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European Journal of Pharmacology 481 (2003) 1–14
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Review

Neuroendocrinology of the pancreas; role of brain–gut axis in pancreatic secretion

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Received 22 May 2003; received in revised form 18 August 2003; accepted 26 August 2003

Abstract

Exocrine pancreatic secretion, attributed initially to neural reflexes (*nervism*), was then found to depend also on enterohormones, especially secretin and cholecystokinin (CCK), released by the intestinal mucosa and believed to act via an endocrine pathway. Recently, CCK and other enterohormones were found to stimulate the pancreas by excitation of sensory nerves and by trigger of long vagovagal or (“brain–gut axis”) enteropancreatic reflexes. Numerous neurotransmitters, such as acetylcholine, and certain neuropeptides, such as gastrin-releasing peptide (GRP), generated by neurons of the enteric nervous system (ENS) of the gut, have been implicated in the regulation of exocrine pancreas. Recently, peptides affecting appetite behavior and originating from the gut, such as leptin and ghrelin, or from the pancreas, such as pancreatic polypeptide and neuropeptide Y, appear to modulate the exocrine pancreas via hypothalamic centers. The aim of this review is to highlight the interaction of nerves and enterohormones in the regulation of exocrine pancreatic secretion.

Keywords: Pancreas; Cholecystokinin; Secretin; Gastrin-releasing peptide; Leptin; Ghrelin; Pancreatic polypeptide

1. Introduction

1.1. Historical background

Scientific interest in the gastrointestinal system started with the writings of Galen (129–200) who identified the digestive organs, especially the intestines and the liver, and associated their functions with the assimilation of nutrients. Discoveries of gross anatomy initiated by Andreas Vesalius (1514–1564) were followed during the 17th and 18th centuries by the description of intestinal lacteals by Aselli (1622), salivary glands by Wharton (1656), intestinal glands by Brunner (1686) and Lieberkuhn (1745), and pancreatic ducts by Virsung (1642) and Santorini (1775) (Kirsner, 1994).

Although Regner de Graaf (1641–1679) made the first pancreatic and biliary fistulas to collect pancreatic juice and bile in dogs, it was not until Claude Bernard (1813–1878) that the important role of the pancreas in the digestion of fat was emphasized (Bernard, 1985). However, another 50 years passed before active physiological research on the digestive system was resumed at the turn of the 19th century and during the early part of the 20th century with discoveries by Ivan P. Pavlov of neural stimulation of digestive glands (Pavlov, 1910), attributing the mechanisms of this stimulation exclusively to neural reflexes (*nervism*). In contrast to neural regulation, W.M. Bayliss and E.H. Starling, trying to clarify the mechanism of pancreatic secretion, discovered secretin in 1902, the first hormonal substance stimulating pancreatic secretion in response to duodenal acid, even after total denervation of the duodenum (site of secretin release) and the pancreas (target organ for secretin) (Bayliss and Starling, 1902). Furthermore, J.S. Edkins identified, in 1905 (Edkins, 1905), gastrin, another non-nervous gastric secretagogue implicated in the postprandial regulation of gastric secretion. The discoveries of non-nervous mechanisms of gastropancreatic secretion are milestones in the development of modern endocrinology. The term *hormone* was coined by Hardy and first applied to secretin as a humoral substance acting entirely through the blood circulation to induce digestive organ activity.

In the second part of the 20th century, with progress in peptide biochemistry, the major gut peptide hormones,

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doi:10.1016/j.ejphar.2003.08.042

known so far only by names such as gastrin, secretin, cholecystokinin (CCK), gastric inhibitory peptide (GIP), and motilin, have been isolated, chemically characterized, and synthesized, together with the identification of genes encoding these peptides and their specific receptors on target cells. In addition, numerous hormonal peptides such as pancreatic polypeptide, peptide YY, neuropeptide Y, somatostatin, gastrin-releasing peptide (GRP), galanin, vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), substance P, leptin, and ghrelin have been discovered in the gut and often also in the brain and found to modulate pancreatic secretion, but their full hormonal status has yet to be determined (Miller, 1999).

Some of the gut peptides, such as CCK, pancreatic polypeptide, peptide YY and neuropeptide Y, somatostatin, leptin, or ghrelin, originally believed to act via endocrine pathways, were then found to act through neural pathways to exert their biological action, providing support to the concept of neuroendocrinology of the digestive system. Thus, the old Pavlovian *nervism* has been "wedded to" with *endocrinology* to yield neuroendocrinology of the gut, explaining the mechanisms cooperating and interacting to adapt the digestive organs' activities to body requirements.

The nervous system, especially its enteric portion (enteric nervous system, ENS), in the digestive system, the so-called the "gut brain," consists of about 100 million neurons (the number equivalent to that in the spinal cord), which appear to cooperate with enterohormones, contributing to the motor, secretory, absorptive, excretory, trophic, or circulatory functions of the digestive system. Most of the gut hormones originally identified in the gut were then localized in the central neurons system and vice versa; the brain neuropeptides and neurotransmitters were identified in the gut so that the "brain–gut axis" has now been proposed to explain the control mechanisms of digestive gland activity and feeding behavior by the central nervous system and its peripheral portion, the ENS, under normal and pathological conditions.

1.2. Structural basis of pancreatic secretion

The pancreas is both an exocrine and an endocrine organ. The exocrine pancreas combines two main functional ele-

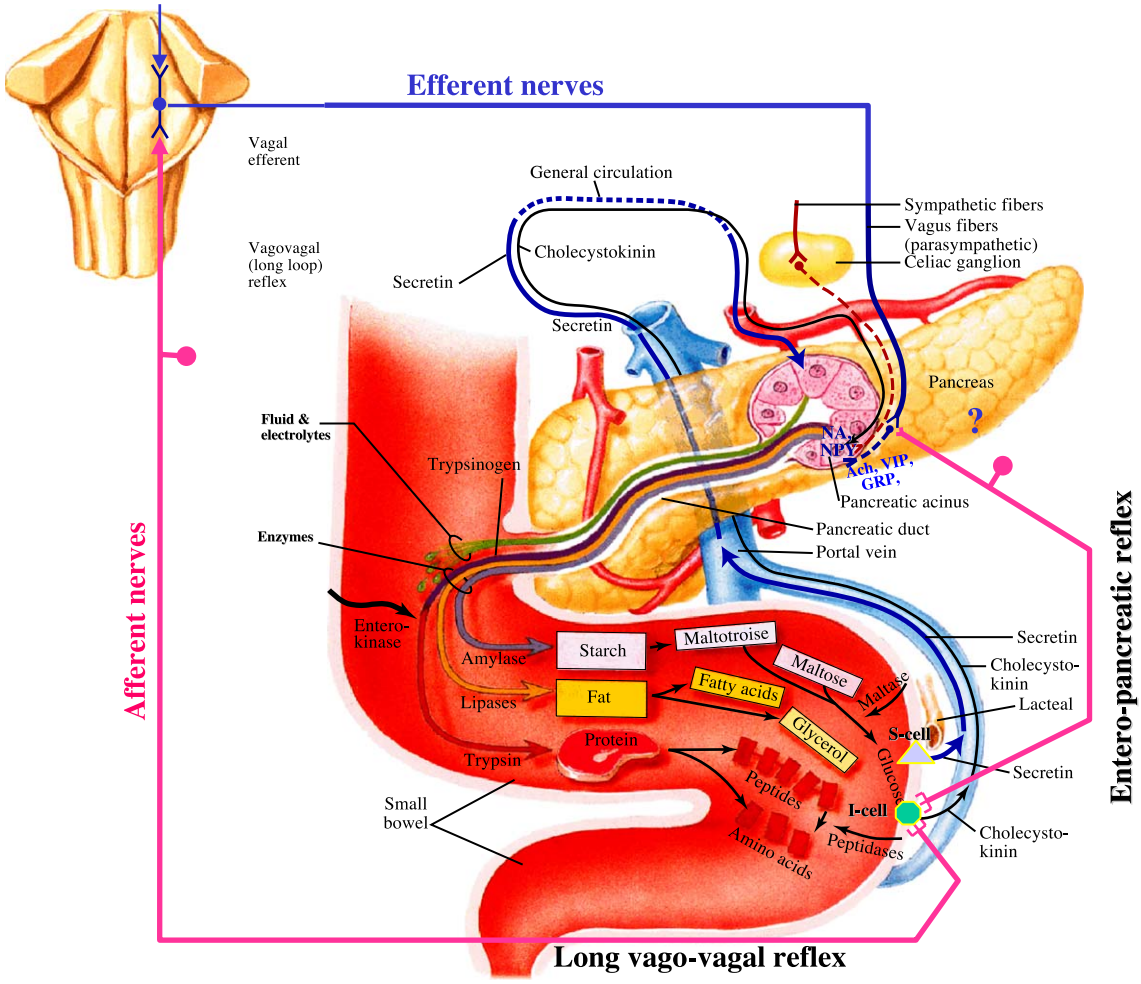

Fig. 1. The stimulatory action of CCK, the major hormone stimulating the exocrine pancreas is mediated by long vagovagal and short enteropancreatic reflexes (modified from Hansen and Koeppen, 2002).

