *nervism* or exclusive role of nerves in control of digestive secretion as proposed by I. P. Pavlov and its school (5), which demonstrated in numerous series of experiments the essential role of the central nervous system and vagal nerves in the stimulation of gastric secretion induced by sham-feeding and ordinary feeding. Various operations on the

stomach in animals and on vagal nerves including truncal vagotomy and selective gastric vagotomy also used in humans in treatment of hyperchlorhydria and peptic ulcerations, were initiated by L. Dragstedt (6). It is a paradox of history that soon after first discovery of hormonal control of pancreatic secretion by non-nervous substance, secretin, by W.M. Bayliss and E.H. Starling at the University of London in 1902 (7), and of gastric secretion by another hormonal substance, gastrin, in 1906 by J.S. Edkins (8), the concept of *nervism* received international recognition and was confirmed by the Nobel prize awarded to Pavlov, the proponent of this concept (*Fig. 1*).

There are little Polish traces at these historical discoveries of secretin and gastrin, however, the fact that our surgeon, L. Rydygier (1), made the first gastrectomy by removing the distal portion of the stomach, which stores and releases gastrin, suggests that with this first gastrectomy, hormonal (gastrin) control of gastric secretion was intuitively considered by a Polish practitioner.

The wide appreciation of acetylcholine and histamine as the principal regulators of a physiological function, was sanctified by awarding the Nobel Prize to H.H. Dale in 1905, while the gastrin concept or "gastrin hypothesis" of Edkins (8) fell into scientific disfavor. In 1938, however, S. Komarow (9), working with P. Babkin at McGill University, presented evidence that a histamine-free extract was highly effective in the stimulation of gastric secretion in cats, the effect was

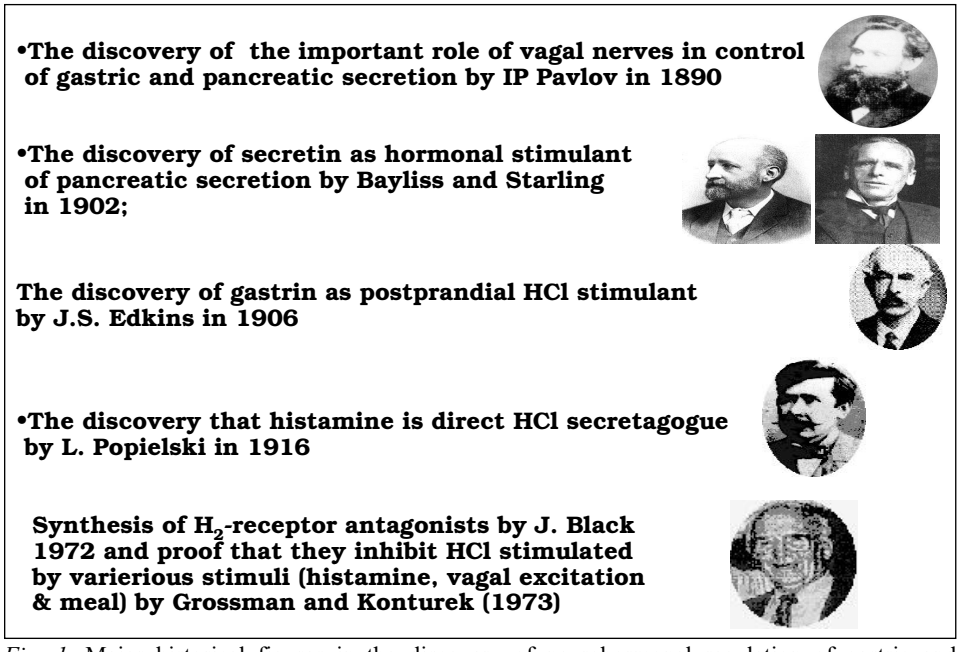


*Fig. 1.* Major historical figures in the discovery of neurohormonal regulation of gastric and pancreatic secretion.

