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Review

Neuroendocrinology of gastric H^+ and duodenal HCO_3^- secretion: the role of brain–gut axis

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Abstract

Gastric H^+ and duodenal HCO_3^- secretions are precisely regulated by neuro-hormonal mechanisms at central and peripheral levels to match the rate of these secretions with the type of stimulation of sensory receptors in the head area (sight, smell, taste, etc.) and in the gastro-intestinal system. Two-way communication pathways operate between the brain and the gut, each comprising afferent fibers signaling sensory information from the gut to the brain and efferent fibers transmitting signals in opposite direction. Short intramural and long extramural reflexes are triggered as well as various gut hormones are released by feeding that "cooperate" with the "brain–gut axis" in the alteration of exocrine and endocrine gastro-duodenal secretion, motility and blood circulation. The malfunction of gastric or duodenal secretory mechanisms may lead to disturbances of gastric H^+-pepsin or duodenal mucus-HCO_3^- secretion and to gastro-duodenal disorders and diseases. This review presents recent advances in pathophysiological mechanisms underlying gastro-duodenal secretory disorders.

Keywords: Stomach; Vagus; Enteric nervous system; Brainstem; Gastrin; Ghrelin; Leptin

Contents

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1. Introduction

1.1. Historical background

Gastric H^+-pepsin and duodenal mucus-HCO_3^- secretions are known to result from the interplay of a variety of neuro-hormonal factors with their stimulatory or inhibitory influence on gastric and duodenal mucosal cells. The research related to the mechanisms of these secretions started at the end of 19th century with the fascinating experiments performed on "sham-fed" dogs in St-Petersburg by I.P. Pavlov (Pavlov, 1902), who, for the first time, was able to stimulate gastric acid secretion with food presented to animals or passing only through their upper part of the digestive tube and proposed the concept of *nervism* or entire neural control of the digestive system. This concept was widely recognized and its proponent awarded with the Nobel Prize in 1905. However, the discovery by Edkins (1906) of the hormone, gastrin, followed, about half century later, by isolation and synthesis of "antral hormone" by Gregory and Tracy (1964), opened the route to "hormonal" concept in the gastrointestinal secretory mechanism.

The discovery in 1920 by Popielski (1920), a fervent supporter of Pavlov's *nervism*, that histamine, a non-nervous and non-gastrin compound, produced in oxyntic mucosa, exerts the most powerful secretagogue action on oxyntic cells, was another important contribution to the development of gastrology, depreciating the role of *nervism* in favor of humoral, namely histamine concept, championed later on by Code (1956). Further pharmacological studies performed by J.W. Black, another Nobel laureate in gastrology during the same century (Black et al., 1972), were based on histamine rather than on gastrin concept. Despite Johnson's unfortunate statement in 1971 that there is "no room for histamine" in control of gastric secretion because of its ubiquity in various organs of the body (Johnson, 1971), Black modified in next year the structure of histamine and succeeded in the synthesis of highly specific histamine H_2-receptors antagonists, showing potent gastric inhibitory efficacy without side effects (Black et al., 1972). Unexpectedly, these new agents, such as burimamide, metiamide and cimetidine, were found to inhibit gastric secretion not only induced by histamine, but also provoked by simple meal or even vagal excitation (Grossman and Konturek, 1974). These results were initially explained by the hypothesis of the receptor interaction at the oxyntic cell membrane, partly supported by in vitro studies of Lloud and Soll (1994). The discovery of H_2-receptors and their specific H_2-histamine antagonists should be considered as a major breakthrough in the physiology of gastric secretion, which obviously reinforces the significant role of histamine in the regulation of gastric secretion as the "final common chemostimulator" of oxyntic cells (Code, 1956). More recent achievements in pharmacological research led to the discovery by Sachs et al. (1976) of Na^+,K^+-ATPase (proton pump) in tubulovesicles of oxyntic cells. Then, inhibitors of this pump, called "proton pump inhibitors" (PPI), such as omeprazole, have been obtained and soon found to be highly clinically useful in the control of gastric acid secretion due to their higher gastric acid inhibitory efficacy than H_2-antagonists. Moreover, their biological half life was found to be remarkably longer, ranging from 14 h for lanzoprazole to 46 h for pantoprazole (Karvar et al., 2002; Shin and Sachs, 2002), than that for histamine H_2-antagonists. These discoveries apparently undermined, at least from a practical point of view, the significance of both gastrin and histamine in the concepts of the gastric secretory regulation.

Does it mean that the neural or gastrinic control is less important than histaminic in the physiological regulation of gastric secretion? To answer this question, have a quick look on the history of research related to the origin and mechanism of production of gastric H^+ secretion.

1.2. Discovery of gastric hydrochloric acid (H^+)

Secretion of H^+, which constitutes the major "parietal" component of gastric juice, is now considered as a result of the interaction of numerous stimulatory and inhibitory neuro-hormonal factors, acting on oxyntic cells after ingestion of food and its digestion. It should be mentioned that Vesalius (1974) was the first to identify among the intra-abdominal structures, including stomach, the unusually "wandering" (vagal) nerves. The question was then raised what functions, if any, could be attributed to these "wandering" nerves in gastric contribution to the assimilation of food. It required almost three centuries before Prout (1824) identified in 1823 the hydrochloric acid in the content of stomach of humans and other species, and four centuries before studies on regulatory mechanisms of gastric secretion began. Pavlov was the first to prove experimentally in the 1880s the functional significance of vagal nerves in this regulation by showing that transaction of vagal nerves abolishes gastric secretion induced by sham feeding and reduces those provoked by ordinary feeding (Pavlov, 1902). With the introduction of microscopy, it was demonstrated that the gastric glands comprise the parietal (oxyntic or acid producing) cells and peptic (pepsinogen producing) cells, while Heidenhain (1878) of Breslav University characterized a "third" type of cell, which adhered to the external surface of oxyntic cells, later identified as enterochromaffin-like cells (ECL cells).

Prout's evidence for the presence of hydrochloric (muriatic) acid in the gastric juice coincided with the ingenious observations by Beaumont (1833) in 1822 on gastric secretory functions in Alexis St. Martin, a French Canadian traveler, who got an accidental gun-shot in the upper abdomen and developed permanent gastric fistula that served to Beaumont as a precious "human guinea pig" for studies on gastric secretion.

2. Gastric mucosal barrier and HCO_3^- mucus secretion

The discovery of gastric H^+ and pepsinogen initiated endless research related to various aspects of this secretion, particularly to the mucosal protection against the corrosive action of H^+ secreted in extremely high concentration (about 170 mmol/l) by apical oxyntic cell membrane into the intracellular cannaliculi. This acid, somewhat diluted by concomitantly secreted water, passes then from the base of the gastric glands to the gastric lumen and finally enters in pulses with gastric propulsive activity to unprotected upper duodenum. The question of autodigestion of gastric mucosal lining exposed to the corrosive products of its own secretion, revitalized after Spallanzani's (1782) famous "experiments" in 1782, showing that gastric juice in vivo is capable of digesting a variety of food including meat or even living organisms, e.g., frog placed in a canine gastric lumen (Dragstedt, 1947). The existence of putative vital forces in the gastric wall, which were initially thought to maintain the viability of the gastric mucosa despite its permanent exposure to concentrated acid-pepsin secretion, was soon abandoned and the active mucus–alkaline secretion was proposed to explain the mucosal resistance to acid–pepsin aggression (Allen and Garner, 1980).