ments: the *acini*, comprising about 84%, and the ductal and centroacinar cells (called principal cells), which include about 5% of gland cell mass, while the endocrine element—the pancreatic islets—contains about 1% of the total cell mass (Gorelick and Jamieson, 1994; Case, 1998). The *acini* of spherical or tubular shape consist of acinar cells specialized to synthesize and store digestive enzymes in secretory vesicles (zymogen granules) and to release these enzymes in response to various secretagogues. Their basolateral membrane represents receptors for various secretagogues including neurotransmitters such as acetylcholine or nitric oxide (NO), and neuropeptides such as GRP or VIP. These receptors have been detected in in vitro isolated cultured acinar cells and found to stimulate secretion of enzymes from zymogen granules (Gorelick and Jamieson, 1994), occupying the apical region of the cells. This apical region is also equipped with microvilli that contain a filamentous actin mesh involved in effective exocytosis of zymogen granules into the lumen of the acini. The tight junctions between the acinar cells act as a barrier to prevent the passage of large molecules, but allow the passage of water and electrolytes. Gap junctions between acinar cells form specialized areas of the plasma membrane of adjacent acinar cells with pores that allow small molecules, such as Ca^{2+} ions molecules, to pass between cells and to serve as an intercellular chemical and electrical communication system (Stauffer et al., 1993). The centroacinar and duct cells, which are largely responsible for HCO_3^- and water secretion, become more columnar further down the ductal tree and are joined by other specialized cell types such as mucus-secreting cells, capable of producing, besides mucus, trefoil peptides, characterized by a three-loop structure held together by disulfide bonds and resistant to autodigestion (Konturek et al., 1997b; Laubitz et al., 2003).

Numerous unmyelinated nerves are present in the pancreas, innervating the glandular cells as well as the vessels. They are distributed through the interlobular connective tissues, where there are intrinsic ganglia, representing peripheral integrative centers of enteropancreatic reflexes. These fibers may belong to cholinergic, adrenergic, or peptidergic as well as sensory neurons and interneurons of the ENS. They transmit the signals through afferent fibers of external autonomic nerves to ENS or CNS and from the ENS or CNS by efferent autonomic neurons to glandular cells of the pancreas. Thus, short enteropancreatic reflexes and long vagovagal reflexes operate in the regulation of the exocrine pancreas. Such reflexes are essential for the action of enterohormones, especially of CCK, on pancreatic enzyme secretion (Fig. 1).

The endocrine portion of the pancreas is located in the islets of Langerhans that contain A-, B-, D-, and F-cells, releasing glucagon, insulin, somatostatin, and pancreatic polypeptide and probably also neuropeptide Y, respectively. Numerous other peptide hormones and neurotransmitters that are involved in the control of its exocrine or endocrine secretion are released by the pancreas. The islet hormones

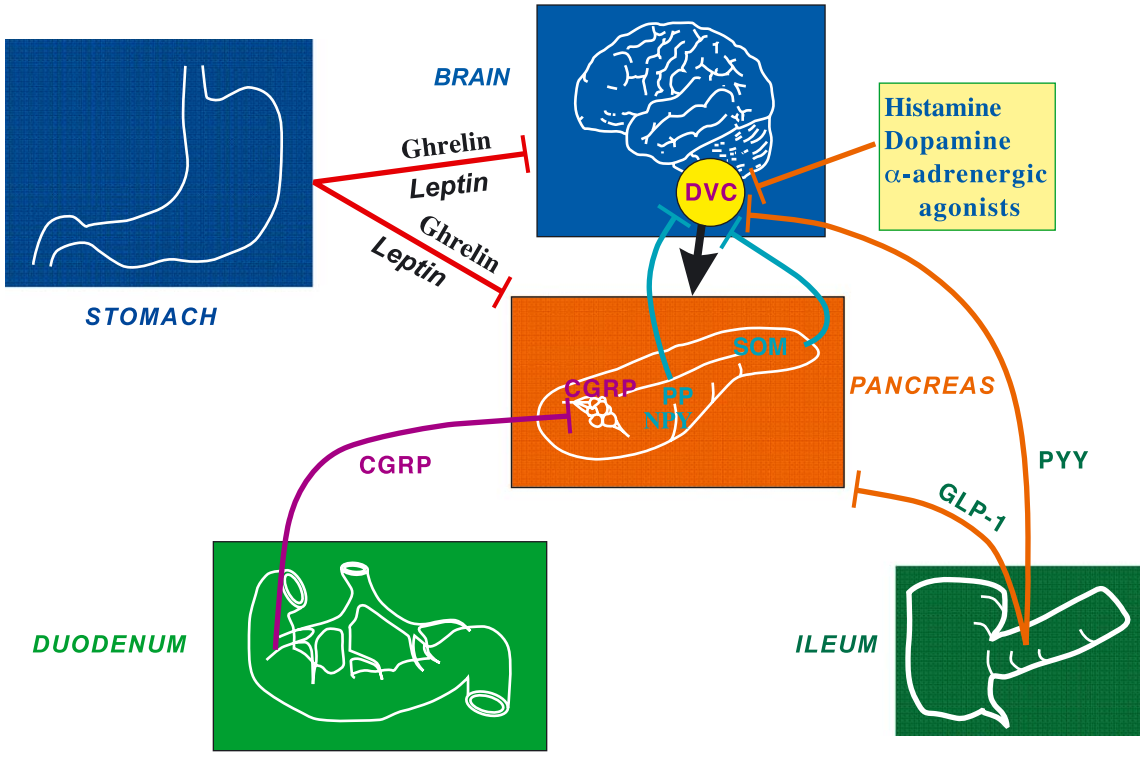

Fig. 2. The inhibition of pancreatic secretion of various hormonal peptides is mediated by a central action on the hypothalamus, *area postrema*, and finally by the dorsal vagal complex (DVC) in the brainstem.

first supply the exocrine component of the pancreas, surrounding acinar cells via the insulino-acinar portal system and thus contribute to the regulation of pancreatic enzyme synthesis, transport and secretion of enzymes, as well as growth of these cells. The disorders of this endocrine portion, such as *diabetes mellitus*, resulting either from the lack of insulin production due to viral or autoimmune damage of B-cells (type I) or their genetic defect, producing insensitive insulin receptors throughout the body (type II), greatly reduce the activity of the exocrine portion of the pancreas, but this is beyond the scope of this review. The pancreatic hormones that reach the general circulation, especially pancreatic polypeptide and its analogs (peptide YY or neuropeptide Y), somatostatin or the appetite-controlling peptides (ghrelin and leptin), inhibit pancreatic secretion, at least in part through the CNS centers, particularly the *area postrema* (Deng et al., 2001a,b) where the receptors for these hormones have been identified. Other peptides such as calcitonin gene-related peptide (CGRP) or glucagon-like peptide 1 (GLP-1) may reach the pancreatic secretory cells directly to inhibit their secretory activity (Fig. 2).