not influenced by blocking cholinergic nerves with atropine. The physiological role of gastrin was questioned, however, due to the discovery by Polish physiologist, L. Popielski of Lvov in 1916 (but published in 1920 (10), that histamine, but not gastrin, is a direct and potent stimulant of oxyntic glands that does not depend upon vagal nerves section or scopolamine. This discovery represents a distinct Polish trace that is still recognized and even received a strong confirmation due to development of the potent antagonists of histamine $H_2$-receptors such as, cimetidine and ranitidine, which have been successfully applied in the treatment of acid-pepsin disorders in humans (11). With the clinical use of $H_2$-receptor antagonists, there were numerous Polish traces in the findings by Grossman and Konturek (12) that these antagonists suppress gastric acid secretion induced, not only by histamine but also by gastrin and ordinary meal or sham-feeding, providing excellent support for the concept of histamine rather than gastrin as a common final chemostimulator of oxyntic cells as suggested by C.F. Code (13). The fact that these drugs are highly effective in the treatment of acid-pepsin disorders indicates the histamine story has provided a practical use of $H_2$-blockers in humans.

*Early phase of gastrointestinal endocrinology*

The discovery of secretin by Bayliss and Starling (7) and gastrin by Edkins (8) marked the birth of a new science of endocrinology, the name originating from the term hormao (from Greek "I excite") proposed by W. Hardy for a chemical messenger by which one organ exercises an influence on another (1). The development of gastrointestinal endocrinology would not be possible without:

1. The physiological identification of numerous new hormones such as cholecystokinin, enterogastrone, incretin, urogastrone, vilikinin duocrinin;
2. Progress in peptide biochemistry initiated by the teams of R. Gregory and Kenner of Liverpool, J. Rehfeld of Copenhagen and E. Jorpes and V. Mutt of Stockholm, N. Yanaihara of Shizuoka in Japan, and
3. Measurement of the tiniest quantities of peptide hormone using technique of radioimmunoassay (RIA) by SA Berson and R. Yalow in 1959.

*Purification of gastrin and gastrin-cholecystokinin family of peptides*

Despite the controversy surrounding the "gastrin hypothesis" of Edkins (8), the isolation of a histamine-free gastrin peptide was achieved by Komarov (9) in Babkin's Department of Physiology at McGill University of Toronto. R. Gregory and his collaborator H. Tracy (14, 15) were successful in purification of gastrin with the help of a Sephadex chromatography. The substance characterized by G. Kenner at Liverpool as heptadecapeptide (2.114 mol. weight) was found to exist in two forms called gastrin I (without tyrosine sulfation) and gastrin II (with sulfation of tyrosine). These gastrin peptides obtained from porcine antral mucosa

were soon found to be almost identical to human gastrin except for the substitution of leucine for methionine at position five (14 - 16). In addition to gastrin with 17 aminoacids (G-17) and 34 amidated and glycine-extended gastrin (G-34), as well as larger molecular gastrin precursors such as progastrin and pre-progastrin, have been identified in secretory granules of the G-cells and also in the gastrinoma (Zollinger-Ellison syndrome) and gastric or colorectal tumors (*Fig. 2*).

When the structure of gastrin became known, several groups of researchers developed gastrin RIA and explored the biochemistry and physiology of this hormone.

With the advent of discovery, purification and synthesis of major gut hormones, our Institute of Physiology developed an international cooperation with major centers of hormonal peptide biochemistry and served as an evaluation center of biological activity and the mechanism of release of these peptides.

Due to close collaboration with R. Gregory and his group at the peptide laboratory of Imperial Chemical Industries, UK, we obtained and used for the first time human pentapeptide (ICI 50123), then called pentagastrin, including the C-terminal sequence of gastrin (Gly-Trp-Met-Asp-Phe-$NH_2$) which showed similar action on gastric acid secretion as gastrin itself (17-20). This peptide was found to induce maximal gastric acid at a dose of 2-4 μg/kg secretion, which is similar to that obtained with histamine, but virtually deprived of the