The next question, still vital, is whether such active mucosal protection based primarily on mucus-HCO_3^- secretion and rich mucosal blood flow (Kaunitz and Akiba, 2002) is merely a local mucosal response to topical acid and other irritants or whether it also involves intramural or extramural neuro-hormonal mechanisms. In the early 1930s, Teorell (1940) suggested that H^+ secreted into gastric lumen might show a small "back-diffusion" into the mucosa in exchange for Na^+ ions (Pausawasdi et al., 2002) and that this results from the permeability characteristics of the gastric mucosa. It has been proposed that the gastric surface epithelium, which is covered by a mucus gel layer, constantly secretes HCO_3^- into the adherent mucus layer to neutralize luminal H^+ diffusing back from gastric lumen towards the mucous epithelial cells, thus creating pH-gradient within the mucus layer and preventing surface epithelial cell from the irritant effect of luminal noxious substances (Allen and Garner, 1980; Flemstrom and Garner, 1982). In the stomach, the tight junctions between adjacent epithelial cells and continuous secretion of mucus-HCO_3^- on surface epithelium form together an efficient protective barrier, with a 200–300-μm-thick mucus layer on its surface and abundant mucosal microcirculation underneath, creates altogether a so-called "mucous barrier". Teorell (1940) proved that surface epithelial cells and adherent mucus containing bipolar phospholipids prevent, due to their high polarity, the ionized mineral acids, such as HCl, from back-diffusing from gastric lumen into the mucosa, but un-ionized organic compounds such as bile salts or acetylsalicylic acid (aspirin), with a relatively low pK_a, can rapidly disappear from the gastric lumen to reach surface mucosal cells by un-ionic diffusion and to cause their damage. The barrier concept was further developed by H.W. Davenport and C.F. Code, who published a series of papers related to the significance of protective gastric mucosal barrier (Code and Scholer, 1955; Davenport, 1992). They proposed that breaking the barrier represents an initial step in the process of mucosal injury with a subsequent cascade liberation of histamine and histamine-like substances, overt mucosal bleeding, and acute gastritis. This can be easily observed by gastroscopy in humans after ingestion of aspirin or concentrated ethanol, but also in experimental animals exposed to various irritants, which are also widely used as animal models of gastric damage for studying the gastroprotective efficacy of various drugs (Brzozowski, 2003).

Kaunitz and Akiba (2002), Isenberg and his associates (Bukhave et al., 1990; Isenberg et al., 1986) and our group (Konturek et al., 1987, 2004c) found that the gastric mucosal barrier, with its tight surface epithelial cells, and the duodenal mucosal barrier, with its leaky epithelial cells (duodenocytes), operate due to an active HCO_3^- mucus secretion, particularly in response to topical application of HCl. The mediators of gastro-duodenal mucus-HCO_3^- secretion appear to be the same, including the cyclooxygenase-1 (COX-1)- prostaglandins (PG) system, the nitric oxide (NO) synthase (NOS)-NO system and capsaicin-sensitive afferent nerves releasing calcitonin-gene related peptide (CGRP) (Brzozowski, 2003; Konturek et al., 2004c), all activated by aggressive H^+-pepsin secretion (Fig. 1). The excitation of afferent nerves triggers reflex stimulus the extramural cholinergic, nitroergic and peptidergic nerves (releasing nitric oxide, vasoactive intestinal peptide, pituitary adenylate cyclase activating peptide), leading to enhanced mucus-HCO_3^- secretion.

Several anti-ulcer and gastro-protective drugs including sucralfate, bismuth salts (e.g., De-Nol), antacids (e.g., Maalox), and exogenous stable prostaglandin E_2 (PGE_2) analogs, such as misoprostol, have been found to be effective in the stimulation of gastro-duodenal HCO_3^- mucus barrier when applied in anti-ulcer therapy (Konturek et al., 1987; Konturek, 2003).

Recent studies by Pausawasdi et al. (2002) using isolated parietal cells demonstrated that cholinergic agonists such as carbachol induce expression of cyclooxygenase-2 (COX-2) in these cells via several signaling pathways leading to an abundant production of prostaglandins (PG) protecting these cells and the entire surface epithelium of gastric mucosa against their damage by secreted H^+. Constitutively expressed COX-1, normally present in gastric mucosa, generates PG, providing day-to-day gastric mucosal protection against gastric acid and any other irritant. The inflammatory process occurring in this mucosa due to infection with, e.g., *Helicobacter pylori* (*H. pylori*), may induce COX-2 by inflammatory products limiting the extent of mucosal damage via enhancing the mucosal defense system.

It should be noted that the spiral *bacterium*, which inoculates the stomach of more than 50% of the world's

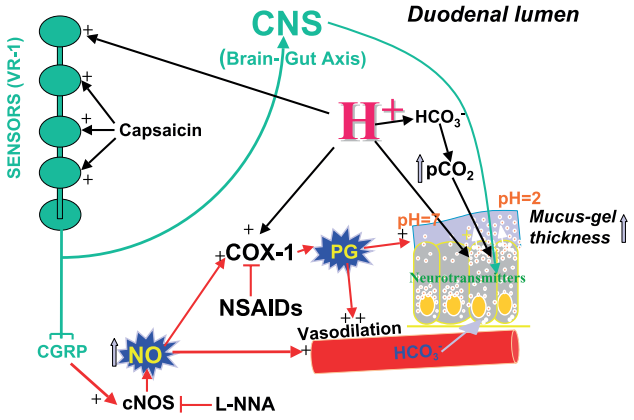

Fig. 1. Gastric acid (H^+) entering the duodenum penetrates leaky duodenal mucosa and stimulates mucosal HCO_3^- secretion that is combined with mucus release and mediated by several mechanisms including COX-1-postanglandin system, constitutive nitric oxide synthase (cNOS)-nitric oxide (NO) system, rise in luminal pCO_2 due to HCO_3^- hydrolysis and excitation of capsaicin sensitive afferent nerves involved in gut-brain axis related duodenal HCO_3^- secretion.

adult population, exhibits an ability to damage mucous cells by "injecting" into these cells its toxic cytotoxins such as CagA and VacA, thereby disturbing the cell immunological resistance to damage as evidenced by enhanced expression and release of proinflammatory cytokines, including interleukin-8, interleukin-1β and tumor necrosis factor-α. This interferes with mucosa cell HCO_3^- secretory activity as well as affects the quality of adherent mucus gel leading to acute and then chronic gastritis. The induction of COX-2 by this *bacterium* may disturb the mucosal protection, but its eradication may restore, at least in part, the disturbed mucosal integrity. Administration of mucosal barrier breaker such as aspirin or ethanol may result in bleeding erosions or exacerbation of chronic gastric ulcerations (Pausawasdi et al., 2002).