2. Regulation of HCO_3^- secretion

Studies on pancreatic exocrine secretion revealed many species-dependent variations in HCO_3^- and volume flow attributed primarily to the ductal and centroacinar cells (Case, 1998) that are specifically equipped with receptors for secretin and VIP, and contain highly active carbonic anhydrase, an enzyme which is important for its ability to produce and secrete high concentrations of HCO_3^-. The pancreas in humans, dogs, and cats shows a rather slight secretion under basal conditions, but responds with an abundant volume flow and high HCO_3^- output in response to secretin stimulation, but negligible volume flow with high enzyme content after CCK or vagal stimulation. In rats, the laboratory animals most often used to study pancreatic secretory mechanisms, the profile of spontaneous versus stimulated (secretin, CCK, vagal nerve) HCO_3^- and water secretion differs from that in humans, dogs, or cats. The spontaneous pancreatic secretion is relatively high in rats, but secretin, CCK, and vagal stimulation results in a rather moderate increase in this secretion. Pigs, like humans, secrete little under basal conditions, but respond with an abundant volume flow in response to secretin, CCK, or vagal stimulation. Whether this variation in HCO_3^-/water secretion reflects a difference in composition of primary fluid secretion or in the rate of ductal cell rate of HCO_3^-/Cl^- exchange is unknown, but obviously, the pancreatic secretory data obtained from animals, especially from rats, may not be relevant to human conditions and, therefore, should be interpreted with caution.

Secretin and VIP act on receptors at the basolateral membrane of ductal and centroacinar cells to increase the cytosolic concentration of cyclic adenosine monophosphate (cAMP) in these cells (Case, 1998). The rise in cAMP increases HCO_3^- secretion by primary activation of a Cl^- channel on the luminal membrane (Gray et al., 1988). The increased Cl^- transport through the apical membrane into the glandular lumen is coupled with the Cl^-/HCO_3^- antiport, resulting in Cl^- for HCO_3^- exchange, particularly when the volume flow of secretion is small. This is the reason for the reciprocal relationship between pancreatic juice HCO_3^- and Cl^- concentrations that could be explained, in part, by the difference in water secretion in pancreatic juice (Case, 1998). With an increased flow rate of secretion, there is also an increased HCO_3^- concentration, while that of Cl^- declines. The Na^+/H^+ antiport with active Na^+/K^+-ATPase, active H^+-ATPase, and secondary active K^+/Na^+ exchange occurs on the basolateral membrane of the ductal and centroacinar cells. Secretin or VIP stimulation results in an apical Cl^-/HCO_3^- antiport that is responsible for increased luminal formation of HCO_3^- originating from the hydration of CO_2, produced locally in the cell as metabolic product, as well as CO_2 released in the extracellular fluid (ECF) by the action of H^+ on HCO_3^-. CO_2, diffusing readily into the alkalinized ductal cells, is hydrated with water, the step catalyzed by high activity carbonic anhydrase in pancreatic ductal cells. The continued movement of H^+ across the basolateral membrane leads to a build-up of intracellular HCO_3^- and to the movement of HCO_3^- to the *acinus* lumen across the apical membrane in exchange for Cl^-. As HCO_3^- is secreted into the duct lumen, Na^+ also moves across the epithelium to preserve electrical neutrality. Na^+ movement through the intercellular pathway is followed by passive water movement into the duct lumen along the osmotic gradient. With enhanced secretin or VIP stimulation of ductal and centroacinar cell receptors, there is a continued increase in the HCO_3^- concentration in pancreatic juice as well as the rise of its pH, combined with the fall in Cl^- concentration. It is interesting that CCK and vagal stimulation, although universally believed to promote predominantly protein enzyme secretion from acinar cells with negligible volume flow in certain species like pigs, cattle, rats, guinea pigs, and rabbits, often used for pharmacological studies, results in a marked increase of fluid secretion. Furthermore, in pigs and guinea pigs, a large number of VIPergic neurons are present in the pancreas and, during vagal stimulation, these fibers release large amounts of VIP, which evokes HCO_3^- secretion in a manner similar to secretin (Stauffer et al., 1993; Deng et al., 2001a). At this point, it may be important to mention that pancreatic acinar cells also can secrete Cl^--rich fluid. This depends upon the presence of a novel, voltage-gated, slowly activating potassium channels current (I_{Ks}) at the basolateral membrane of acinar cells, which contributes to NaCl secretion by these cells. Secretin appears to augment the amplitude of I_{Ks}, and so does carbachol stimulation, suggesting the existence of vagus secretin synergism in the Cl^- secretion by acinar cells (Gray et al., 1988; Kim et al., 2001).

In conscious, fully adapted dogs (Konturek et al., 1986a) and in humans with an intubated pancreatic duct (Domschke et al., 1976), the peak in basal pancreatic HCO_3^- secretion reached only about 1–2% of the maximal response of the gland to secretin, while in rats, it was closer to 10% and could be suppressed by about 50% on muscarinic blockade (Chariot et al., 1990) and by about 40% with antisecretin serum (Guan et al., 1991) but not by a CCK receptor antagonist (Niebel et al., 1991). The spontaneous fluctuations of basal secretion should be taken into account (e.g., in dogs, the peak fluctuations of HCO_3^- output may reach about 10% and protein enzyme output may reach about 30% of their postprandial outputs) (Konturek et al., 1986a). Since isolated pancreatic gland does not exhibit the intrinsic rhythmicity, it is obvious that transient changes in secretion observed in conscious animals can be attributed to the rhythmic activity of extrapancreatic stimuli. This is consistent with the observation in dogs with autotransplanted pancreas, which showed rhythmicity in enzyme secretion (Zimmerman et al., 1992). Motilin, whose plasma level was shown to change in phase with the fluctuations of basal pancreatic secretion and which, when injected alone, may induce the premature migrating myoelectric complex accompanied by an increase in pancreatic secretion, was implicated in the regulation of interdigestive pancreatic secretion. The fact that atropine blocked the cyclic changes of basal pancreatic secretion (Lee et al., 1986) indicates that the enteric nervous system, probably modulating the release of motilin, is involved in the regulation of interdigestive pancreatic secretion (Konturek et al., 1986a; Lee et al., 1986) (Fig. 4).

The primary goal of pancreatic HCO_3^- secretion in response to secretin in humans or dogs is the neutralization of gastric acid entering the duodenum. In this process, HCO_3^- originating from the pancreatic and biliary duct cells and duodenal mucosa provides an intraluminal pH optimal for the activity of pancreatic and intestinal brush border enzymes involved in protein, lipid, and carbohydrate digestion, as well as in the absorption of digestion products. Duodenal pH is the major regulator of secretin release, and the major source of inhibitory duodeno-gastric reflexes (Konturek et al., 1971). The threshold value for secretin release and stimulation of pancreatic HCO_3^- is 4.5 (Grossman and Konturek, 1974; Fahrenkrug et al., 1978; Chey and Konturek, 1982). Below this threshold, the amount of HCO_3^- secreted is directly related to the increase in plasma secretin concentration and this depends upon the total amounts of titratable acid delivered to the duodenal mucosa (Meyer et al., 1970; Chey and Konturek, 1982). Chey et al. (1979) obtained evidence that, in conscious dogs, the postprandial release of secretin plays a crucial role in the secretion of HCO_3^- and fluid because the immunoneutralization of secretin by specific antibodies blocked the increase in pancreatic fluid and HCO_3^- secretion. A similar finding was reported by Konturek et al. (1986b) using a specific secretin antiserum to suppress the pancreatic HCO_3^- response to meal stimulation. Konturek et al. (1971) were the first to report that cholinergic innervation plays a significant role in the release and action of endogenous secretin released by duodenal acid and in the action of exogenous hormone on pancreatic volume flow and HCO_3^- secretion, suggesting the involvement of cholinergic control of local enteric neurons in the release and action of secretin. Zabielski et al. (1994) found that temporary suppression of vagal conductivity by cooling the *vagus* abolished the stimulation of exocrine pancreas by exogenous secretin in conscious calves.

