Gut regulatory peptides are produced by mucosal endocrine cells and released both into the circulation as well as into the gut lumen. Following stimulation the distribution between the circulation and gut lumen changes in favor of the gut lumen. In the blood plasma, the biological half-life of gut regulatory peptides is counted in single minutes due to high aminopeptidase activity and liver extraction. In the gut lumen, however, regulatory peptides retain their biological activity much longer, especially in newborn and young animals. A series of studies was performed in neonatal calves and pigs to explore the role of luminal cholecystokinin (CCK) on the regulation of exocrine pancreatic secretion. In anaesthetized neonatal calves, CCK was secreted into the duodenal lumen, and electrical vagal stimulation increased CCK release into the duodenal lumen but not into the circulating blood. In conscious calves, luminal CCK-8 stimulated pancreatic protein secretion by a neurohormonal mechanism dependent on a duodenal mucosal CCK receptor and vagal nerve activity. Immunocytochemistry pointed to an association of mucosal CCK, receptor and vagal nerve components in the small intestine of neonatal calves. Experiments in calves and pigs with CCK-8 infusions into the duodenal branches of the right gastroepiploic artery confirmed the results of luminal CCK-8 and questioned the physiological relevance of a direct mechanism of CCK on the pancreatic acini.

Key words: cholecystokinin, vagal nerve, pancreatic juice, neurohormonal control
INTRODUCTION

Gut regulatory peptides in the lumen of the gastrointestinal tract

The first suggestions that gut regulatory peptides can be secreted into the lumen of the gastrointestinal (GI) tract probably came from studies performed over 60 years ago by Brunschwig and co-workers (1, 2) who showed that human gastric juice contains a polypeptide substance that could inhibit the secretion of gastric acid. It now appears quite likely that somatostatin was that substance. Gastrin was the first regulatory peptide to be detected in the stomach lumen of humans (3), and since then many regulatory peptides, including somatostatin, secretin, cholecystokinin (CCK), substance P, polypeptide YY (PYY) (4-8) have been found in the lumens of the stomach and small intestine of humans and experimental animals. In the stomach, chef cells release leptin (9, 10) and A-like cells in the oxyntic mucosa, ghrelin (11, 12); in the lower part of the intestine (jejunum, ileum and colon) epithelial enterochromaffin cells release guanylin (13). Interestingly, the peptides detected in the GI lumen retain their biological activity. Furthermore, authors consistently emphasize that the concentration of regulatory peptides in the GI lumen or the calculated output into the lumen is greater than the analogous venous concentration or output, both under control conditions and after stimulation. The regulatory peptides in the gut lumen originate from the mucosal epithelial cells, but not exclusively, since substantial amounts of regulatory peptides are synthesized in the auxiliary glands of the GI tract, and arrive in the GI lumen with saliva, e.g. leptin (14), and with pancreatic juice, e.g., insulin and somatostatin (15). In neonatal and suckling mammals, colostrum and milk are another important source of gut regulatory peptides (16-18). In vitro studies revealed that despite disadvantageous conditions in the stomach and gut lumen (acidic pH values and/or abundance of proteolytic enzymes), regulatory peptides are remarkably stable in gastrointestinal fluids (19, 20). Worth emphasizing is that their survival is much better in digestive juices collected from neonates than from adults. In part this is probably due to some protein fractions of the colostrum and milk, like acid-soluble casein fractions. Thus the degradation rate of gastrin incubated for 20 min in the intestinal juice collected from newborn pigs is below 15%, while in weaned and adult pigs, between 40 and 50% (20). These results suggest that the biological half-life of regulatory peptides in the intestinal lumen may be much longer than in the blood plasma.

In 1981 Konturek and co-workers (21) were first to demonstrate the effect of luminal gut regulatory peptides on the secretion of pancreatic juice. In conscious fistulated dogs, they showed that intraduodenal administration of somatostatin reduces pancreatic juice secretion in a dose-related manner. The implication coming from their study stimulated research on local, duodenally-mediated mechanisms that control the secretion of pancreatic juice. This paper briefly
reviews the luminocrine action of CCK on the regulation of exocrine pancreas function.