Considering duodenal mucus-HCO_3^- secretion in response to topical H^+, delivered into the duodenal bulb in pulses by emptying the stomach, it should be emphasised that the duodenal mucosa behaves somewhat differently than gastric mucosa in response to topical acid. Isenberg and his colleagues (Bukhave et al., 1990; Isenberg et al., 1986) and Kaunitz and Akiba (2002) using chambered human or animal duodenum confirmed an earlier proposal that, unlike gastric mucosa, where tight epithelial cells constitute the main component of protective mucosal barrier against H^+, in the duodenum, H^+ is easily penetrating the duodenocytes, but does not damage them, though it transiently decreases their intracellular pH (pH). This strongly activates the basolateral Na^+-HCO_3^- cotransporters, allowing for massive inward movement through baso-lateral membrane of HCO_3^- from the extracellular space. This leads to the activation of the HCO_3^-/Cl^- exchangers in the apical membrane of duodenocytes, resulting in marked stimulation of HCO_3^- secretion together with mucus gel. The bulk of mucus and alkaline secretion neutralizes H^+ ions entering the duodenal lumen, thereby securing duodenal mucosal neutrality and integrity (Fig. 2).

Sjoblom and Felmstrom (2003) provided evidence that neurally released melatonin and vasoactive intestinal peptide participate in the mechanism of neural stimulation of duodenal mucus-alkaline secretion by topical H^+-activating the vago-vagal reflexes and their brainstem centers, similar to those involved in the control of gastric or pancreatic secretion (Glad et al., 2003; Konturek et al., 2003). The neuronal pathway involved in the activation of gastro-duodenal mucus-alkaline secretion with the contribution of melatonin was proposed by Reiter et al. (2003), just reinforcing Flemstrom's idea implicating melatonin in gastro-duodenal protective mechanisms.

As shown by Isenberg and his group (Bukhave et al., 1990; Isenberg et al., 1986), *H. pylori* infection reduces duodenal HCO_3^- mucus secretion (despite increasing mucosal PGE_2 generation) and this allows for excessive penetration of gastric H^+ and other irritants into the mucosa, damaging duodenocytes with subsequent formation of gastric metaplastic loci in the duodenum that become the "*locus minoris resistentiae*" for duodenal *H. pylori* infection and, finally, for ulcer formation. It appears that the *H. pylori* infection of the gastro-duodenal mucosa activates the vago-vagal reflexes (gut–brain axis) that, together with direct damaging action on mucosal cells and inhibitory effect of *bacterium* on D cells, and stimulatory action of *N*-α-methylhistamine on G-cell in antral mucose result in hypergastrinemia and enhancement of gastric H^+ secretion, contributing to ulcerogenesis (Fig. 3). Following the pharmacological eradication of *H. pylori*, basal and H^+-induced duodenal HCO_3^- mucus secretion are quickly restored even despite the reduction in mucosal PG generation (Bukhave et al., 1990).

The question remains whether *H. pylori*-induced gastric and duodenal mucosal damage is merely a local phenomenon or involves also the extragastric, namely, neurohormonal mechanisms. To answer this question, several

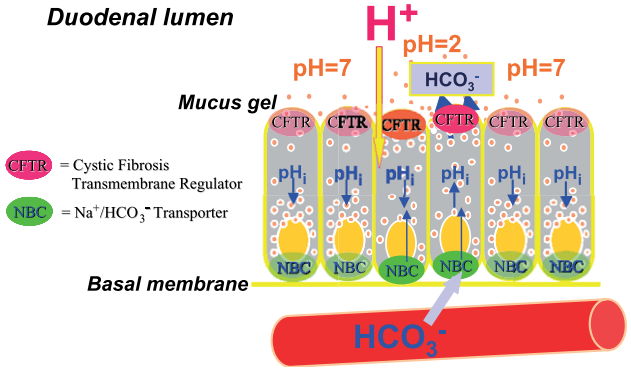

Fig. 2. Acidification of duodenal mucosa leads to infusion of H^+ into duodenocytes and drop of intracellular pH that is immediately followed by activation of sodium-bicarbonate transport (NBC) of HCO_3^- from the extracellular fluid to duodenocytes that restores intracellular pH and leads to secretion of HCO_3^- involving CFTR regulator into the duodenal lumen.

tools were employed: (1) inactivation of sensory afferent nerves that serve to signal the brain the changes occurring in the gastrointestinal tract; (2) surgical vagotomy to eliminate the influence of vagal nerves supplying gastro-duodenal area; (3) intracerebral application of various hormonal substances to determine whether the cerebral centers influence the gastro-duodenal mucus-HCO_3 response to topical irritants such as aspirin or *H. pylori* application; and (4) determination of expression of cFOS in intrinsic and extrinsic neurons involved in the transmission of gut–brain–gut signals (Brzozowski, 2003). Using a wide spectrum of tools, several researchers were able to reveal that the gastro-duodenal mucosa is equipped with a variety of neural sensors that respond to the action of luminal irritants such as H^+, ethnol, various drugs, e.g., nonsteroidal anti-inflammatory agents, or even physiological changes such as chemical ingredients of food, its osmolarity and pH as well as motility and tension of the gut wall. Through activation of chemo-, osmo-, mechano- and noci-receptors of gastroduodenal mucosa, the afferent nerves are mediating short local or intramural and long, vagal or extramural (axonal and spinal or cerebral) reflexes triggered by luminal H^+ or *H. pylori* and affecting, among others, also mucus-HCO_3^- secretion and mucosal gastro-duodenal mucosal barriers and mucosal integrity as well as mucosal microcirculation (Brzozowski, 2003) (Fig. 3). The space limitation of this review does not allow for the detailed presentation of the evidence, obtained, in part, from animal experimentations, supporting the involvement of extragastric neuro-reflexes in the maintenance of gastro-duodenal mucosal integrity, but it is of interest that, e.g., experimental chronic gastric ulcers in rats infected with *H. pylori* or with gastric mucosal damage by acidified aspirin or ethanol are greatly augmented following capsaicin-induced inactivation of afferent sensory nerves or vagotomy. This could be interpreted that both sensory afferent nerves and vagal efferent nerves are not only involved in the pathogenesis of gasro-duodenal mucosal lesions but also are required for normal course of their healing and for the maintenance of mucosal integrity (Konturek et al., 2004a). In humans with *H. pylori*-infected stomach such course of post-eradication ulcer healing probably also involves the long vago-vagal reflexes initiated by activation of gastric mucosal sensors by *H. pylori* and its cytotoxins and inflammatory products as well as the *H. pylori* infection related reactive oxygen species. Also, the development and subsequent repair of aspirin- and ethanol-induced gastric mucosal lesions may involve the brain–gut axis, starting with the irritation of mucosal chemo-receptors by noxious chemicals and their mucosal toxic products such as reactive oxygen species, This is supported by experimental evidence that inactivation of sensory afferent fibers with capsaicin or subdiaphragmatic vagotomy presumably eliminating the activity of both afferent and efferent vagal pathways greatly delays the lesion healing and worsens the lesion induced by these local irritants (Konturek et al., 2004d; Pausawasdi et al., 2002). As mucosal lesions and ulcerations induced by either *H. pylori* infection and aspirin, ethanol or ischemia-reperfusion that were thought to involve predominantly local mechanism are greatly affected by inactivation of afferent sensory fibers with neurotoxic dose of capsaicin or by vagotomy, it is tempting to assume that the brain–gut axis is involved in the pathogenesis of ulcer formation and in the healing of these ulcers via neural mediation of local mucosal changes including gastric blood flow at the ulcer area (Brzozowski, 2003). This does not exclude the contribution in mucosal repair processes of local anti-ulcer and protective humorals such as prostaglandins, gastrin, somatostatin, ghrelin, leptin, etc., that may modify the final outcome of mucosal ulcer healing and repair processes connected with the alteration of brain–gut axis (Pausawasdi et al., 2002).