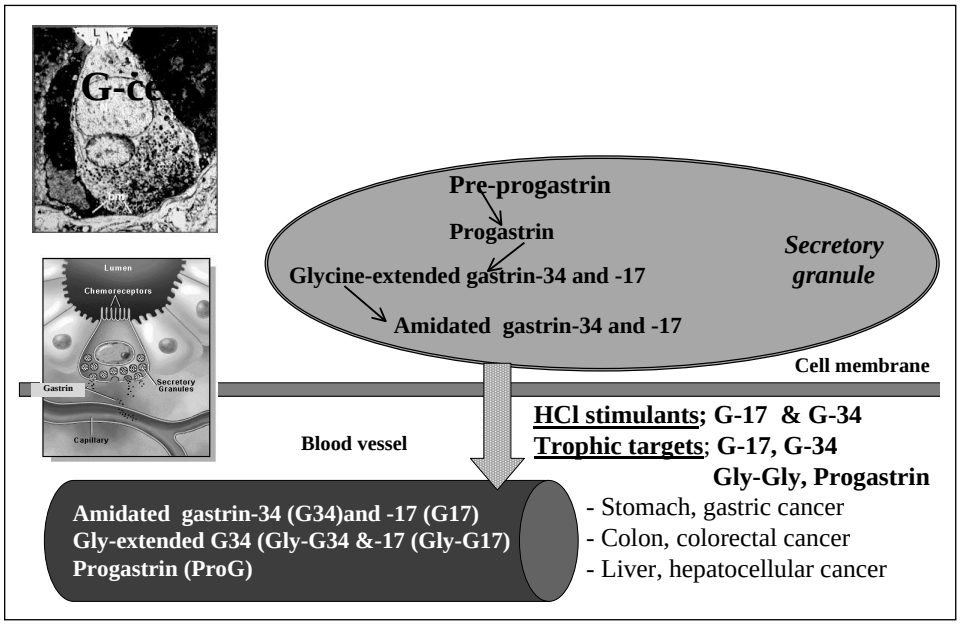


*Fig. 2.* Gastrin, its molecular forms in circulation and their precursors as potent stimulants of gastric acid secretion on growth factor for gastrointestinal mucosa and cancer cells.

major side-effects of histamine (18, 19). It was found to be useful in testing gastric secretory activity and to potentiate histamine-induced gastric acid secretion (20). Vagotomy or atropine reduced gastric acid secretion induced by lower doses of these stimulants without affecting the maximal gastric secretory capacity.

From the same ICI peptide laboratory, we obtained the supply of urogastrone-epidermal growth factor (EGF), a 53 amino acid peptide, previously called urogastrone found by us to be produced by the salivary glands and pancreas and released in urine (hence urogastrone). Its major physiological function was found to be an inhibition of gastric acid secretion, the stimulation of the proliferation of gastro-intestinal mucosa and gastric protective activity against various noxious agents (21 - 24).

*Studies on secretin and vasoactive intestinal peptide*

Secretin originally discovered by Bayliss and Starling on the beginning of XXth century was chemically characterized and found to exhibit chemical homology with other peptides such as vasoactive intestinal peptide (VIP), gastric inhibitory peptide (GIP), and glucagon (*Fig. 3*). Due to collaboration with V. Mutt of Sweden and E. Wunsch of Germany, we obtained a highly purified and