**CCK is present in the gut lumen**

The cells synthesizing CCK (I-cells) are located in the epithelial layer of the small intestinal mucosa (22), most abundantly in the duodenum and proximal jejunum (23, 24). The apical membrane of the CCK-producing cell contacts the luminal contents, and the basal membrane is commonly thought to be a major site of CCK release into the blood stream. From circulating blood, CCK may regulate the function of the gallbladder, exocrine and endocrine pancreas, and is possibly also involved in a satiety mechanism and in many other mechanisms. In conscious rats with bile and pancreatic fistulae, Miyasaka et al. (25) demonstrated that plasma CCK concentrations did not parallel intestinal CCK concentrations following bile and/or pancreatic juice diversions. In addition, intravenous infusion of a pharmacological dose of CCK-8 did not increase the CCK concentration in the intestinal mucosa. The luminal content was not searched for CCK in their study. However, CCK-like immunoactivity has been detected in the lumen of the small intestine, both under control conditions and following stimulation by feeding and perfusion of the duodenum with nutrients (26). More recently, Sun et al. (27) showed that CCK is present in the lumen of the canine duodenum in multiple molecular forms including CCK-8, CCK-33, CCK-39, and CCK-58 as the predominant one. Interestingly, this was not negligible "leakage", but quite the reverse, considerable amounts of CCK were found in the lumen in comparison with the amount released into the blood stream; moreover, lumen CCK retained full biological activity. In anaesthetized calves with a perfused duodenal loop, the CCK pool in the duodenal lumen was independent from that in the circulating blood, since electrical vagal stimulation affected the release of CCK into the duodenal lumen but not into the portal or peripheral blood (28). On the other hand, in that study, iv CCK boluses did not change the release of CCK into the duodenal lumen. In the calf model, the bile duct was ligated, thus preventing any interference from CCK sequestered by the liver and otherwise secreted into the bile (29).

There is no available study on the visualization of CCK release into the gut lumen, however, Okumiya et al. (8) demonstrated the release of gastrin from intestinal gastrin-producing cells using immunoelectron microscopy (Fig.1). They observed changes of subcellular localization of gastrin granules (massive migration from basal to apical region) as well as gastrin release into the small intestinal lumen in an apocrine-like manner induced by carbachol. Without carbachol stimulation, gastrin granules were localized mostly in the basal region of the cell and released through the basal cell membrane. Using a similar approach, Fujimiya et al. (30, 31) and Okumiya and Fujimiya (32) have shown that enterochromaffin cells actively release the regulatory amine, serotonin, as
well as chromogranin A (a protein co-stored with serotonin in enterochromaffin cells) into the lumen of the small intestine, and that the luminal release of serotonin was higher than that into the vasculature. Luminal release of serotonin could be reduced by tetrodotoxin, atropine and hexamethonium, suggesting involvement of neuronal pathways (33). It is worth mentioning that luminal serotonin was found to enhance the transepithelial permeability of the luminal regulatory peptides (34). These morphological data help to understand the route by which gastrointestinal regulatory peptides may appear in the intestinal lumen following stimulation. Gastrin-producing cells are morphologically similar to CCK-producing cells in the small intestine, and according to Tsumuraya et al. (35), there may be a few common CCK/gastrin producing cells in the duodenal mucosa, thus we can assume that a similar secretory pattern appears in CCK-producing cells as well.

