The Role of the Gut in Controlling Nutrient Intake

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Near the end of the nineteenth century, Pavlov suggested that digestive secretions including exocrine pancreatic secretion were exclusively controlled by neural reflex mechanisms (1). In 1902, only a few years later, Bayliss and Starling published their centennial paper on secretin, opening the field of gastrointestinal endocrinology while arguing that neural regulation of the pancreas was "superfluous and improbable" (2). In the following decades, especially after the discoveries of gastrin and cholecystokinin (CCK), it was generally accepted that digestive processes (gastric acid secretion, exocrine pancreatic secretion, biliary secretion, and gallbladder contraction) were mainly regulated by hormones. Looking back it seems to be strange that investigators have tended for decades to adopt an "all-or-nothing" approach to explain the regulation of the various digestive functions. Current appreciation of the complexity of mechanisms governing most biologic phenomena leads us to accept that digestive processes are regulated through an interplay of multiple neural and hormonal pathways (Fig. 1).

INTEGRATED DIGESTIVE PROCESSES TO MEALS

The major function of the different digestive processes is to participate in a coordinated way in an efficient digestion of macronutrients to optimize their absorption. The stomach acts primarily as a reservoir for food components eaten during a meal, but also as a principal organ in the initial stages of mixing and digestion of macronutrients. The role of gastric acid in digestive processes is probably not of major importance in healthy subjects, but acid and pepsin prepare the macronutrients for further breakdown.

Gastric Acid Secretion

Stimulatory and inhibitory pathways both at rest and during meal ingestion control acid secretion; the postprandial response is usually divided into three distinct phases: cephalic, gastric, and intestinal phases of secretion (3–5).
The cephalic phase of acid secretion is activated by thought, taste, smell, sight, and swallowing of food (3). Acid responses to cephalic stimulation amount to 50% to 60% of maximal secretagogue-stimulated acid responses in humans (3,6,7). Cephalic phase stimulation of gastrointestinal secretions (acid secretion, exocrine pancreatic secretion) occurs by central stimulation of the vagus nerve and is under cholinergic and peptidergic control (8). The hormone gastrin plays, however, a physiologic role in the cephalic phase secretion; the intravenous infusion of a selective gastrin receptor antagonist dramatically reduced the cephalic acid response in healthy subjects, suggesting that the peptide is integrated in the neural control circuit (9). The principal mediator of the gastric phase of acid secretion is gastrin. Gastric distension and, more important, chemical constituents of food provide the strongest stimulation of gastrin release during the gastric phase of secretion (4,5,10). The intestinal phase of acid secretion is predominantly inhibitory. Fat, acid, and hyperosmolar solutions within the intestinal lumen induce inhibition of acid response.

**Exocrine Pancreatic Secretion**

The major function of exocrine pancreatic secretion is to participate in efficient digestion of macronutrients. Pancreatic digestive enzymes have an obvious role in this process, but pancreatic bicarbonate secretion is thought to be crucial for creating a functional intraluminal milieu for the action of enzymes. As for acid secretion, it
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is useful to conceptualize postprandial pancreatic secretion as being the net result of three phases—cephalic, gastric, and intestinal (8,11). The phases overlap due to aboral progression of food through the digestive system and they interact with one another.

The cephalic phase of pancreatic secretion is initiated by the sight and smell of appetizing food. The magnitude of the secretory response ranges from 25% to 50% of maximal postprandial pancreatic secretory response (11). In humans, the pancreatic responses to cephalic stimulation are brief and disappear after cessation (11) of the stimulus. The cephalic phase of both gastric and pancreatic secretions is generally assumed to be primarily mediated by vagal cholinergic pathways. Recently the concept was expanded because a distinct cephalic phase was demonstrated that regulates gastropancreatic secretion and antroduodenal motility (11). The mechanisms involve cholinergic pathways, with partial mediation via peptide release (12–14). When cephalic stimulation is initiated during late interdigestive phase I and early phase II of duodenal motility, an immediate increase of gastric acid output and pancreatic enzyme secretion is noted. Pancreatic bicarbonate secretion is, however, not stimulated with a cephalic phase stimulus. Again, antroduodenal motility is enhanced in parallel with secretion. The cholinergic antagonist atropine abolishes the increase in acid output, in pancreatic enzyme secretion, and in antroduodenal motility in response to cephalic stimulation supporting the hypothesis that the cholinergic system is the major regulator of the cephalic phase of these digestive processes.