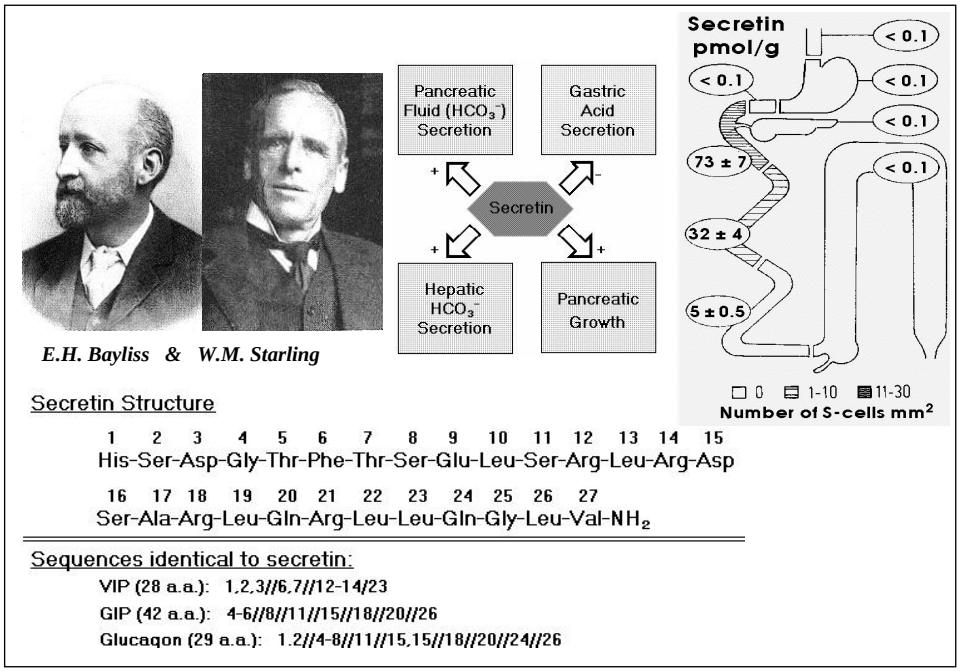


*Fig. 3.* Discoverers of secretin, its structure, sequence homology with VIP, GIP and glucagon and localization and release and biological actions.

synthetic secretin for pancreatic secretory studies and cyclic AMP formation in pancreatic acinar and ductal cells. The localization of the release of secretin by gastric acid was found to be confined to the upper portion of the small bowel and this hormone was found to stimulate pancreatic and hepatic $HCO_3$ secretion, to inhibit gastric acid secretion and to stimulate the growth of pancreatic tissue. The dose-response curves for natural and synthetic secretin was obtained in humans in whom pancreatic juice was obtained by endoscopic cannulation of the pancreatic duct (25 - 29). The study with synthetic secretin stimulation of pancreatic secretion collected directly from the pancreatic duct is still quoted as a reference study for secretin-stimulated pancreatic secretion. Dr V. Mutt also offered us vasoactive intestinal peptide (VIP), which in some species, such as cats was found to be a full secretin-like agonist of pancreatic secretion, but in humans it caused only partial stimulation of pancreatic secretion when applied alone, but inhibited this secretion when combined with secretin.

With the observation of periodic fluctuations of gastrointestinal motility and accompanying changes in gastric and pancreatic secretion, we tested the effects of 13-NLE-motilin which was newly synthesized by E. Wunsch, on the secretory and motor activity of the stomach and pancreas, and found this peptide released during phase II and III of the migrating motor complex (MMC) could be responsible for both motor and secretory components of this complex recorded by special electrodes inserted into the wall of the gut of dogs or by pressure recording in human stomachs (30 - 32). These studies explained the mechanism of phase II/III of MMC and related gastric and pancreatic secretory changes as being caused by periodic release of motilin.

A very fruitful collaboration was also developed with Dr A.V. Schally of Polish ancestry and later Nobel Prize laureate on studies of somatostatin, gastrin-releasing peptide (GRP), pancreatic polypeptide (PP) and opiate peptides such as enkephalins (*Fig. 4*). It was revealed that somatostatin and its precursor, prosomatostatin, are highly effective inhibitors of gastric and pancreatic secretion, intestinal motility and visceral circulation (34 - 40). Because of its release in the antral and duodenal mucosa, it could correspond to the previously proposed inhibitors such as antrogastrone and enterogastrone, believed to serve as autoregulators of gastric secretion. At present, this collaboration focused on somatostatin analogs with target oriented activity that bind and damage cells expressing receptors for these peptides.