The mechanism of absorption of luminally released CCK is not known, though an enterocyte transcellular pathway seems more probable than an paracellular one. Glatzle et al. (36) recently have shown that chylomicron lipid components release endogenous CCK, which activates CCK₁ receptors on vagal afferent nerve fibre terminals, which in turn initiate a vago-vagal reflex inhibition of gastric motility in rats. It seems probable that luminal CCK would permeate through the enterocyte lineage from the gut lumen into the interstitial fluid together with triglycerides, lipoproteins and other lymph constituents. However, Glatzle et al. (36) have questioned this solution by showing the presence of CCK in the upper part of the mesenteric lymph duct at a concentration of around 9 pM, which they considered to be below the threshold for activation of the vagal

Fig. 1. Changes in subcellular localisation of gastrin granules and gastrin release without stimulation and following stimulation with carbachol. Schematic illustration refers to the immunoelectron study by Okumiya et al. (8).
afferents. On the other hand, they did not examine the CCK concentration in the interstitial fluid just behind the epithelial cell layer nor CCK hydrolysis in the mucosa and lymph. The mechanism of luminal CCK absorption needs further elucidation.

One can ask about the physiological role of CCK in the duodenal lumen: Is it only waste or does it play a role in the GI tract? Sun et al. (27) speculated that a part of the luminal CCK, which would survive degradation by proteolytic enzymes, may regulate the function of intestinal mucosal cells or intestinal motility, according to earlier observations by Sninsky et al. (5). Accordingly, a few years later studies with pharmacological blockade of the intestinal mucosal CCK₁ receptor have demonstrated that luminal CCK may regulate duodenal myoelectric activity (37), control crypt cell proliferation, and enhance the maturation of intestinal epithelium in neonatal calves (38). Pharmacological block of mucosal CCK₁ receptors with FK480 was also effective beyond the gut-the size of the pancreatic acinar cells and the cell number per acinus were significantly reduced in neonatal calves (38).

**CCK affects the activity of vagal mucosal afferent nerves**

Low concentrations of CCK-8 have been reported by Cottrell and Iggo to excite vagal afferent receptors located in the mucosa of the proximal duodenum in sheep (39). Blackshaw and Grundy (40) have demonstrated in ferrets that close intraarterial injection of CCK-8 increases the electric discharge in single fibers originating from the gut segment where the hormone was applied. The CCK-responsive fibers were identified as the tension receptor afferents related to contractile activity as well as the mucosal receptor afferents with a conduction velocity in the C-fibre range. The mucosal receptor afferents were localized in the corpus and antrum but mostly in the duodenum, and could respond to as low doses of CCK-8 as 3 pmol, but not to intraduodenal glucose and tryptophan or to distension. The responses of mucosal receptor afferents were enhanced by a mucolytic agent, acetylcysteine, which shortened the latency and increased the amplitude of responses, which were not affected, however, by cholinergic blockade with atropine and hexamethonium. Blackshaw and Grundy (40) concluded their study by suggesting that although activation of mucosal fibres from the gut by luminal stimuli has weak effects on vagal effferent fibre discharge, the reflexogenic potency may be enhanced if a large number of mucosal afferents would be stimulated simultaneously. Richards and co-workers (41) provided further evidence in anaesthetized rats by showing that mesenteric nerve bundles contained one to two afferent fibres responding to CCK-8 in a dose-related manner (threshold dose <5 pmol), and the administration of CCK₁-receptor antagonist (devazepide) abolished an enhanced discharge in vagal afferent fibers induced by CCK-8 application. The CCK-sensitive subpopulations of mesenteric afferent nerves slowly adapted to luminal hydrochloric acid and were not
sensitive to intestinal distension. Luminal application of lignocaine transiently abolished the response to CCK, which further confirms the localization of receptor afferents within the intestinal mucosa. Abdominal vagotomy eliminated the responses to CCK suggesting that the CCK-sensitive mucosal afferents exclusively follow the vagal pathway to the central nervous system to trigger various reflexes controlling behavioral and gastrointestinal effects involving inhibition of gastric motility and stimulation of pancreatic secretion (41). Consistently, studies in rats have indicated that intraduodenal sodium oleate, a major stimulator of pancreatic secretion, evoked the firing in the mucosal afferent fibres that could be abolished by the CCK$_1$ receptor antagonist, devazepide (42).