Li et al. (1990) found that intraduodenal infusion of a concentrate of acid perfusate from the donor rat to the recipient animal raised the plasma secretin concentration in these rats. This was found to be mediated, at least in part, by secretin-releasing peptides (S-RP) (Fig. 3). This S-RP appears to be secreted by the proximal intestinal mucosa and by the pancreatic glandular cells (Li et al., 2000), and then delivered into the duodenal lumen to stimulate the S-cells to release secretin. Partially purified S-RP infused into the duodenum of anesthesized rats increased pancreatic fluid and HCO_3^- secretion and raised the plasma secretin level. These secretory effects were blocked by vagotomy, atropine, and capsaicin, suggesting a neural control of S-RP release by the intestinal mucosa (Konturek et al., 1971; Li et al., 1995). The S-RP isolated from canine pancreatic juice (Song et al., 1999; Li et al., 2000) has some homology with pancreatic phospholipase; therefore, it is likely that phospholipase A_2 can have a specific receptor-mediated action on secretin-releasing cells, which may represent an alternative function of the enzyme in intestinal endocrine S-cells (Song et al., 1999). Pancreatic phospholipase A_2 activity was also detected in extracts of intestinal mucosa, and intravenous administration of antiphospholipase A_2 serum inhibited the release of secretin, the stimulation of pancreatic HCO_3^-, and also the water flow in response to duodenal acidification (Chang et al., 1999; Li et al., 2001a). These results demonstrated that: (1) S-RP is similar in structure to phospholipase A_2 and (2) S-RP originating from the pancreatic juice or intestinal mucosa is released into the gut lumen to stimulate the S-cells releasing secretin. Whether luminal duodenal acid stimulates pancreatic secretion entirely via secretin released by phospholipase A_2, or predominantly by its direct action on S-cells remains to be determined. It may be of interest that enkephalin, which had been reported (Konturek et al., 1978) to inhibit pancreatic secretion, was recently found to inhibit the release of S-RP and secretin (Li et al., 2001b). The complexity of secretin release is further increased by the implication of somatostatin, which is known to inhibit pancreatic secretion (Konturek et al., 1976), in the release of enkephalin, which in turn acts on the exocrine pancreas by suppressing the S-RP (Sarr et al., 1996). Thus, an old idea of Bayliss and Starling (1902), that secretin is released by duodenal acid and acts via purely endocrine pathways, is no longer tenable, and S-RP, which is under neural control and released by the

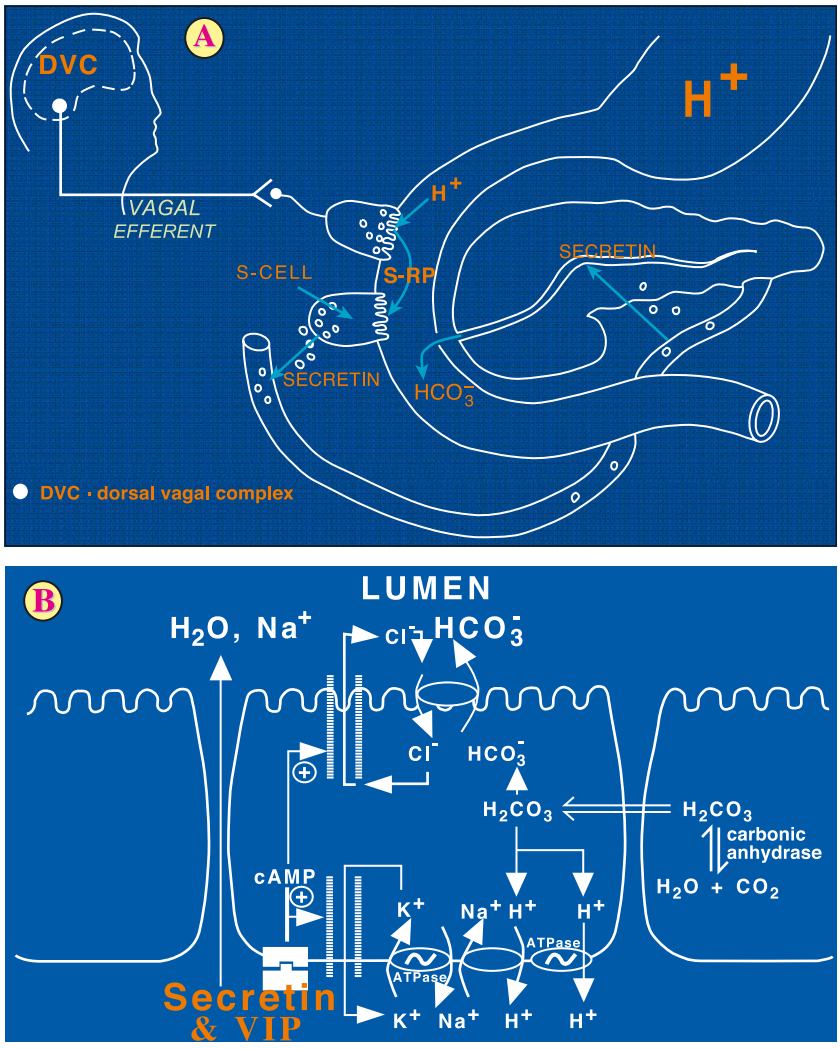

Fig. 3. The release of secretin from S-cells in duodenal or jejunal mucosa is mediated, in part, by S-RP involving vagal efferents (A). Secretion of HCO_3^- by ductal cells of the pancreas involves its active transport of HCO_3^- in exchange for Cl^-, on the luminal membrane and proton (H^+) pump and H^+/Na^+ exchanger on basolateral membranes of these cells (B).

intestinal mucosa and the pancreas into the intestinal lumen, appears to account for the complexity of the neurohormonal mechanism controlling pancreatic HCO_3^- secretion and volume flow.

3. Regulation of pancreatic enzyme secretion

Pancreatic enzymes are synthesized, packaged, stored, and released from acinar cells by the process of exocytosis, which involves multiple subcellular organelles. Most of the packaging of newly synthesized enzymatic protein occurs in the Golgi stack. A membrane-bound G-protein facilitates the transfer of enzymatic proteins from endoplasmic vesicles into the cisterns. Secretory granules in the cytoplasm can migrate to the apical cell membrane to be released into the lumen of the *acinus* (Case, 1998; Williams, 2002).

3.1. Receptors and intracellular mediators of enzyme secretion

Hormones such as CCK, neuropeptides, including GRP and VIP, and neurotransmitters, especially acetylcholine released by preganglionic and postganglionic enteric neurons, act via activation of specific receptors to induce the fusion of zymogen granules with the apical plasma membrane of acinar cells, resulting in the release by exocytosis of digestive enzymes into the *acinus* lumen. The process of binding of secretagogues to membrane receptors, ultimately leading to enzyme exocytosis, involves the receptor-mediated generation of intracellular messengers, intracellular mediators, and exocytosis (Williams, 2002).

Receptors for pancreatic secretagogues are believed to belong to the receptor family characterized structurally by seven hydrophobic transmembrane domains and functionally by their interaction with G-proteins (Ji et al., 2001;

Williams, 2002). The CCK_1, the muscarinic M_3, and the GRP receptors interact with the heterotrimetric G-protein complex, leading to the stimulation of phosphoinositide-specific phospholipase Cβ activity (Ji et al., 2001). Phospholipase C activity leads to the hydrolysis of phosphatidylinositol-4,5-biphosphate and the formation of inositol-1,4,5-triphosphate and 1,2-diacylglycerol. This occurs within seconds in response to high secretagogue concentrations. Inositol-1,4,5-triphosphate then binds to intracellular receptors, forming channels activating the release of Ca^{2+} from intracellular stores. The 1,2-diacylglycerol produced by phosholipase C activates protein kinase C. The major intracellular messengers involved in the regulation of pancreatic secretion are inositol-1,4,5-triphosphate, Ca^{2+}, 1,2-diacylglycerol, and cAMP (Williams, 2001). The first three are predominant in the acinar cells and increase after the activation of phosphoinositide-specific phospholipase C by CCK or acetylcholine, while cAMP is the predominant messenger in centroacinar and ductal cells activated by secretin or VIP. The central role in stimulus–secretion coupling in acinar cells is played by Ca^{2+}, which originates both from intracellular stores and ECF passing through the active Ca^{2+} channels in the plasma membrane. Physiological concentrations of secretagogues induce only a transient and repetitive increase in Ca^{2+} named "Ca^{2+} oscillations" or "spikes." The increase in Ca^{2+} in acinar cells is combined with the rise of IP_3 traversing gap junctions from one acinar cell to another (Williams, 2002). Ca^{2+} then activates the kinases and phosphatases and this activation involves calmodulin as a Ca^{2+} receptor and a catalytic kinase or phosphatase domain. Ca^{2+} can also activate protein phosphatase 2B, which is identical to calcineurin (Compos-Toimil et al., 2000). Secretin and VIP bind with membrane receptors to increase intracellular cAMP, which in turn stimulates protein kinase A.