Several studies have been performed to elucidate the newly synthesized cholecystokinin (CCK) that was found to be released from the upper part of the small bowel by fat and protein digestion products and to inhibit gastric secretion, gastric emptying and motility (*Fig. 5*). Most important it was suggested that neural innervation is involved in the action of CCK on exocrine pancreatic secretion and food intake in rats acting via stimulation of CCK-receptors on afferent vagal nerves (40-47). Indeed, we and others confirmed that CCK

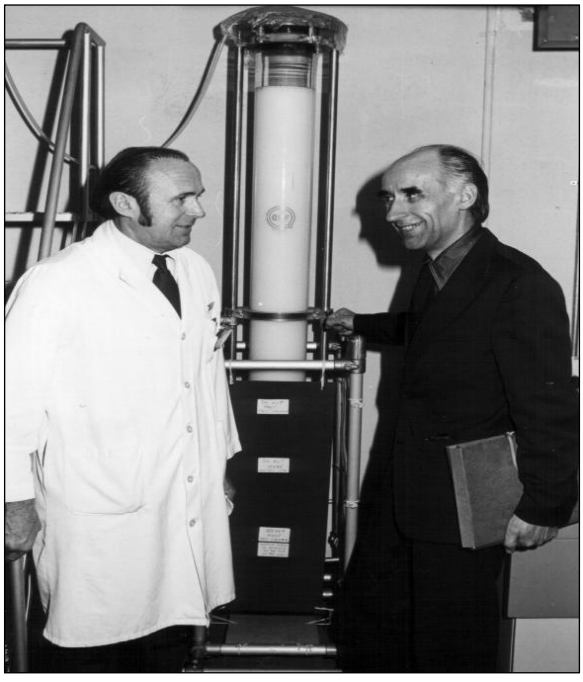

*Fig. 4.* Collaboration with Dr A.V. Schally (on the right) from New Orleans resulted in determination of biological activity of seceral neuropeptides auch as TRH, somatostatin, GRP, enkephalins, etc.

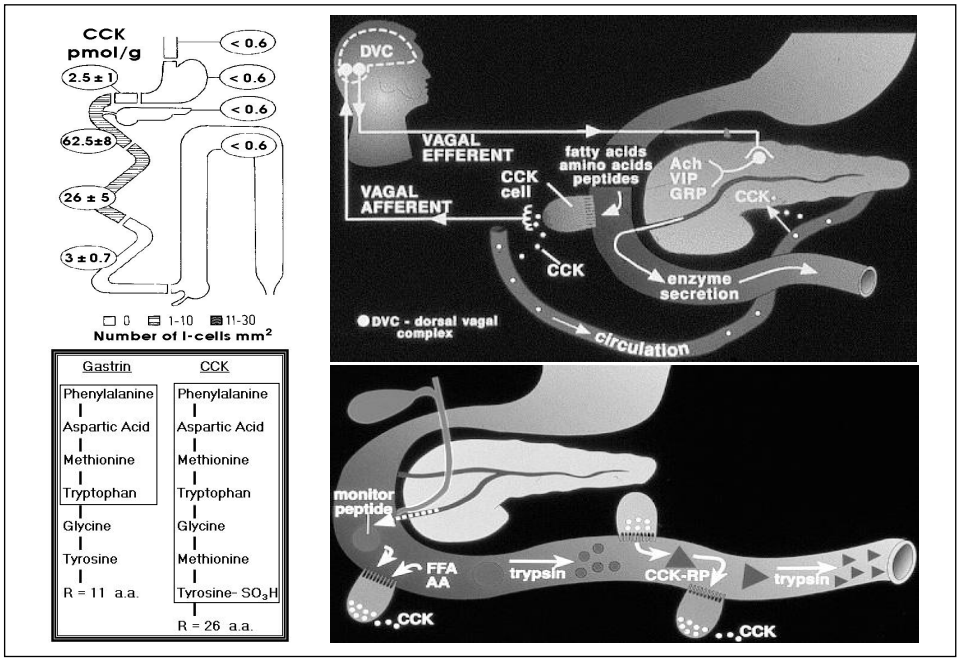


*Fig. 5.* Localization of cholecystokinin (CCK) release in the gut, structure of its C-terminal portion of molecule as compared to gastrin (on the left) and the mechanism of the release and actions of CCK. (Modification from figs 12, 13. *J Phisiol Parmacol* 1998, supplement 2; p.17)

released from the endocrine I cells of the upper small intestine acts predominantly on target organs such pancreatic acinar cells, gastric emptying and gall-bladder contraction by stimulation of specific $CCK_1$-receptors at afferent nerve terminals in the gastrointestinal wall and activation of long- and short vagal reflexes (*Figs 6 and 7*). It is of interests that the pancreatic juice contains the so called monitor peptide that may stimulate the I cells to release CCK and enterocytes release so called CCK-releasing peptide acting on I cells to stimulate the release of CCK (48 - 50).