It is difficult to study the gastric phase of exocrine pancreatic secretion. The stomach determines the rate of gastric emptying of food components and thus the pancreatic secretory response by regulating duodenal loads of nutrients. The stomach disperses solid food into small particles, thereby facilitating their digestion (15,16). In addition, there is some degree of intragastric digestion of dietary proteins by pepsin and of dietary lipids by gastric lipase (17). The role of gastric lipase in lipid digestion has probably been underestimated in the past; new data reveal that gastric lipase can substantially digest dietary fat (18). The extent of these digestive processes probably determines the magnitude of intestinal phase stimulation of the pancreas by generating peptides and free fatty acids, which are important luminal stimulants. Intestinal phase stimulation accounts for the majority of the pancreatic response to a meal, and is therefore predominant in the net postprandial secretory output.

The proximal small intestine is the only site where acid acts to stimulate pancreatic bicarbonate secretion and it is probably the most important site at which digestion products of fat and protein act to stimulate pancreatic enzyme secretion. Long-chain fatty acids generated through fat hydrolysis are the most potent stimulants of pancreatic enzyme secretion followed by amino acids and peptides (11). The mediators of pancreatic enzyme and bicarbonate secretions during intestinal phase stimulation include cholinergic mechanisms and hormones (13,14,19). The two classical hormones, secretin and CCK, are two major players in this regulation (Table 1). Long-chain fatty acids, proteins, and amino acids are the most potent stimulants of CCK release (20,21), whereas the effect of glucose is minor (Fig. 2). The ability of
TABLE 1. Physiologic actions of cholecystokinin

- Stimulation of pancreatic enzyme secretion
- Interaction with secretin to stimulate pancreatic bicarbonate secretion
- Stimulation of gallbladder contraction
- Inhibition of gastric emptying
- Inhibition of food intake
- Inhibition of gastric acid secretion

long-chain fatty acids to stimulate CCK release is distinctly greater than that of protein or of amino acids.

Is the postprandial release of CCK sufficient to stimulate pancreatic enzyme secretion? Data from our laboratory have provided convincing evidence that endogenous CCK is an important regulator of the intestinal phase of pancreatic enzyme secretion (19,22). The observation was further substantiated in studies using specific CCK receptor antagonists: administration of a CCK receptor antagonist reduced the enzyme response to intestinal food stimulation by approximately 50% to 60% (19,22). The fact that the stimulatory effect of endogenous CCK can only partially be blocked by specific CCK receptor antagonists supports the existence of additional control mechanisms. Studies performed in patients after vagotomy have provided experimental evidence that the pancreatic enzyme response to intestinal stimulation is reduced by 60% (23,24). In agreement with this observation, intestinal phase stimulation of pancreatic enzyme output was suppressed by 60% to 90% when the cholinergic blocker atropine was given without affecting plasma CCK concentrations (25). The data support the view that pancreatic enzyme secretion is crucially dependent on the cholinergic system with hormones modulating the response.

FIG. 2. The role of fat digestion on gastrointestinal functions (CCK release). FFA, free fatty acids; MG, masoglycerides; TG, triglycerides.
Acid in the proximal small intestine stimulates exocrine pancreatic secretion, particularly pancreatic bicarbonate (11). The phenomenon indicates an important role for gastric acid as an intestinal regulator of pancreatic secretion. The mediator of this effect is the hormone secretin. Secretin is released predominantly by acid entering the duodenum. The biologic characterization of human secretin and its release after a meal have provided the experimental basis for this hypothesis (26). The amount of secretin released after a meal is, however, very small. It has been recognized for a long time that secretin interacts with other pancreatic secretagogues to stimulate pancreatic fluid and bicarbonate output. An interaction between secretin and CCK or between secretin and the cholinergic system has been proven (27,28).