4. Interdigestive and postprandial secretion

Pancreatic enzyme secretion occurs continuously in the interdigestive (fasting) state when the upper gastrointestinal tract is cleared of food, as well as in the digestive state. As mentioned before, the interdigestive secretion in humans and in other species (*carnivores*) is cyclic and follows the pattern of the migrating myoelectric complex (Fig. 4). The underlying mechanism of this cycling is believed to involve cholinergic activation and is accompanied by the rise in plasma motilin, which triggers the migrating myoelectric

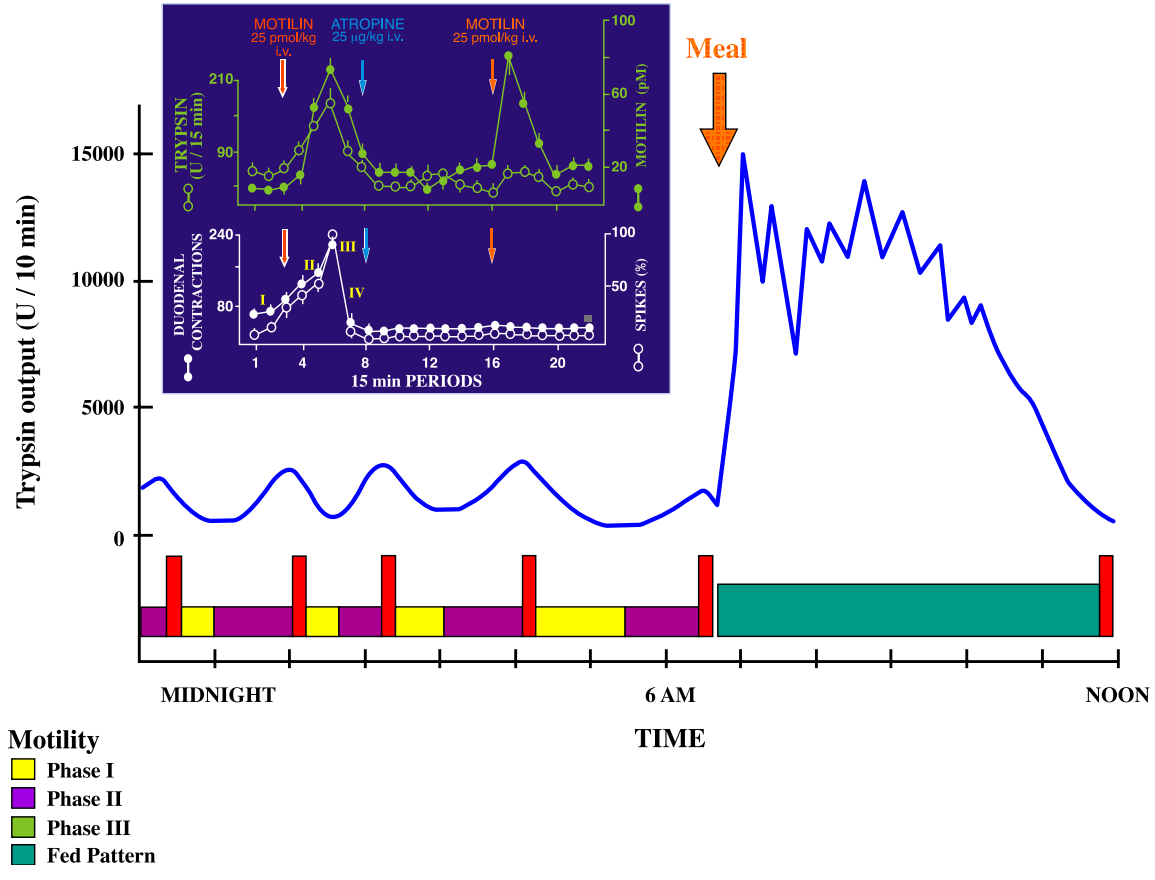

Fig. 4. Interdigestive pancreatic trypsin secretion as related to phases of MMC and postprandial enzyme secretion. Atropine infused intravenously inhibits the exocrine pancreatic secretion and the fluctuations in plasma motilin. Exogenous motilin may trigger MMC even after atropinization, but fails to stimulate exocrine pancreatic secretion in atropinized dogs (Konturek et al., 1986a,b).

complex cycle, and pancreatic polypeptide, which inhibits the motor and secretory components of this cycle. The fluctuations of interdigestive pancreatic secretion have been related to the "housekeeping" function of the migrating myoelectric complex (Konturek et al., 1986a), but in omnivores (e.g., pigs) and herbivores (e.g., cattle), the migrating myoelectric complex pattern is always present in the intestines, independent of the feeding state. Since these fluctuations of secretion also occur after feeding, it was suggested that migrating myoelectric complex is involved in nutrient digestion (Zabielski and Naruse, 1999). As cyclic basal pancreatic secretion can be seen continuously in these species, the migrating myoelectric complex pattern can be regarded as permanent and implicated in food digestion and absorption.

Dominguez-Munoz et al. (1995) studied the changes of basal pancreatic secretion (determined by a standard intubation technique) in the early phase of acute pancreatitis in humans and found that this interdigestive secretion maintained a normal cyclic pattern, suggesting that the mechanisms involved in this secretion operate normally in acute pancreatitis and that pharmacological inhibition provides a rational basis for early therapeutic inhibition of pancreatic secretion in humans with this pancreatitis.

Basal pancreatic enzyme secretion is relatively low as compared to the maximal response of the organ to exogenous CCK. The secretion starts almost immediately after the meal with three overlapping phases: cephalic, gastric, and intestinal phases, contributing, respectively, to about 20%, 10%, and 70% of the total postprandial response to a meal.

The postprandial phases, especially the cephalic phase, have been attributed mainly to vagal stimulation, with the efferent cholinergic nerves releasing acetylcholine in the pancreas and GRP-releasing neurons releasing gastrin from antral G-cells. It, in turn, stimulates acinar cells via CCK_2 receptors (Chariot et al., 1990). This cephalic phase can be induced by sham feeding in dogs (Konturek et al., 1990) or modified sham feeding in humans (Konturek and Konturek, 2000), as well as by insulin hypoglycemia or 2-deoxy-D-glucose glucocytopenia, which stimulates the bulbar vagal centers with subsequent cholinergic excitation of exocrine pancreas, and GRPergic release of gastrin, which contributes to the activation of pancreatic acinar cells (Fig. 5). Suppression of muscarinic receptors with atropine results in almost complete inhibition of gastric acid and in about 50% reduction in pancreatic protein output. A similar reduction in pancreatic protein secretion was achieved by selective blockade of CCK_1 receptors with L-364,718 or CCK_2 receptors using S-0505 (Aihara et al., 2003). This indicates that cephalic–vagal stimulation induced by physiological (sham feeding) and pharmacological (insulin or 2-deoxy-D-glucose) means acts on the exocrine pancreas in part via