The existence of CCK receptors in the gut mucosa suggested by electrophysiology recordings have been further supported by autoradiographic studies in rats by Lin and Miller (43). Their competition studies using selective CCK ligands revealed that the vagal CCK receptors are heterogenous. Accordingly, Miyasaka et al. (44) have found expression of the CCK$_1$ and CCK$_2$ receptors m-RNA in the duodenal mucosa of the rat using RT-PCR technique. Recently, an association of mucosal CCK$_1$ and CCK$_2$ receptors with neural components of the small intestine has been indicated in calves and rats using immunocytochemistry (45). The CCK receptors were localized in the intestinal villi within the lamina propria, however, little immunoreactivity could be observed close to the basal part of the enterocytes. In order to visualize the vagal sensory innervation of the gut, Berthoud et al. (46) labeled the vagal afferents in vivo using injection of the lipophilic carbocyanine dye Dil into the nodose ganglion of rats. The Dil-labeled vagal afferent fibers were found with terminal arborizations mainly between the crypts and in the villous lamina propria. In both areas, vagal terminal branches came in close contact with the basal lamina, but did not appear to penetrate it so as to make direct contact with epithelial cells or to penetrate between the epithelial cells into the lumen. The overall density of vagal afferent mucosal innervation was variable in their preparations. Many villi showed no evidence for such innervation while other areas had quite dense networks of arborizing terminal fibers in several neighboring villi. Using a similar approach, Berthoud and Patterson (47) examined the anatomical relationship between vagal afferents and I-cells in the rat small intestine. They demonstrated that the CCK immunoreactive cells were more abundant than vagal afferent fibers, and the both were present throughout the small intestine in the crypt and villi region. Most of the labeled vagal afferent axons distributed within the crypt and villous lamina propria were at distances of tens to hundreds of microns to the nearest CCK immunoreactive cell. Only a few of the CCK immunoreactive cells were in close (< 5 microns) anatomical contact with vagal afferent axons which, bearing in mind the fast migration of epithelial cells along the villi, should be considered accidental. It seems that the migration of epithelial cells does not allow the existence of direct communication between the I-cell and nerve terminals that might facilitate the signals driven by CCK. These anatomical
studies suggest that CCK released from the I-cells may acts on vagal sensory fibers in a paracrine fashion as well as helps to understand the sense of the luminal release of CCK: since only some of the villi contain the sensory fibres for CCK, the release of CCK into the gut lumen might be a safe way (little biodegradation in the lumen) to spread the stimulus over a larger receptive area. Accordingly, the process of luminal CCK absorption by enterocytes may be an important link between the food and CCK-vagal mechanisms controlling gastrointestinal function.

*Mucosal and luminal CCK control the secretion of pancreatic juice through vagal afferent pathways*

According to classical hormone theory, exogenous CCK evokes dose-dependent stimulation of pancreatic enzyme secretion. However, effective doses increase the concentration of CCK in the circulating blood to a level that can not be achieved by any stimulation of endogenous release of CCK. Thus these effects have to be considered pharmacological. On the other hand, low doses of exogenous CCK (keeping the increase in the circulating blood within the physiological range) hardly affect pancreatic secretion and can not convincingly explain its role in the regulation of pancreatic secretion. Moreover, stimulation with a low dose of CCK can be abolished by atropine or cold blockade of the vagal nerves, suggesting involvement of neural pathways. Magee and Naruse (48, 49) explained this by an interplay between the nervous and hormonal regulation.