REGULATION OF APPETITE AND SATIETY

Control Circuits in Appetite and Satiety

Appetite, in particular the role of the gastrointestinal tract in its control, was a subject of lively experimental interest to Pavlov and his contemporaries. In the middle of the past century, scientific interest in appetite shifted almost exclusively to the brain. In the past three decades, a new interest in the role of the gut in the regulation of food intake has grown. For most people, the amount and the composition of food eaten vary considerably from one meal to the next and from one day to the next. Nevertheless, food intake is highly regulated. Emotions, social factors, time of day, convenience, and costs are but a few variables that are not biologically regulated, but nonetheless affect meal-to-meal energy intake. As a consequence, daily energy intake is variable within an individual and not correlated with daily energy expenditure (29–31). Despite short-term mismatches, most people match energy intake to energy expenditure with great precision. The new information containing the knowledge of the different control circuits of energy homeostasis has recently been summarized (29,30). The decision to begin or to stop eating is certainly derived from complex processes. Many factors have been identified as contributors to the control of eating; in particular, several peptides and hormones acting peripherally and in the central nervous system, and neural feedback loops from the gut that involve activation of a variety of gastrointestinal chemoreceptors and mechanoreceptors as well as hepatic chemoreceptors have been identified (32,33). The growing number of signaling molecules involved in this regulatory system of energy homeostasis highlights that this process is complex but also imperfectly understood. Here the focus will be on specific preabsorptive aspects of this complex system, in particular the role of the gastrointestinal tract in the control of food consumed during individual meals. The major determinant of the meal size is the onset of satiety, a biologic state induced by signals generated during food ingestion that leads to meal termination. Several lines of evidence support the hypothesis that control of the meal size is a component of the feeding response (32–36). Satiety information generated during meal intake is largely conveyed to the hindbrain by means of afferent fibers of the vagus from the upper gastrointestinal tract (36). This information converges
in the nucleus tractus solitarius (NTS), an area in the brainstem that integrates sensory information from the gastrointestinal tract, as well as taste information from the oral cavity (34–36). Satiety-induced signals that read the NTS are initiated by a mechanical or chemical stimulation of the stomach and the small intestine during food ingestion. The mechanisms involved include hormonal signals such as CCK or glucagon-like peptide-1 (GLP-1); both peptides are released when neuroendocrine cells lining the intestinal lumen are stimulated by nutrients (37–43).

The primary route for transferring information from the gastrointestinal tract to the central nervous system is provided by afferent nerve fibers running in the vagal, splanchnic, and pelvic nerve trunks. Despite the attention given to the autonomic efferent functions of these nerves, their complement of afferent fibers is far from trivial. Vagal afferent neurons have their bodies in the nodose ganglia, while splanchnic afferents have theirs in the dorsal root ganglia. The afferent nerve fibers are activated by nutrients through chemical changes in the gut lumen and by mechanical deformation of the digestive tube. Activation of afferent peptidergic neurons results in the release of peptides at both central and peripheral locations. The role of small intestinal nutrients in activating chemical and mechanical changes in regulating food intake will be discussed in the next paragraph.

**Effects of Small Intestinal Nutrients on Food Intake**

As mentioned before, powerful signals arise from the upper gastrointestinal tract during the course of meal intake. At present, the peptides most likely to serve as satiety signals are CCK, GLP-1, and bombesin-like peptides. These signals include those produced by orosensory stimulation, gastric distension, and most important, by the stimulation of specific chemoreceptors that are triggered by nutrients in the lumen of the small intestine (44–49). The initial sites of action of these peptides are peripheral within the gastrointestinal tract. The peptide-induced satiety messages are then transmitted to the central nervous system by afferent neurons and received in visceral sensory fields of the dorsal hindbrain. The central neural processing required transforming ascending satiety messages into appropriate behavior (the cessation of eating) and the appropriate sensation (satisfaction) is almost entirely unknown.

The small intestine is a crucial source of satiety signals. In humans, infusion of nutrients (lipids, carbohydrates) into the small intestine is associated with suppression of food intake to a much greater extent than when the same nutrients are given intravenously (46–49). The interaction of nutrient with specific receptors in the small intestine stimulates the release of satiety hormones such as CCK or GLP-1 (50). Both CCK and GLP-1 slow down gastric emptying, thereby prolonging postprandial gastric distension (51–53). Nutrients in the small intestine also delay the transit of food through the small intestine, prolonging the time for absorption. Finally, signals from the small intestine modulate the sensations arising from gastric distension after meal ingestion so that they are perceived more as physiologic fullness rather than as discomfort (54). The last mechanism could be responsible for specific
symptoms such as fullness and early satiety perceived by patients with nonulcer dyspepsia.