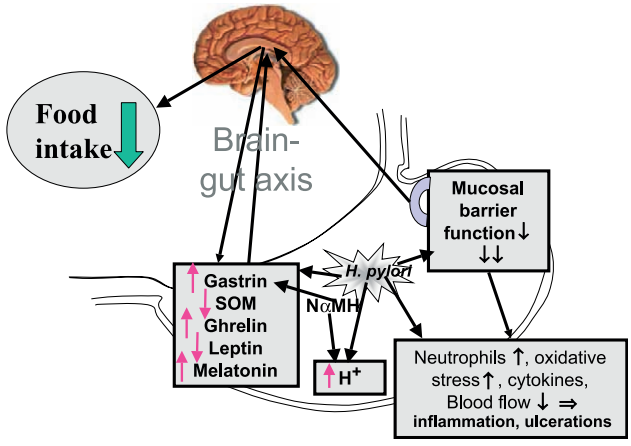

Fig. 3. Role of brain–gut axis in the mucosal damage and probably also peptic ulcer formation in the stomach or duodenum caused by *H. pylori* infection.

3. Regulation of gastric acid secretion

Besides the mucus-HCO_3^- component, called "non-parietal component", and playing a major protective role in maintaining gastric mucosal integrity, gastric secretion also comprises a very dynamic "parietal component" secreted by the oxyntic cells and characterized by highly concentrated H^+ and variable volume flow of gastric secretion that is dependent upon the degree of gastric secretory stimulation. Postprandial secretion has been classically divided into three overlapping phases, cephalic, gastric and intestinal, each including neural, usually vagal and hormonal, predominantly gastrin–histamine components, resulting in the excitation of oxyntic cells with their transformation from resting state with rich cytoplasmatic tubovesicles, storing inactive Na^+,K^+-ATPase (or proton pump), to active state with shuffling of these tubovesicles into the apical membrane of numerous intracellular canaliculi of oxyntic cells to increase their surface the number of active proton pumps and ability to release H^+ in high

concentration into the gastric lumen (Karvar et al., 2002; Martinez et al., 2002).

The mechanism of H^+ secretory stimulation by oxyntic cells in gastric glands is virtually the same during all three phases but the contribution of neural (vagal) and hormonal components varies depending upon the type of secretory stimulants and the phase of secretion (Schubert, 2003).

3.1. Neural control

Pavlov (1902) was the first to provide experimental evidence that neural regulation of gastric (and pancreatic) secretion is mediated through the vagal nerves. After analysis of his own results obtained from "sham-fed" dogs (with opened esophageal fistula to prevent the swallowed food from entering the stomach) and gastric pouches fashioned from the oxyntic gland area with full vagal innervation (to "mirror" the secretory activity of intact stomach), he concluded that the nervous (cephalic) phase of gastric secretion is entirely neurally mediated. It is initiated by stimulation of various receptors in the head area, followed by transmission of sensory information to brain-stem vagal nuclei and then relayed to efferent fibers originating from two vagal complex nuclei, the dorsal motor nucleus and ambiguous nucleus, to supply the oxyntic glands. Since subdiaphragmatic vagotomy abolished the sham-feeding-induced gastric secretory response and electrical stimulation of vagal nerves restored this secretion, the evidence for the most important role of vagal reflex stimulation in the mechanism of gastric secretion was considered at the time to be proven. Since sham-feeding-induced copious gastric (and pancreatic enzyme) secretion reaching over 50% of the total acid response to a meal was dramatically reduced by subdiaphragmatic vagotomy, Pavlov concluded that this postprandial secretion is entirely vagally mediated. Unfortunately, Pavlov at the end of his "neuro-gastro-pancreatic" research, which gave him world acclaim and a Nobel Prize, was discouraged by undeniable evidence of hormonal (gastrin, secretin) and humoral (histamine) control of gastro-pancreatic secretion, left classic gastrointestinal physiology research and focused his interest on conditioned reflexes using salivary glands as effector organs.

Just checking Pavlov's original *nervism* concept, we used his model of secretory excitation, i.e., by the most physiological neural stimulation such as sham-feeding in dogs, with esophageal fistula and "modified sham-feeding" by chewing and spitting of food in humans before and after vagotomy and/or antral mucosectomy to eliminate, respectively, the vagal component and the major endogenous source of gastrin (Konturek et al., 1990; Konturek, 2003; Szafran et al., 1990). We confirmed that in both species (dogs and humans) sham-feeding caused very potent stimulation of gastric acid secretion, reaching about 50–60% of pentagastrin-maximum. Several interesting findings have been obtained in these experiments: (1) this neural stimulation of gastric secretion was accompanied, especially in dogs, by a significant rise in the plasma levels of gastric acid stimulatory hormones, including gastrin, ghrelin, cholecystokinin (CCK) and a small rise in plasma gastrin-releasing peptide (GRP) (probably of neuronal origin) combined with the increment in the plasma levels of gastric inhibitory hormones such as pancreatic polypeptide (PP), peptide YY (PYY_{3-3}), leptin and secretin (Fig. 4); (2) the removal of antral mucosa in dogs completely abolished plasma gastrin response and also significantly reduced acid response to sham-feeding; and (3) anticholinergics such as atropine actually increased plasma gastrin response to sham-feeding, while causing almost complete suppression of acid response to this procedure (Konturek, 2003). Our recent results with vagal stimulation obtained in dogs by various techniques including classic sham-feeding as well as that induced by insulin hypoglycemia or 2-deoxy-D-glucose cyto-hypoglycemia confirmed that the highest response to vagal stimulation did not exceed 50% of that attained with exogenous stimulus such as histamine or gastrin applied in a dose inducing maximal gastric acid secretory response. This stimulation was, however, accompanied by the rise in plasma concentration of gastrin that probably contributed, at least in part, to this stimulation because the blockade of gastrin receptors (CCK_2-receptors) by agent S-0509 (Sasaki et al., 2000) caused a significant reduction in gastric acid response to sham feeding. The contribution of CCK was probably negligible to this stimulation because the blockade of receptors for CCK (CCK_1-receptors) with a specific blocker, L-364,718, failed to affect this neurally mediated stimulation of gastric acid secretion (Konturek et al.,