We were also involved in studying the action of prostaglandins mainly of E series on gastrointestinal functions (51-56). Methyl analogs of these prostaglandins were found to inhibit gastric secretion and exert the protective activity against gastric mucosal damage by various noxious agents (54-56). This so called gastric cytoprotection of PGE was championed by A. Robert, of the USA, who believed that PGE may be an ideal natural anti-ulcer agent in animals and humans. Indeed, methyl analogs of prostaglandins such as arbaprostil or misoprostil were found to accelerate ulcer healing in humans (56), but some side effects such as diarrhea and proaborptive activity limited the usefulness of these agents to prevent acute gastric mucosal damage by non-steroidal anti-inflammatory drugs (NSAID) such as aspirin.

Soon after the discovery of the gastroprotective activity of the prostaglandins, we found that most of the GI hormones, especially gastrin, CCK, GRP and growth

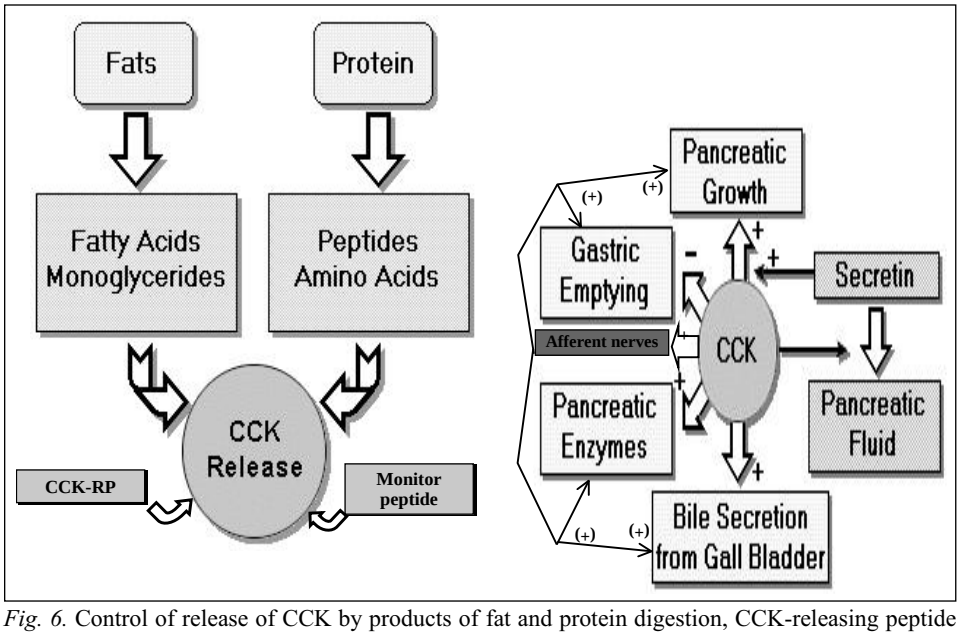


*Fig. 6.* Control of release of CCK by products of fat and protein digestion, CCK-releasing peptide and peptide monitor (on the left) and the action of CCK on pancreatic and biliary secretion, gastric emptying and pancreatic growth as mediated by vago-vagal reflexes (on the right).