Two decades ago it was observed that lipids perfused to the small intestine induced a cascade of events related to the regulation of appetite and satiety: Welch et al. (46,49) could show that perfusion of corn oil to the jejunum of healthy volunteers induced early satiety and reduced energy intake; furthermore, jejunal infusions of corn oil decreased hunger feelings. On the basis of their work, Welch and coworkers suggested that the effects were caused by CCK release (49). The work suggested therefore a preabsorptive site of action for the inhibitory effect of fats on short-term food intake in humans. In support of this hypothesis, the following compelling evidence is available: 1) intravenous infusion of fat has no effect on food intake (46,49); and 2) when fats are infused into the small intestine of rats, food intake is reduced within 10 minutes of the start of the infusions, but radiolabeled fat does not appear in the blood until 30 minutes after the start of the infusions. In later studies it was documented that inhibition of fat hydrolysis through the specific lipase inhibitor orlistat abolishes the fat-induced satiety signals from the small intestine (55,56). In agreement with these observations it was shown that only long-chain fatty acids are able to reduce food intake and stimulate early satiety; medium-chain fatty acids on the other hand have no effect. The mechanisms that mediate the satiating effect of fats in the small intestine initialized by long-chain fatty acids include the release of CCK. The action of CCK is mediated through CCK-A receptors as administration of a specific CCK-A receptor antagonist completely suppresses the signal (30–32). The results imply that the generation of long-chain free fatty acids through fat hydrolysis is a critical step for fat-induced inhibition of food intake. Impairment of the satiating effects of intestinal nutrients, particularly products of fat hydrolysis, favors the development of obesity.

The signals from the small intestine interact with other regulatory factors controlling food intake and satiety. Nutrients in the small intestine such as long-chain fatty acids interact with gastric distension to regulate appetite (55,56). Satiety peptides also combine with other signals to influence meal size. For example, when low-dose CCK8 is coupled with a mild gastric distension, meal size is reduced synergistically (42).

It has become apparent, however, that redundant systems are active. Both CCK and GLP-1 are able to inhibit food intake. CCKA receptor or GLP-1 receptor knockout mice do, however, not affect the nutrient status of the animals (57,58), supporting the hypothesis that redundant systems are operative. These systems may replace either peptide when one is absent. In contrast to the results with knockout mice, it has been found that rats lacking CCK-A receptors are obese and display an altered meal pattern (59). Also, continued CCK-leptin administration reduced food intake and body weight more than leptin alone did (CCK alone had no effect on body weight) (60–62). These observations indicate that interactions between different satiety signals are important.

Another putative satiety signal from the gut is the intestinal hormone, GLP-1.
The physiologic actions of GLP-1 are summarized in Table 2. The peptide is released in response to food intake, particularly by small intestinal carbohydrates (63). In animal studies and also in humans, GLP-1 was found to produce a significant reduction in energy intake compared to control studies (40,43,64,65). There is compelling evidence that GLP-1 infusion at physiologic concentrations inhibits ad libitum energy intake and that the effect of GLP-1 is dose dependent (43). The effect is not only seen in healthy subjects, but also in patients with diabetes type 2 and patients with obesity (43). Obesity is associated with a reduction of the postprandial GLP-1 response and it is therefore not surprising that the reduction in energy intake following intravenous GLP-1 is reduced in overweight compared to lean subjects (43). GLP-1 release is triggered by carbohydrates in the small intestine. When carbohydrates are infused into the small intestine, food intake is reduced, whereas the intravenous infusion of carbohydrates has no such effect (66,67).

**SUMMARY**

Although satiety peptides, released by nutrients in the small intestine, can alter the size of individual meals, their repeated administration does not necessarily alter body weight. From current understanding it is most likely that these satiety factors can potently affect food intake over the course of individual meals but by themselves have limited influence on energy homeostasis. Like other homeostatic systems, energy homeostasis is notable for its highly integrated and redundant nature. It is therefore not surprising that multiple control systems exist and that many central nervous system pathways participate in the response to these signals. The peptides that serve as satiety signals are the prime regulators of digestive functions (gastric acid secretion, gastric emptying, exocrine pancreatic secretion). Regulatory peptides, released from the gastrointestinal tract by the local action of digested food, function therefore 1) as positive feedback signals to stimulate digestive processes, and 2) as negative feedback signals to limit the amount of food consumed during individual meals.

**REFERENCES**


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**DISCUSSION**

*Dr. George A. Bray:* A very interesting discussion of CCK and its potential short-term signaling role. You had two other peptides on your model. You had a bombesin and you had GLP-1. Would you like to tell me what your views of those two are? And then would you like to tell me about the CCK-B receptor and whether it really is a CCK receptor as opposed to a gastrin one.