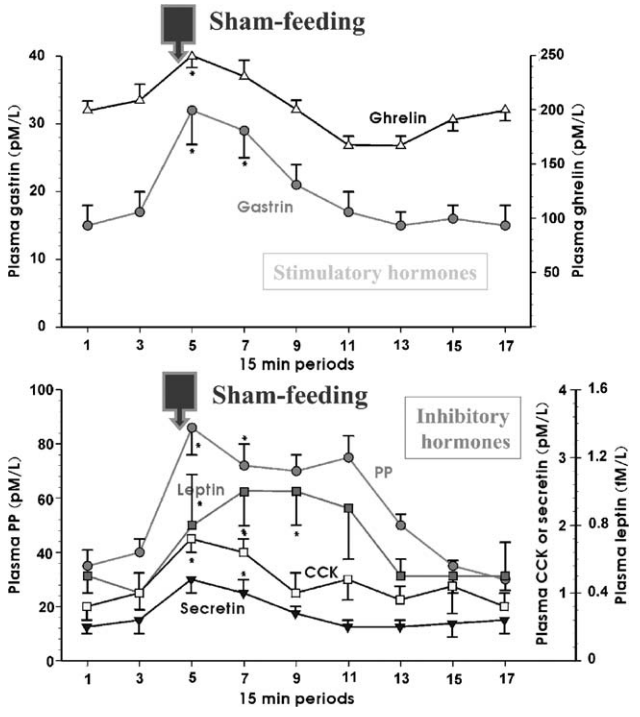

Fig. 4. Plasma levels of immunoreactive hormones originating from the gut and either stimulating (upper panel) or inhibiting (lower panel) gastric acid secretion during and after sham-feeding.

2004b,c). The most effective inhibitor of this secretion was atropine, which almost completely eliminated the sham-feeding- as well as insulin- and 2-deoxy-D-glucose-induced gastric acid secretion (Fig. 5). There is no doubt therefore that vagal-cholinergic component plays a most important role, while gastrin represents only a minor component of vagally excited gastric acid secretion. Probably vagal-cholinergic component interacts with neurally released gastrin (by gastrin releasing peptide) on oxyntic glands leading to augmented gastric acid secretion.

This vagal-cholinergic stimulation of oxyntic cells never reaches a maximal value that can be obtained with potent exogenous stimulants such as gastrin or histamine in humans and animals. This limitation of gastric acid reponse to vagal-cholinergic stimulation is probably caused by local paracrine action on oxyntic cells of somatostatin released from the D cells in oxyntic mucosa by luminal H^+ but remaining under the inhibitory influence of cholinergic nerves and locally released histamine from the ECL cells acting via H_3-receptors as well as amylin colocalized in the G cells to enhance their secretory activity by autocrine mechanism (Fig. 5). In the antral mucosa the D cells and somatostatin release are under the inhibitory influence of cholinergic nerves but are stimulated by neuronal vasoactive intestinal peptide (VIP), histamine released from enterochromaffin (EC) cells and antral natriuretic peptide (ANP) (Schubert, 2003). It is of interest that sham-feeding caused a small but significant increase of plasma ghrelin that was elevated already before sham-feeding but quickly decreased after this procedure suggesting that this hormone could be responsible for feeding behaviour accompanying sham-feeding in fasted animals and contributes to the initial part of the stimulation of gastric acid secretion (Konturek et al., 2004c).

These results seem to point out that the mechanism of cephalic or vagally stimulated sham-feeding is quite complex, and this complexity is further enhanced by recent

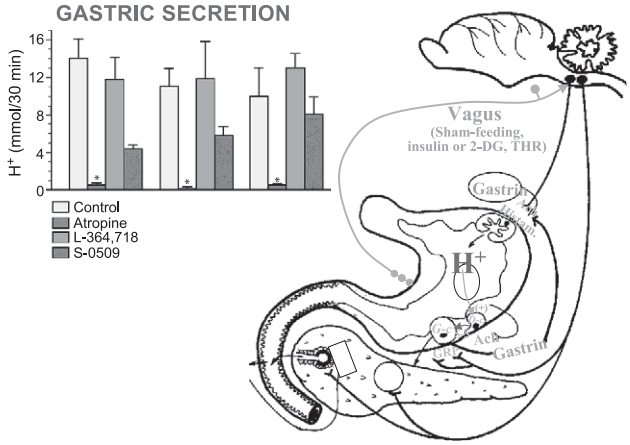

Fig. 5. Gastric acid output in response to sham-feeding, insulin, 2-deoxy-G-glucosa or TRH before and after blockade of muscarinic receptors with atropine (25 μg/kg), CCK_1-antagonist with L-364,718 or CCK_2-antagonist, S-0509 given i.p. at a dose of 10 mg/kg. G-c = gastrin cell, D-c = cell producing somatostatin, GRP=neuronal gastrin releasing peptide.

studies indicating that it is centrally injected or endogenously released in the brain (by cold) by thyrotropin releasing hormone (TRH) from the neurons projecting from the caudal medullary raphe nuclei to the dorsal vagal complex. TRH might participate in the neural stimulation of gastric secretion and alterations in blood flow (Tache and Yang, 1990; Martinez et al., 2002). This is confirmed by the fact that intracisternal application of TRH causes an increase in gastric acid secretion and the formation of acute gastric lesions. Furthermore, the intracisternal administration of a thyrotropin-releasing hormone-1 receptor antisense oligonucleotide can abolish sham-feeding-induced gastric secretion in conscious rats. This stimulus for vagal excitation and gastric secretion may originate from the brain itself (Schubert, 2003) and may contribute to vagally induced stimulation of gastric secretion during the sham-feeding.

3.2. Hormonal control of gastric secretion; controversies with gastrin–histamine involvement

After the discovery of gastrin in the antrum by Edkins (1906) and its publication in the *Journal of Physiology*, Pavlov initially disdained the importance of these discoveries, but then ordered their verification in his lab. Under his supervision, however, the hormonal (gastrin) contribution to the regulation of gastric secretion was amply confirmed (Babkin, 1914). The verification of the "Edkins hypothesis" led him to accept, though reluctantly, the importance of hormonal control of gastric secretion, and this was probably the major reason for his departure from gastro-intestinal physiology to research on conditioned reflexes (Babkin, 1914).