*Fig. 2.* Arguments against cholecystokinin (CCK) acting as a hormone to control the exocrine pancreas. CCK, which is secreted by the I cells in the small intestine epithelium and then released into the blood, is to a great extent eliminated before it can reach the pancreas due to liver extraction, inactivation by plasma aminopeptidases, and dilution in the circulating blood. (From Konturek et al. 2003)
systems at the level of intrapancreatic nerves and ganglions. However, studies comparing the secretory responses to CCK-8 administered into the general circulation or locally into a branch of the right gastroepiploic artery, which supplies the proximal duodenum (but not the pancreas), showed more pronounced responses following the intraarterial infusions in both conscious and anaesthetized animals (50-53). This led to the conclusion that the information driven by CCK must be switched into a neural mechanism before leaving the gut. Moreover, if we consider the classic hypothesis of hormonal action of CCK via the blood, we have to bear in mind first, that the blood plasma contains enzymes, endopeptidases and aminopeptidases, capable of deactivating CCK (54), and second, that the intestinal blood promptly transports these newly-released gut peptides to the liver, an important site of gut peptide deactivation (29). It seems unlikely, therefore, that a message precisely generated in response to food or other local stimuli in the upper gut would be arbitrarily modified in the first pass by the liver and blood plasma enzymes well before reaching the presumed target organ - the exocrine pancreas (Fig. 2).

That vagal nerves participate in controlling the exocrine pancreas has been known for more than a century and has been well documented (for references see recent reviews (55, 56)). A hypothesis on the common neurohormonal mechanism involving CCK and vagal nerves was drawn by Grossman (cited in (57)) based on measuring the latency of pancreatic enzyme response to intraduodenal stimulants versus intraportal CCK infusion in conscious dogs (58). The hypothesis was further strengthened by demonstrating in electrophysiology studies that CCK-sensitive vagal afferent fibers are located in the duodenal mucosa (39-41). The first experimental evidence that exogenous CCK can stimulate the secretion of pancreatic juice via indirect mechanism(s) located in the proximal duodenum and related to vagal nerve activity was shown in 1991 at the 23rd European Pancreatic Club Meeting in Lund (50, 51). These results were obtained in anaesthetized and conscious pigs and were soon confirmed in conscious calves (52) and anaesthetized rats (59, 60). In pig and calf experimental models, the intraarterial infusions of CCK-33 or CCK-8 into the right gastroepiploic artery supplied the regulatory peptides to a proximal duodenum and a small part of the pylorus close to the duodenal bulb, but not to the pancreas (52, 53). The intravenous infusions into the jugular vein distributed the CCK in the entire general circulation. In large animal studies, intravenous infusion was used as a control to close intraarterial application of CCK, whereas in rat studies, it was the only route of CCK administration. In anaesthetized pigs, the model was refined by implanting catheters in the gastric and right gastro-epiploic arteries, thereby the infusions of CCK-33 could be made exclusively to the duodenum/stomach, duodenum/pancreas or general circulation, respectively (61). In calves, intraarterial infusion of CCK-8 (10 and 100 pmol/kg b. wt.) induced secretion of pancreatic juice rich in enzymes, without affecting the concentration of CCK in the peripheral blood plasma (52). The intraarterial stimulation was
greater and had a shorter lag time than the respective intravenous stimulation. Cold blockade of vagal nerve conductivity in conscious calves diminished the effect of intraarterial CCK-8, and delayed and decreased the pancreatic response to intravenous CCK-8, suggesting that vagal reflexes are particularly important in the local duodenal mechanism (52). In piglets, the intraarterial infusion of a physiological-like dose of CCK-8 (15 pmol/kg b. wt.) stimulated pancreatic secretion whilst intravenous infusion was ineffective (53). Participation of mucosal CCK₁ receptors has been indicated following studies with intraduodenal application of a poorly absorbable CCK₁ receptor antagonist from the benzodiazepine family, tarazepide (Solvay Pharmaceuticals), in conscious calves (37). In the rat model, Li and Owyang (59, 60) showed that exogenous CCK-8 infused intravenously at large doses may stimulate pancreas protein secretion directly, while low concentrations may stimulate it via vagal afferent (capsaicin-sensitive) pathways. CCK receptors, predominantly of the CCK₁ type, located on the peripheral vagal afferent fibres, were suggested to be a target site for this mechanism. Gastroduodenal but not jejunal administration of capsaicin abolished the response to low doses of CCK (59), confirming that the mechanism might originate in the gastroduodenal area. Thus, currently there is strong evidence for neuronal rather than endocrine action of CCK on pancreatic secretion (55, 62, 63). The evidence for such neuronal action of cholecystokinin on the pancreas also derives from earlier studies in dogs in which atropine was found to inhibit the pancreatic secretion induced by endogenous stimulants of CCK such as leucine or tryptophan (23), but also by lower, more physiological doses of CCK.