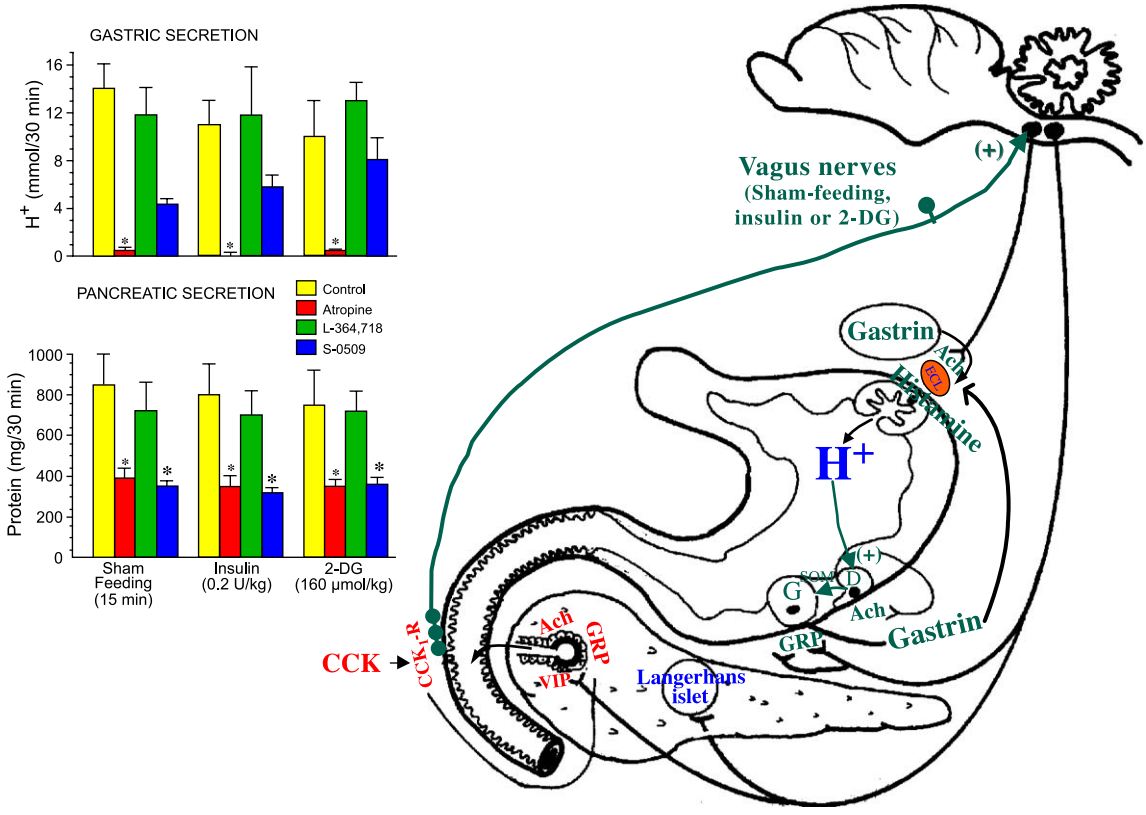

Fig. 5. Peak (30 min) gastric acid and pancreatic protein outputs induced by sham feeding, insulin hypoglycemia, or 2-deoxy-D-glucose from gastric and pancreatic fistula dogs without (control) and with administration of atropine (25 µg/kg), CCK_1 receptor antagonist L-364-718 (10 mg/kg), or CCK_2 receptor antagonist S-0509 (10 mg/kg). Asterisk indicates a significant ($P<0.05$) decrease as compared to vehicle control value (Konturek and Konturek, 2000).

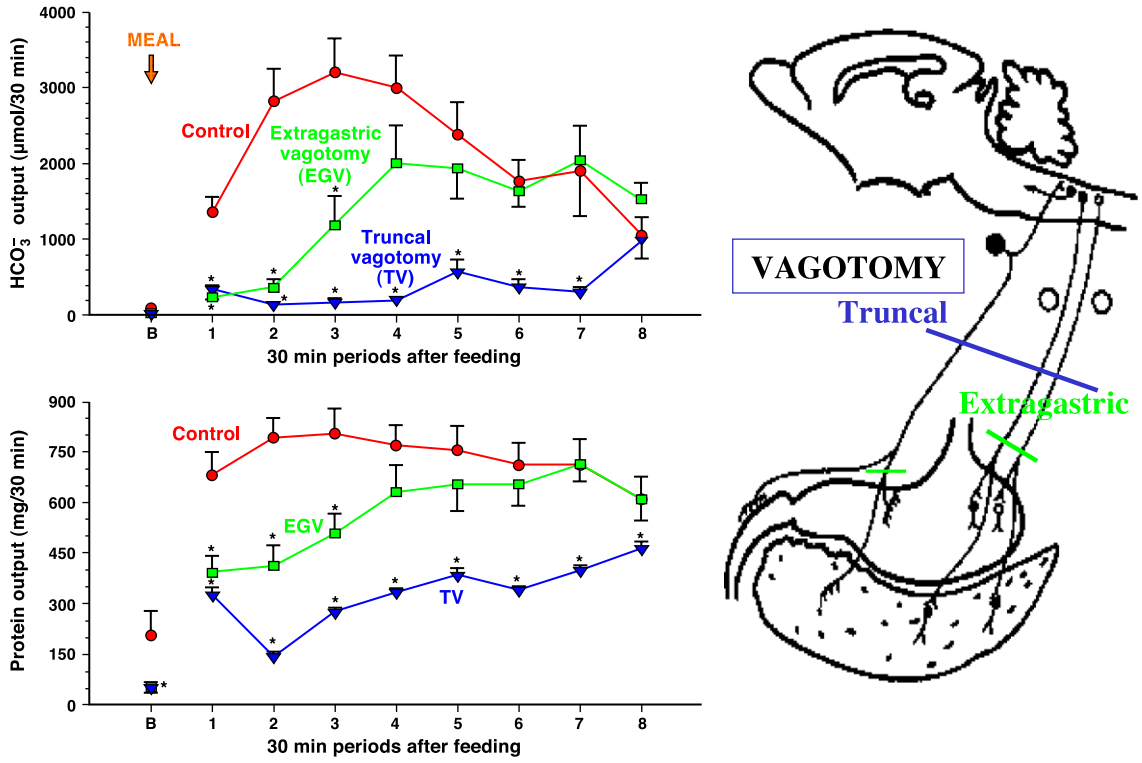

Fig. 6. Effect of extragastric and truncal vagotomy on pancreatic HCO_3 and protein outputs in dogs. Asterisks indicate significant decrease below the control value in dogs with intact vagal nerves (Debas et al., 1975).

release of acetylcholine and muscarinic receptors at the pancreatic secretory cells and by gastrin and CCK through CCK_1 and CCK_2 receptors, respectively. The crucial role of vagal nerves in the cephalic phase of pancreatic secretion is supported by results of our study showing that truncal vagotomy actually eliminated pancreatic HCO_3^- and protein secretion in response to sham feeding (Fig. 6) (Debas et al., 1975).

During the intestinal phase, the major role has been attributed to CCK and secretin, released from endocrine I

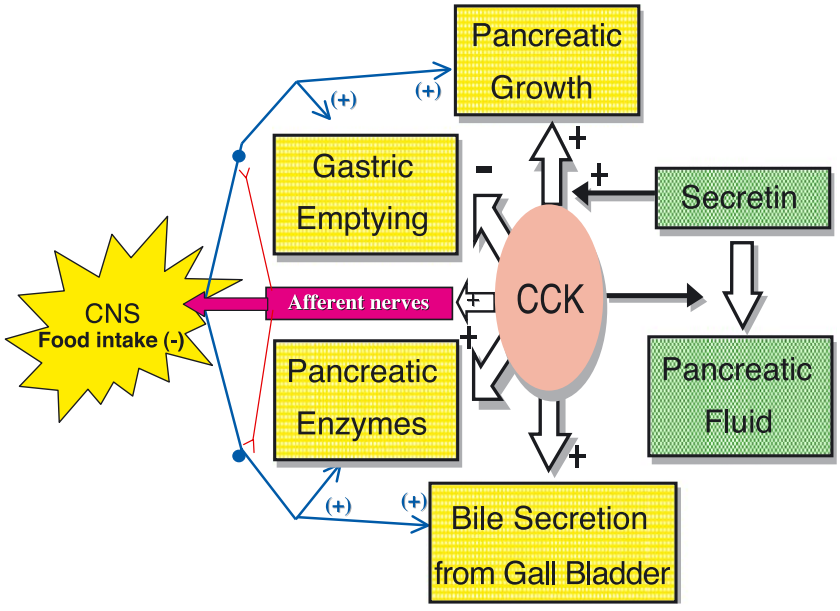

Fig. 7. Schematic presentation of the action of CCK through the receptors on afferent nerves and vagovagal or short enteropancreatic reflexes on pancreatic and biliary secretion, gastric emptying, pancreatic growth, and the interaction of this hormone with secretin on pancreatic volume flow.

and S-cells by protein and fat digestion products and by gastric acid entering the duodenum, respectively, but the relative contribution of these hormones and their potentiating interaction on postprandial pancreatic secretion has not been fully elucidated. There is little doubt that CCK plays a crucial role in the overall stimulation of pancreatic secretion as documented by the rise in plasma CCK level and the inhibitory effect of blockade of CCK_1 receptors on this secretion, but its major pathways of action appear not to be endocrine, as was proposed in the past, but neural, involving the sensory receptors at afferent nerves and long vagovagal reflexes or short enteropancreatic reflexes, as depicted in Fig. 1. CCK appears to affect, through the same neural pathway, not only pancreatic secretion, but also bile secretion and gall bladder contraction as well as gastric emptying and pancreatic regeneration (growth) (Fig. 7).