The cephalic or anticipation phase is usually accompanied by increased appetitive behavior and by the plasma increment of various gut hormones related to the food intake. One of them is ghrelin, which was found to be released from the X/A cells of oxyntic mucose in an empty stomach (similarly to motilin with which it shares close chemical homology and similar spectrum of biological action) at the time of sham-feeding, leading to some increase in gastric acid secretion and gastrin release as well as the alteration in gastric motor activity (Konturek et al., 2004c). Also, alcohol, which releases ghrelin, increases gastric secretion while increasing the appetitive behavior (Fig. 6), whereas gastric distention, leptin, petide YY_{3-36} (PYY_{3-36}), oxyntomodulin, glucagone-like peptide-1 (GLP-1) and amylin released from intestinal or pancreatic endocrine cells show opposite effects (Fig. 7).

3.3. Gastric phase of gastric secretion

The gastric phase of gastric secretion, which, according to Edkins (1906), is to be mediated by hormone gastrin, also appears to involve short and long vago-vagal reflexes initiated by the distention of the stomach by food and chemical irritation of gastric mucosal receptors by products

of food digestion. However, both vagal nerves and gastrin appear to act mainly indirectly on gastric glands, i.e., via releasing histamine from the ECL cells located in close vicinity of the oxyntic cells to stimulate their H_2-histamine receptors.

3.4. Discovery of histamine secretagogue activity and its relation to gastrin

L. Popielski, a former pupil of Pavlov in St. Petersburg, appointed in 1904 to be chairman of the Department of Pharmacology in Polish Lvov (Lemberg) in the eastern part of Galicia, former Polish province, initially investigated mostly neural control of exocrine pancreatic secretion, being a fervent supporter of neural reflex nature of this control in agreement with the dogma of Pavlov's *nervism* (Popielski, 1912). However, just before his lethal exit, he obtained sample of pure histamine, at that time called beta-imidazolylethyl-amine or simply "Beta-I", discovered earlier by Berger in collaboration with H. Dale (Modlin and Sachs, 1998) who somehow missed the action of this amine on gastric secretion. Following the accidental discovery of the potent secretagogue effect of histamine, Popielski still persistently rejected the "Edkin's hypothesis" or the "gastrin concept" of gastric secretion and believed that gastrin has no role in the stimulation of gastric acid secretion. Popielski (1920) using pure synthetic histamine found that this compound administered subcutaneously to dogs with a gastric fistula induced an abundant and dose-dependent gastric acid stimulation. This secretion was not affected by vagotomy or scopolamine, indicating that it acts directly on parietal cells independently of vagal nerves and cholinergic innervation (Popielski, 1920). As stated by Babkin (1914) in his famous book *Secretory Mechanisms of the Digestive Glands*, it is a historical paradox that the secretagogue action of histamine was discovered by a man who spent practically his entire research career under the strong influence of

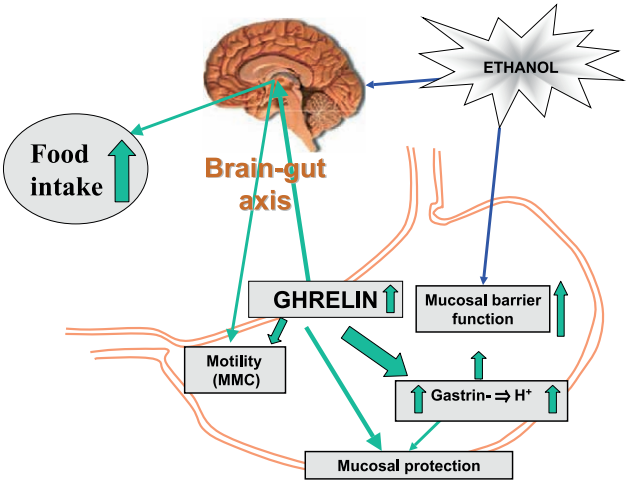

Fig. 6. Effect of ethanol intake on food intake via release of ghrelin and activation of brain-gut axis.

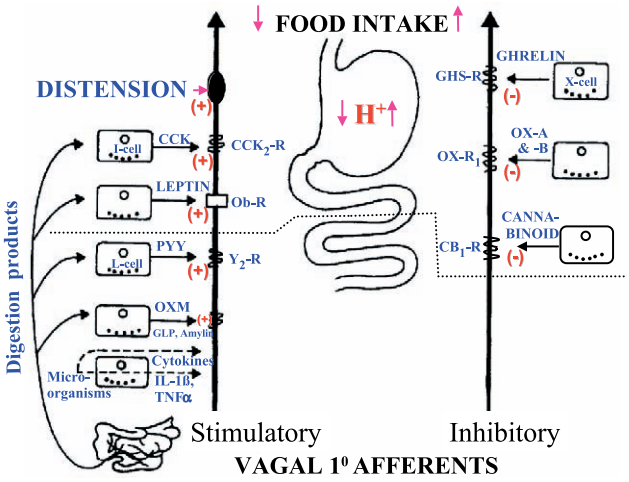

Fig. 7. The influence of orexigenic and anoroxigenic peptides on food intake and gastric acid secretion acting via G-protein-coupled receptors on stimulatory or inhibitory afferent nerves affecting the satiety center in the hypothalamus.

Pavlov's *nervism* in contesting the theory that the gastric digestive glands could be regulated by gastrin (Popielski, 1920). His discovery related to extremely potent gastric secretagogue activity of histamine apparently was at variance with the concept of the hormonal regulation of gastric acid secretion (Edkin's hypothesis) until 1964, when Gregory and Tracy (1964) of Liverpool isolated, purified, and finally synthesized gastrin, showing that it is a peptide. With the progress in gastrin purification and chemical identification, attempts were made to "revitalize" the "Edkin's hypothesis" of gastrin. Uvnas (1942) demonstrated in a series of experiments on sham-fed Pavlovian dogs provided with antral pouches that gastrin release remains under vagal control, as sham-feeding effectively stimulated gastric secretion only in dogs with a preserved and innervated antral portion of the stomach (Olbe, 1964). Following antrectomy, a background minute dose of gastrin (to mimic the amounts of hormone released physiologically) restored fully the sham-feeding-induced gastric secretion, indicating a potentiation between gastrin, histamine and vagus in the stimulation of gastric acid secretion (Olbe, 1964). In the meantime, however, Code (1956) collected mass evidence for establishing that histamine, rather than gastrin, is the "final common chemo-stimulator" of oxyntic cells by showing that (1) histamine, as shown by Popielski, acts directly on oxyntic cells to stimulate H^+ secretion; (2) histamine can be detected in large amounts in oxyntic mucosa, being released locally by ECL cells, expressing active histidine decarboxylase to transform histidine into histamine; (3) histaminase, which destroys histamine, cannot be detected in oxyntic mucosa; (4) histamine is released into the blood draining the stomach after meal and can be detected in urine following acid secretion; and (5) histamine is released by stimulants of gastric secretion such as food or gastrin. Then, Code described the pathway of histamine generation and metabolism, showing that it originates from histidine by its