Zabielski et al. (64) found in conscious suckling calves that luminal administration of CCK-8 resulted in the stimulation of pancreatic juice flow, bicarbonate and protein output in a dose-related manner. The protein secretory increments for equimolar intravenous infusions were, however, greater than for intraduodenal infusions. The effect of luminal CCK-8 was delayed by several minutes in comparison with intravenous CCK-8, which may be related to the time

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**Fig. 3.** Protein output increment (mg/kg) in response to intravenous (100 pmol/kg b. wt.) and intraduodenal (300 pmol/kg b. wt.) 5 min infusions of CCK-8 in conscious calves with and without atropine (A) and/or CCK₁ receptor antagonist, tarazepide (TA) pretreatment. Asterisks indicate statistical difference from the respective control infusion (* P < 0.05, ** P < 0.01). Adapted from ref. 37.
needed for CCK-8 to permeate to the mucosal receptors, but in contrast to the later it was atropine-sensitive, indicating involvement of a cholinergic mechanism. Application of tarazepide helped to clarify the mucosal CCK-related mechanism. It was shown that an intraduodenal bolus administration of tarazepide led to immediate reduction of pancreatic secretion well before any tarazepide was detected in the portal or peripheral blood. The reduction of pancreatic secretion was observed for several hours (37). Pharmacological block of mucosal CCK, receptors with tarazepide alone as well as in combination with atropine, totally abolished the pancreatic response to intraduodenal CCK-8. Tarazepide also reduced the response to iv CCK-8, suggesting that a part of the response to intravenous infusion was also dependent on the mucosal mechanism (Fig. 3). Plasma CCK was not affected by intraduodenal CCK-8, though as expected it markedly increased following intravenous CCK-8. Interestingly, pancreatic responses in juice outflow and in protein output to intraduodenal and intravenous CCK-8 were not parallel (i.e., volume increments for the applied doses were comparable between intravenous and intraduodenal infusions, whereas the response in protein output to intraduodenal CCK was much smaller

\[ \text{CCK} \]

\[ \text{Pancreas} \]

\[ \text{Ach, GRP, VIP} \]

\[ \text{Duodenum} \]

\[ \text{Vagal afferents} \]

\[ \text{Vagal efferents} \]

\[ \text{Physiological doses} \]

\[ \text{Pharmacological doses} \]

\[ \text{CCK} \]

\[ \text{CCK}_1 \]

\[ \text{I-cell Enterocyte} \]

\[ \text{CNS} \]

\[ \text{Short reflex} \]

\[ \text{Physiological doses} \]

\[ \text{Pharmacological doses} \]

\[ \text{CCK} \]

\[ \text{Duodenum} \]

\[ \text{Vagal afferents} \]

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\[ \text{Physiological doses} \]

\[ \text{Pharmacological doses} \]

\[ \text{CCK} \]

\[ \text{CCK}_1 \]

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\[ \text{CNS} \]

\[ \text{Short reflex} \]

\[ \text{Physiological doses} \]

\[ \text{Pharmacological doses} \]

\[ \text{CCK} \]

\[ \text{Duodenum} \]
than that to intravenous infusions). This may suggest the involvement of two distinct local mechanisms for CCK-8; luminal, stimulating more pancreatic fluid, and extraluminal, affecting rather the pancreatic enzymes, but both of these mechanisms depend on neural pathways. The neurohormonal mechanisms related to duodenal and mucosal CCK and vagal nerves that control the secretion of pancreatic juice are proposed in Fig. 4.

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