Studies on animals and humans with either the suppression of proteolytic activity from the intestine by soy bean trypsin inhibitors, or the diversion of pancreatic juice from the intestines showed an increased pancreatic secretion that is mediated by CCK (Green and Lyman, 1972; Li et al., 1989; Louie et al., 1986). The release of CCK appears to be regulated by at least three CCK-releasing factors: monitor peptide secreted by acinar cells (Fushiki et al., 1984), luminal cholecystokinin-releasing factor (LCRF), and diazepam-binding inhibitor produced by intestinal cells—enterocytes (Herzig et al., 1996; Spannagel et al., 1996). These releasing peptides are inactive in the interdigestive period because of their quick digestion by free luminal trypsin. These peptides appear to remain under neuronal (cholinergic) and neurocrine (somatostatin) control. After a meal, when trypsin is bound by food products, the releasing peptides escape from trypsin digestion, causing necessary release of CCK to compensate for the initial stimulus, leading to a well-regulated negative feedback mechanism and, therefore, to a correct maintenance of homeostasis.

5. Mechanisms of action of gut hormones on pancreatic secretion; brain–gut axis

The classic simplified picture of postprandial pancreatic secretion that gut hormones, such as CCK, act via endocrine pathways was changed with the discovery that efferent vagal nerves to the pancreas release not only acetylcholine but also other neurotransmitters, such as GRP and VIP. The proposed pathway of pancreatic stimulation in response to the main pancreatic secretagogues, such as CCK, is a vagovagal reflex stimulation. Studies of Owyang (1996) revealed that low physiological doses of CCK that occur after a meal act primarily on vagal afferent pathways and stimulate the exocrine pancreas via cholinergic vagal efferents (Fig. 8). Only large doses of CCK act directly on acinar cells or via local intrinsic neurons. Owyang (1996), using anesthesized rats, demonstrated that atropine and hexamethonium almost completely abolished the pancreatic protein response to low, but not high, supraphysiological doses of CCK. Similar effects were obtained using local capsaicin deactivation of afferent nerves or transection of afferent nerves. Thus, there is strong evidence for a neuronal, rather than an endocrine, action of CCK on pancreatic secretion (Fig. 9). The evidence for such neuronal, rather than endocrine, pathways for the action of CCK on the pancreas derives from earlier studies in animals, such as dogs, in which atropine was found to inhibit the pancreatic secretion induced by endogenous stimulants of CCK such as leucine or tryptophan (Konturek et al., 1972), but also by lower more physiological doses of CCK. Our more recent studies, in collaboration with Gabryelewicz et al. (1990), showed that pancreatic enzyme secretion induced by CCK + secretin was inhibited not only by loxiglumide, a specific CCK_1 receptor antagonist used for the first time in humans, but also by atropine, indicating that neuronal pathways do play a role in the action of CCK on pancreatic enzyme secretion

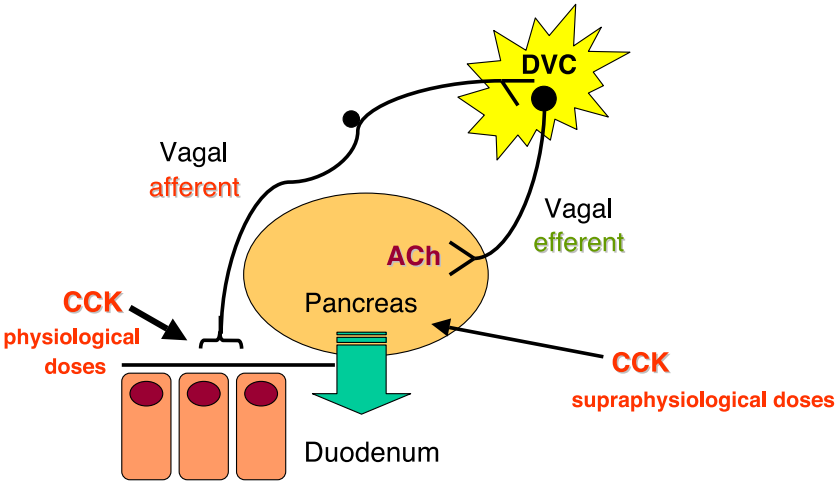

Fig. 8. Schematic presentation of the pancreatic secretion via activation of afferent nerves by physiological doses of CCK and by the action of CCK in larger doses directly on the pancreatic acinar cells (Owyang, 1996).

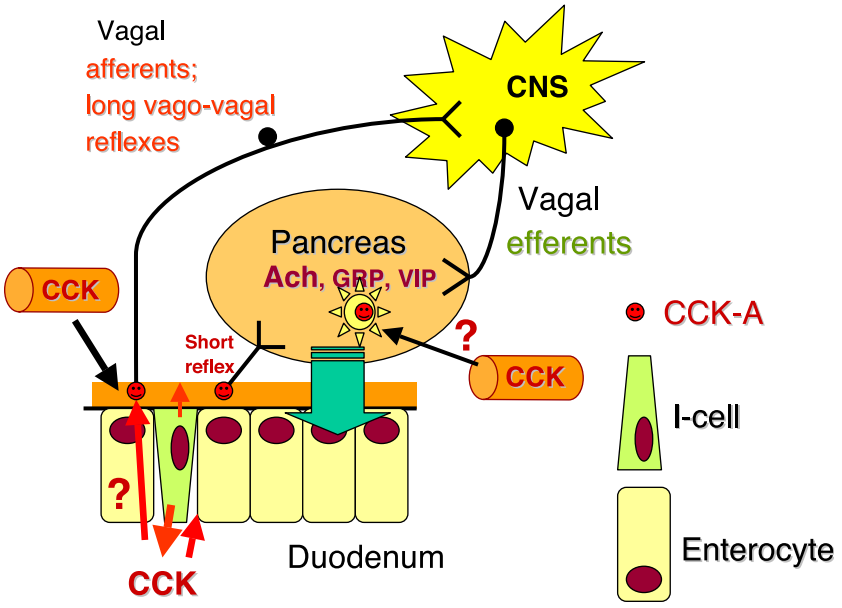

Fig. 9. Neural and possible endocrine pathways of action of CCK on pancreatic secretion with acetylcholine, GRP, and VIP as final stimulants of acinar cells. Possible direct stimulation of acinar cells by circulating CCK in high concentrations.

in humans. The neural reflex stimulation of the exocrine pancreas by CCK is supported by a finding of Blackshaw and Grundy (1990), who demonstrated in ferrets that close intraarterial injection of this hormone increases the electric discharge in single fibers originating from the gut segment where the hormone was applied. Richards et al. (1996) provided evidence that the administration of CCK_1 receptor antagonists reduced the enhanced discharge in vagal afferent fibers induced by CCK application. Zabielski et al. (1995) observed in conscious calves that intraluminal administration of CCK-8 resulted in some stimulation of exocrine pancreatic secretion and that the effects of both intraluminal and intravenous CCK-8 are atropine-sensitive. Since the CCK_1 receptors were detected by immunocytochemistry in the intestinal mucosa and the blockade of these receptors resulted in a decrease in the pancreatic response to intraduodenal CCK (Zabielski et al., 1998, 2002), it is reasonable to assume that luminally released hormone, or more accurately *lumone*, may also act through the reflex excitation of pancreatic secretion, at least in animals. The proposed picture of the mechanism of action of CCK is presented in Fig. 9.