decarboxylation by histidine decarboxylase (HDC) and by methylation of its side chain to yield methyl derivatives. These methylated histamine derivatives were found to be even more powerful gastric stimulants, but when converted to a 1-4-methyl derivative by methylation at the imidazole ring, they lost their stimulatory effectiveness. It is now well established that gastrin and acetylcholine act on ECL cells in antral mucosa to release histamine, which in turn stimulates via H_2-receptors at the oxyntic cells. Three other histamine receptors have been identified (H_1, H_3 and recently H_4). Gastrin was found to stimulate the production, storage, and release of histamine from ECL cells and to aid the proliferation of these cells. Several other substances such as cytokines (e.g., interleukin-1), aspirin, indomethacin, dexamethasone, lipopolysaccharide were found to stimulate HDC activity and to release histamine (Ayada et al., 2003). Hypergastrinemic states such as observed in patients with *gastrinoma* or following prolog treatment with potent antisecretory drugs such as H_2-receptor antagonists cimetidine or ranitidine or potent proton pump inhibitors (omeprazole, lanzoprazole, pantoprazole, etc.) may develop ECL-cell hyperplasia and carcinoid tumors with excessive production and release of histamine (Peghini et al., 2003).

As mentioned before, two types of gastrin/CCK-receptors have been identified including CCK-1-receptors specific for CCK and CCK-2 receptors recognizing both gastrin and CCK (Noble and Roques, 2002). The CCK-2 receptors are present in oxyntic cells to stimulate H^+ secretion mediated by intracellular increase in Ca^{2+} concentration, while histamine acts on these cells through the H_2-receptors and intracellular adenylate cyclase-cyclic AMP system activating protein kinases and eventually Na^+,K^+-ATPase or proton pump of parietal cells. Specific antagonists of CCK_2- receptors such as S-0509 (see Fig. 5) (Sasaki et al., 2000) are effective inhibitors of gastric acid secretion and are useful tool in examining acid-pepsin secretion. CCK-2 receptors were also found to inhibit gastrin-induced gastric acid secretion in animals but no studies with that antagonist have been carried out in humans. Surprisingly, gastrin-deficient mice have impaired basal and gastrin-stimulated H^+ secretion, but their parietal cells in vitro respond normally to major secretagogues such as gastrin, histamine or acetylcholine, and possess intact intracellular mediators for these secretagogues such as the release of Ca^{2+} and adenylate-cyclic AMP system mediating their effects on H^+ secretion, suggesting that intracellular Ca^{2+}-related signaling pathway is upregulated to compensate for the loss of gastrin effect via CCK-2-receptors (Hinkle et al., 2003). Furthermore, as gastrin is known to enhance histamine production in ECL cells, the deficiency of gastrin in these animals results in the decrease in histamine content in oxyntic mucosa.

3.5. Gastrin and its receptors in gastric cancerogenesis

It is of interest that both gastrin and CCK-2 receptors have been found to be overexpressed in gastric and colorectal cancers suggesting that gastrin, the most powerful mucosal cell growth promoting factor, may act in local loop enhancing the proliferation and growth of tumor cells (Hartwich et al., 2001; Konturek et al., 1999, 2000a,b, 2001a) (Fig. 8). In this respect, it should be mentioned that CCK-2 receptors have been localized in the progenitor zone of gastric gland and found to participate in the stimulation of gastric (and colonic) mucosal cell growth and differentiation (together with TGFα) into various types of cells of these glands. The use of gastrin-like agonists and specific CCK-2 antagonists may have potential in the regulation of mucosal growth and differentiation, e.g., in atrophic gastritis and in the control of gastrointestinal tumor growth expressing CCK-2 receptors (Hartwich et al., 2001). This is in keeping with the observation that in CCK-2 knockout mice, the growth and differentiation of ECL cells as well as their function are altered resulting in the atrophy of the oxyntic mucosa and reduction in parietal cells mass (Chen et al., 2002). Histamine released from normally functioning ECL cells acts on at least two types of histamine receptors: H_2-receptors at the oxyntic cells to stimulate H^+ secretion and H_3-receptors (activated by appropriate H_3-agonists) which have been reported to stimulate H^+ secretion in vitro and inhibit that in vivo. The former effect is probably mediated by somatostatin inhibition, while the latter by possible action on H_3-receptors in the brain, where application of histamine was found to exert an inhibitory action on gastric H^+ secretion.

Regarding the link of *H. pylori* infection and hypergastrinemia it should be mentioned that side chain (not an imidazole ring) methylated histamine (*N*α-methyl histamine) has been found in infected *H. pylori* but not in healthy stomach. This *N*α-methyl histamine appears to be a powerful releaser of gastrin from antral G cells and cancer cells and also a stimulant of gastric H^+ secretion,

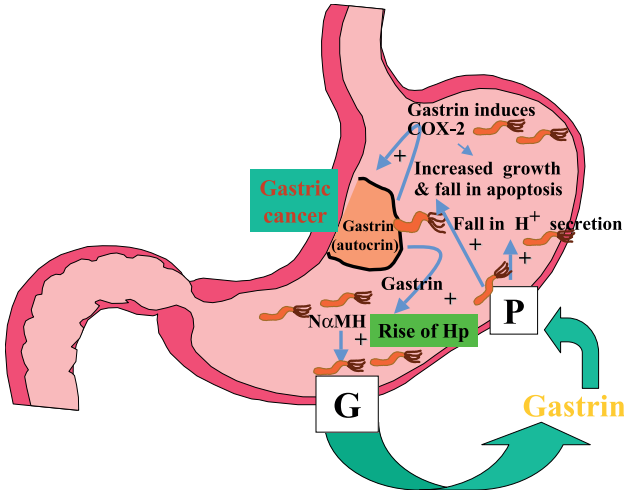

Fig. 8. Concept of gastric cancerogenesis capable of expressing gastrin and its receptors causing autocrine stimulation of cancer cells, expression of COX-2 and cytokines. *N*α-methylo-histamine stimulates G cells and cancer cells to release gastrin.

acting on G cells primarily through HH_2 histamine receptors (not through H_3-receptors as originally proposed) to release gastrin (Konturek et al., 2001b; Saitoh et al., 2002). The *H. pylori* infection is usually accompanied by hypergastrinemia and hyperchlorhydria that can be partly normalized upon eradication of the germ in patients with infection and reduced in patients with gastric cancer. The implication of this finding is the fact that most gastric cancers are infected with *H. pylori* and accompanied by hypergastrinemia, probably stimulating cancer cells to growth so *H. pylori* eradication in patients with potential risk of cancerogenesis such as atrophic gastritis of oxyntic gland area should be performed to prevent the *H. pylori*-related gastric cancerogenesis as postulated before (Uemura et al., 1997; Uemura et al., 2001; Watson and Gilliam, 2001).