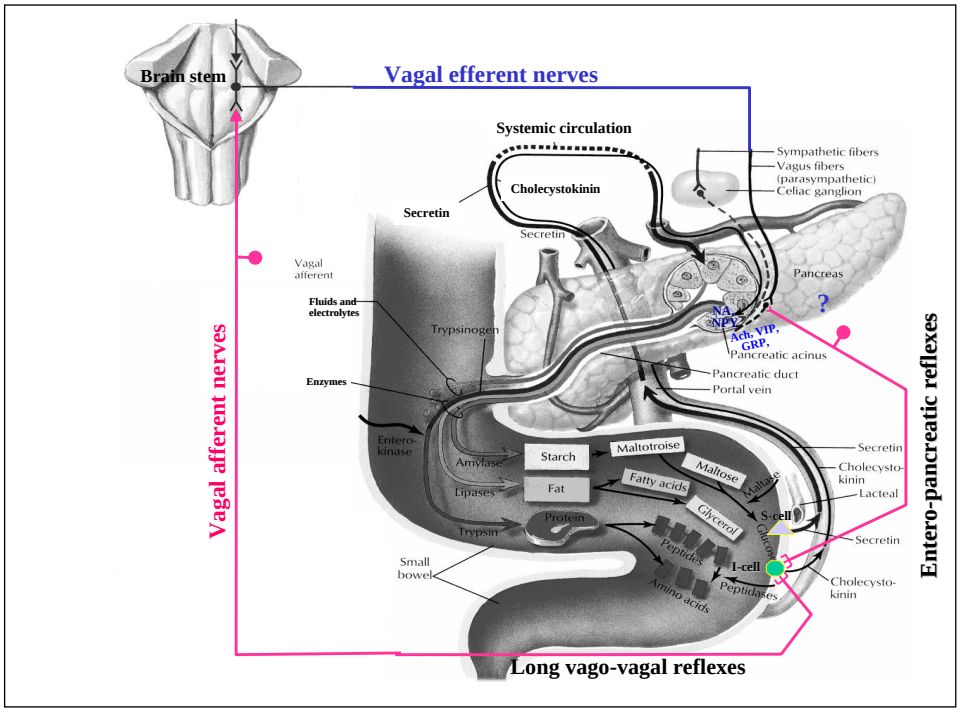


*Fig. 7.* CCK stimulates pancreatic secretion by activation of short and long vago-vagal reflexes. (Modification of Hansena J.T. & Koeppena B.M., 2002)

factors such as EGF (57 - 60), exhibit gastroprotective action against various types of mucosal irritants. The mechanism of this protection has been attributed to the release of endogenous prostaglandins, nitric oxide and stimulation of sensory afferent nerves releasing calcitonin-gene related peptide (CGRP) (59).

The wider use of prostaglandin analogs was at this time reduced by the newly discovered $H_2$-receptor antagonists such as ranitidine or cimetidine and proton pump inhibitors designed by G. Sachs (USA) working for Hassle, then the Astra Company of Sweden. We also had an opportunity to test those agents in animals and then in humans to ascertain their extremely potent and long acting gastric inhibitory activity and ulcer healing efficacy (56). These agents were found to suppress gastric acid secretion induced by all modes of gastric stimulation; nonetheless one early observation was a marked increase in plasma gastrin level. Soon it became obvious that these proton pump inhibitors (PPI) such as omeprazole, lanzoprazole or pantoprazole excessively stimulate ECL-cells, resulting in the formation of carcinoid tumors. It is worthy to note that Polish Polfa in Starogard also synthesized and provided a novel PPI called prasol (now Polprasol) which was found in our lab and in clinical trials to be equipotent with omeprazole but only recently was admitted to Polish market.

*Studies on CCK-related peptides.*

CCK is structurally related to gastrin as its C-terminal amino acids are identical to those in gastrin and exist in several molecular forms such as 8 (CCK-8), 33 (CCK-33), 39 (CCK-39) and 54 (CCK-54) amino acid forms. The structural feature that determines whether a peptide behaves like gastrin (stimulates gastric acid secretion) or CCK (stimulates gallbladder contraction and pancreatic enzyme secretion) is the location of the tyrosyl residue. In peptides with gastrin-like activity, the tyrosyl residue is in position 6 from C-terminus, while in CCK-like peptides tyrosyl residue is in position 7 from the C-terminus. Sulfation of the tyrosyl in the gastrin peptide does not affect its potency (gastrin I and gastrin II), whereas tyrosyl residue in CCK is always sulfated to maintain the biological activity. The minimal active fragment for the CCK pattern of activity is the C-terminal heptapeptide. Unlike gastrin, which binds preferentially to receptor termed $CCK_2$-receptors, CCK-like peptides bind to receptors called $CCK_1$-receptors. The RIA of CCK and the effects of blockade of specific receptors for gastrin and CCK greatly helped to elucidate the physiological activity of these hormonal peptides.