Pancreatic polypeptide and somatostatin released by the F-cells and D-cells of pancreatic islets, respectively, and peptide YY released by the nutrients from the ileal mucosa are potent inhibitors of pancreatic secretion. Deng et al. (2001a,b,c) provided evidence that these hormonal peptides act on the area postrema to inhibit pancreatic secretion (Fig. 10).

Recently, the gastric mucosa was found to express and release two major hormones affecting appetitive behavior, namely ghrelin, which is considered as a hunger peptide, and leptin, which is also expressed in adipose tissues and stimulates the hypothalamic satiety center and inhibits food intake. Ghrelin negatively regulates leptin and, vice versa, leptin inhibits the release and action of ghrelin on food intake, so that this interaction has been described as "ghrelin–leptin tango" (Cummings and Foster, 2003). Both these hormones act on hypothalamic centers via endocrine pathways and by stimulating the receptors of sensory fibers in the gastric mucosa; moreover, both inhibit pancreatic secretion (Konturek and Konturek, 1995; Konturek et al., 2001, 2003; Zhang et al., 2001; Jaworek et al., 2002). According to Matyjek et al. (2003), circulating leptin may control pancreatic secretion in rats by the inhibition of a neurohormonal mechanism of this secretion involving CCK and vagal nerves. Ghrelin exerts an inhibitory action on the exocrine pancreas through the intrapancreatic neurons (Zhang et al., 2001).

Recently, NO and CGRP have been suggested to play a role in the control of pancreatic secretion and pancreatitis (Konturek et al., 1997a). NO is produced in the epithelium, endothelium, and macrophages of the gastrointestinal tract and the pancreas from L-arginine by constitutive NO synthase (cNOS). The gastrointestinal tract is very active in NO release; therefore, attempts have been made to define the possible role of NO in exocrine pancreatic secretion. Using a cNOS inhibitor, L-nitroarginine derivative L-NNA, we found that such blockade of NOS resulted in a dose-dependent reduction in CCK + secretin-stimulated pancreatic secretion in dogs, which was accompanied by a reduction in insulin and polypeptide secretion—effects that were reversed by the addition of L-arginine (Konturek et al., 1993; Bilski et al., 1995). These results indicate that NO alters exocrine pancreatic secretion and that this alteration is mediated by changes in pancreatic blood flow (Fig. 13). It

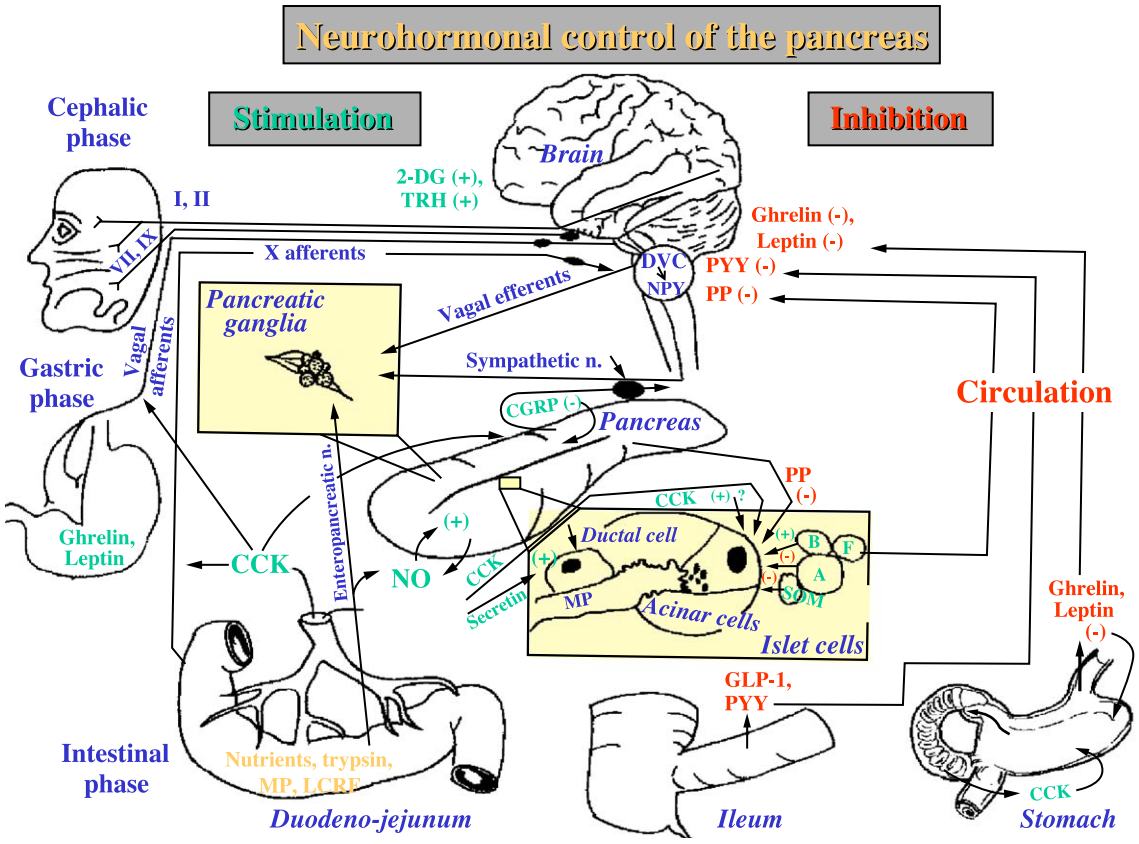

Fig. 10. Neurohormonal stimulatory and inhibitory mechanisms of pancreatic secretion during cephalic, gastric, and intestinal phases involving long vagovagal and short enteropancreatic reflexes activated by CCK acting on sensory receptors on afferent nerves. Various hormonal and humoral substances stimulate or inhibit the pancreatic secretion acting either through the CNS or directly on the exocrine pancreas.

should be mentioned that L-nitro-arginine (L-NMMA) was also highly effective in inhibiting pancreatic enzyme secretion in humans; these effects are reversed by the addition of L-arginine to L-NMMA (Konturek et al., 1997a).

We have evidence that in rats, endogenous NO may be released from afferent nerves by stimulation with low doses of capsaicin and that such stimulation attenuates the development of pancreatitis induced by caerulein (Jaworek et al., 1997). This is supported by the fact that low doses of capsaicin that stimulate the release of CGRP and NO or exogenous CGRP can prevent damage to pancreatic acini provoked by caerulein overstimulation.

6. Conclusions

In summary, the mechanism of pancreatic secretion under basal conditions and following a physiological stimulus, such as a meal, is very complex. The major role in the stimulation of enzyme-rich pancreatic secretion is played by vagal nerves, the enteric nervous system, and enteric nerve-released neuropeptides such as gastrin-releasing peptide, vasoactive intestinal peptides, and neurotransmitters, especially acetylcholine, CCK, and nitric oxide, and other neuropeptides. These substances are involved as modulators of pancreatic secretion, partly by excitation of sensory receptors of sensory nerves, giving rise to short enteropancreatic and long vagovagal reflexes affecting pancreatic secretion and blood flow. Under physiological conditions, sensory afferent pathways rather than pancreatic acinar cells themselves are the primary targets, where gut peptides such as CCK affect the postprandial pancreatic secretion as well as bile secretion, gastric emptying, and pancreatic growth. Peptides of the pancreatic polypeptide family such as peptide YY and neuropeptide Y, and partly somatostatin, inhibit pancreatic secretion by suppressing the activity of vagal centers in the brainstem. This supports an old Pavlovian concept of *nervism* that the neural system is the major regulator of pancreatic enzyme secretion. Pancreatic bicarbonate secretion appears to be dependent on the pH of duodenal contents and duodenal acid loads, and the mediator of this secretion is mainly secretin acting in an endocrine way on centroacinar or ductal cells of the pancreas, but it appears that secretin release peptide is released by enterocytes under cholinergic control. A feedback system involving the release from the pancreas and the gut peptides inhibiting the release of CCK from I cells and secretin from S-cells has been postulated to regulate pancreatic enzyme and bicarbonate secretion, but its physiological role in the overall regulation of the exocrine pancreas has not been fully elucidated.

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