Attempts were made to neutralize gastrin G-17 using high affinity antibodies against this gastrin molecule (gastrimmune) (Watson and Gilliam, 2001) to reduce its immunogenic activity and tumor-growth-promoting effect. Some positive results, namely, the slowing of the progress of the tumor growth, were reported in this respect in colorectal cancer treated with gastrimmune (Smith et al., 2000a,b). The problem of local tissue irritation by gastrimmune and the failure to neutralize all types of gastrin produced in cancer tissue (Konturek et al., 2002), especially progastrin, slowed down the research in this field.

3.6. Inhibitors of gastric secretions

Gastrointestinal mucosa is capable of producing and releasing numerous inhibitors of gastric acid secretion including somatostatin, cholecystokinin (CCK), calcitonin gene-related peptide (CGRP), adrenomodulin, amylin, pituitary adenylate cyclase-activating peptide (PACAP), antral natriuretic peptide (ANP), pancreatic polypeptide (PP) and prostaglandins (Schubert, 2003).

The most potent physiological inhibitor of oxyntic cells and G cells is 14- or 28-amino acid somatostatin, which is released by the D cells present in close proximity of the G cells in *antrum* and of the oxyntic cells in *fundus* to inhibit these cells by paracrine mechanisms. It is released by the action of H^+ on the receptors of the D cells and since its major effect is the inhibition of gastrin release and gastric acid secretion, it may be considered as a typical feedback controller of gastric secretion. Its inhibitory effect is also mediated by the inhibition of histamine release from ECL cells through activation of their membrane receptors termed SSTR2 (Allen et al., 2002), present in the ECL cells, releasing histamine and in oxyntic cells suppressing gastric H^+ secretion. Potent analogs of somatostatin such as sandostatin have been used to identify the localization of *gastrinoma* metastases and to inhibit the progression of this tumor and its metastases (Smith et al., 2000a,b).

Calcitonin gene-related peptide (CGRP) belongs to the neuropeptide family of peptides including adrenomedulin, amylin and calcitonin (Poyner et al., 2002). In the stomach CGRP is present predominantly at the terminals of sensory afferent in the oxyntic and antral gland area (Hagner et al., 2002; Kawashima et al., 2002). This peptide plays an important role in the axonal reflex inhibition of gastric acid secretion and vasodilation.

Adrenomodulin is present in ECL cells and plays a role in mucosal repair and defense against various irritants. It acts via the neurons of enteric nervous system and stimulates somatostatin release, thus inhibiting histamine release and gastric acid secretion (Poyner et al., 2002).

Amylin is colocalized with somatostatin in D cells and enhances somatostatin release via autocrine mechanisms, resulting in the inhibition of histamine release and gastric acid secretion as well as in the suppression of food intake. Its release is stimulated by cholecystokinin, epinephrine and glucagons-like peptide that act on D-cell receptor-dependent activation of Ca^{2+}/protein kinases and adenylate cyclase pathway (Beales and Calam, 2003; Halford et al., 2004).

Pituitary adenylate cyclase activating peptide (PACAP) is a member of the secretin family of peptides together with glucagon and vasoactive intestinal peptide (VIP). It is present in enteric neurons (Gower et al., 2003b) and inhibits histamine release from the ECL cells and somatostatin from the D cells (Gower et al., 2003a), leading to the inhibition of gastric acid secretion (Miampamba et al., 2002; Sandvik et al., 2001; Zeng et al., 1999).

Antral natriuretic peptide (ANP) first isolated from antral myocytes was identified in the enterochromaffin cells (EC cells) of oxyntic and antral mucosa. It acts via NPR-A receptors to stimulate somatostatin release from antral and oxyntic mucosa D cells and subsequently inhibits gastrin release and gastric acid secretion (Gower et al., 2003a,b).

Prostaglandins are ubiquitous substances, which are products of the arachidonic metabolism via cyclooxygenase (COX)-1 and/or COX-2 pathway. As mentioned before COX-1-derived prostaglandins are important in the maintenance of mucus alkaline secretion and mucosal blood flow that serve to maintain mucosal defense and protection against various local irritants including H^+, which is known to stimulate the activity of COX-1. Gastric H^+-induced COX-1 promotes prostaglandin release that interacts with gastric secretory stimulants and inhibitors, and while the latter predominate under basal conditions, the former prevail postprandially, when three phases of secretory mechanism overlap to stimulate gastric secretion via neuro-hormonal mechanisms. As mentioned before COX-2 is induced by carbachol in oxyntic cells and its products, prostaglandins, may serve as gastric protectors against various irritants including its own highly concentrated acid secretion (Pausawasdi et al., 2002). Certain proton pump inhibitors such lanzoprazole are also effective in the induction of COX-2 and in the increase of gastrin release, resulting in the attenuation of mucosal damage caused by local irritants such as ethanol (Tsuji et al., 2002).

4. Concluding remarks

(1) The most potent stimulant of oxyntic cells appears to be histamine as discovered approximately 80 years ago by Popielski and confirmed later by numerous investigators, particularly Code, to be the major gastric acid secretagogue and final common chemostimulator of oxyntic cells.

(2) Histamine is released by food and other gastric secretagogues, especially gastrin, from the ECL cells, which in the antral mucosa stimulate D cells acts by the H_3-receptor to release somatostatin that acts by local paracrine route controls gastrin release and H^+ secretion by oxyntic cells as well as inhibits the D cells to limit the inhibition of gastric acid secretion.

(3) Peptic ulcer, which may be a result of *H. pylori* infection, is accompanied by hyperchlorhydria and this is regularly associated with hyperhistaminemia, originating from excessive stimulation of ECL cells by increased concentrations of gastrin, as well as hypergastrinemia induced by the action on *N*α-methyl histamine, a product of *H. pylori*-infected stomachs.

(4) Gastric and colorectal cancer appear to be capable of expressing progastrin and gastrin and its specific receptors, CCK-2, which may be involved in the local stimulation of tumor growth and proliferation. These progastrin and gastrin detected in tumors may stimulate the expression of COX-2 and release prostaglandin that might be implicated in tumor growth by inhibition of apoptosis and enhancement of angiogenesis.

(5) The neuro-hormonal pharmacology of the stomach and duodenum succeeded in the discovery and clinical use of potent inhibitors of gastric acid secretion such as histamine H_2-receptor antagonists and proton pump inhibitors that abolish all modes of gastric acid secretory stimulation, but, unfortunately, result in hypergastrinemia which may help in the spread of *H. pylori* infection towards the proximal part of the stomach with subsequent fundic atrophy and cancerogenesis. The eradication of *H. pylori* abolishes hyperchlorhydria and hypergastrinemia, and is successful in the treatment of peptic ulcer and probably also in the prevention of *H. pylori*-related gastric cancerogenesis.

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