Our Institute was involved in elucidation of the release and action of CCK (see *Figs 5-7*). We were first to localize the area in the small bowel which releases CCK from endocrine I-cells (40). Using CCK-RIA, as well as the stimulation of pancreatic enzyme secretion, inhibition of gastric secretion and gastric emptying and gall bladder contraction, we found that CCK is predominantly released in the first 50 cm of the upper small bowel including the duodenum and upper jejunum (41 - 45). These effects of endogenous CCK were confirmed using exogenous peptide and specific $CCK_1$-receptor antagonists, such as loxiglumide and devazepine. We were first to demonstrate in dogs and humans that CCK has enterogastrone-like activity to inhibit gastric acid secretion (41 - 42). Long before vagal nerves had been proposed to mediate the biological effects of CCK by Owyang (43), we showed that the effects of CCK involve cholinergic nerves as its effect was suppressed by atropine (44, 45). Using specific antagonists of receptors for CCK, gastrin and GRP, we proposed that GRP is capable of releasing both CCK and gastrin and that the secretory and trophic effects of this peptides could be abolished by the pretreatment with specific GRP, CCK and gastrin antagonists (47, 48).

Based on the prevention of CCK effects on the pancreas using loxiglumide and devazepine, which are specific antagonists of $CCK_1$-receptors, we proposed that these antagonists could be useful in the prevention of acute pancreatitis induced in rats by overstimulation with caerulein. Indeed these antagonists were found to protect the pancreatic tissue against the damage induced by caerulein. Similar protective effects were recorded using pancreatic polypeptide and its C-terminal hexapeptide, which were shown previously to inhibit exocrine pancreatic secretion in dogs.

With the era of *Helicobacter pylori*, numerous studies showed infection with this germ raising plasma gastrin (63, 64), while numerous epidemiological studies emphasized the involvement of this infection in the gastric cancerogenesis (65, 66). We were first to report that precancerous conditions such as atrophic gastritis with intestinal metaplasia leads to an enhanced release of gastrin, and may stimulate the cancer cell proliferation (63, 64). In cooperation with J. Rehfeld from Copenhagen, we found that not only gastrin but also its precursor, progastrin, are produced locally in a tumor in excessive amounts and are released into the circulation. Following removal of the tumor, a marked decrease in plasma and tumor gastrin and progastrin has been noticed. Using RT-PCR, it was documented that tumor tissue upregulates gastrin and its receptors as well as cyclooxygenase-2 (COX-2) (66). The later enzyme is known for its tumor growth-promoting action, the decrease of proapoptotic proteins such as Bax, and the increase of antiapoptotic proteins such as Bcl2. This suggests that progastrin and gastrin exhibit potent influence on COX-2 expression, and that a blockade of the COX-2, using specific antagonists, may be useful in the control of gastric and colorectal tumor growth and metastases.

*Concluding remarks*

1. With the isolation, purification and synthesis of peptide hormones of gastrin-CCK and secretin-VIP family numerous physiological studies were undertaken also by Polish researchers to elucidate their biological action in health and diseases.
2. We were first to use gastrin and its analogs, particularly pentagastrin in testing gastric secretory activity to replace histamine producing similar maximal acid output but accompanied by numerous side-effects.
3. In addition to the stimulation of gastric and pancreatic secretion, gastrin, CCK, and GRP were found for the first time to protect gastric mucosa against the damage by various irritants in similar fashion to that of prostaglandin.
4. With the era of *Helicobacter pylori* and its implication in gastric pathologies, especially atrophic gastritis and gastric cancer, the overexpression of gastrin and its precursor progastrin has been detected and found to be accompanied by an increased expression of COX-2 and antiapoptotic proteins that may be involved in the growth of gastric and colorectal cancer.
5. The detection of overexpression of gastrin and its precursor progastrin combined with upregulation of COX-2 observed in experimental cancerogenesis and in gastric and colorectal cancer in humans may serve as an early marker of gastric or colon cancerogenesis.

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