*Dr Christoph Beglinger:* Because of lack of time, I left out all my slides on GLP-1, but probably GLP-1 is the best candidate at the moment for looking at food intake. There have been at least three different groups, which have clearly demonstrated, that the infusion of GLP-1 induces satiety and reduces food intake in healthy volunteers, in patients with diabetes type 2 and in obese patients. A recent meta-analysis published in the *Journal of Metabolic Disorders*, just 2 or 3 months ago, has summarized the effects of GLP-1 on food intake in man. Now GRP is the human analogue of the bombesin-like peptides. The problem is that we do not have good antagonists for GRP to define its physiological role. We did the studies on gastrin-releasing peptides some years ago; the results revealed that the effects of GRP were dose-dependent in inhibiting food intake, but a significant effect occurred only at very high doses of GRP infusion, doses which are clearly above the usual maximum for the stimulation of acid secretion or stimulation of gallbladder contraction, two well known effects of GRP. So if you compare the biological effects of GRP or of bombesin at doses of up to 50 pmol/kg/hr, you will induce the comparable effects on acid secretion with maximal acid output occurring at these doses. If you want to inhibit food intake, then you need two or three times higher doses to achieve this effect. As GRP is a neurotransmitter and not a circulating hormone, it is difficult to mimic physiology by infusion. The effects of GLP-1 or CCK, on the other hand, can occur at physiological plasma concentrations suggesting that they are indeed endogenous physiologic factors in the regulation of appetite. Molecular biology has told us that CCK-B receptors are the same as gastrin receptors and so you can call them
either gastrin receptors or CCK-B receptors according to your preference, but they are the same.

**Dr. Vay Liang W. Go:** My first question is related to the fatty acid effect on CCK release. A long chain fatty acid needs to be emulsified in bile salt to be able to stimulate CCK release from the gut. Now, if you block that effect, you will not have a gallbladder contraction. Will you be able to emulsify the fatty acid to have its continued effect? That’s the first question I have. The second question is when you give an antagonist, presumably orally, does it need to be absorbed to have its effect? I don’t know whether the effect is local or systemic. Have you looked at blood levels and the effects of your antagonist in relation to blood level?

**Dr. Christoph Beglinger:** With respect to the orlistat?

**Dr. Vay Liang W. Go:** No, the relation to the CCK-A receptor antagonist. When you feed the CCK-A antagonist?

**Dr. Christoph Beglinger:** It’s absorbed.

**Dr. Vay Liang W. Go:** The question is: Is it a local effect, or, I wonder, a systemic effect?

**Dr. Christoph Beglinger:** It’s probably a systemic effect. Ninety percent of loxiglumide is absorbed and therefore it’s probably a systemic effect. Now, you always have some bile acid in the small intestine, even if you don’t stimulate gallbladder contraction, and you have CCK dependent and a CCK non-dependent bile acid output into the small intestine. Therefore the bile acids that are present are probably sufficient to generate the first emulsification of the triglycerides and to generate free fatty acids, which will in turn stimulate gallbladder contraction, and with that you will have a lot of bile in the small intestine.

**Dr. Vay Liang W. Go:** So, the cephalic phase control of gallbladder contraction contains enough bile salts to emulsify fatty acid.

**Dr. Christoph Beglinger:** Absolutely.

**Dr. Marcello Giovannini:** During your lecture I thought about human milk. During the infant’s meal, during breastfeeding, the lipids increase, and also the long-chain polyunsaturated fatty acids, leading the breastfed infant to self-regulate its satiety. Do you know if there is any feedback mechanism getting lost in obesity, in case of formula-feeding?

**Dr. Christoph Beglinger:** The major problem, so far, is that we do not have a receptor for the long-chain fatty acids and this is one of the unresolved mysteries. So by which mechanism fatty acids stimulate CCK release is still not clear and therefore there is a link missing in my hypothesis.

**Dr. Wolfgang Langhans:** You alluded to the protection role of GLP-1 and, given the time lines of a meal and the times of gastrointestinal transit, I would like to know your view on the exact role of GLP-1 in this context, that is, do you perceive GLP-1 as a meal-ending satiety signal, or how does that work?

**Dr. Christoph Beglinger:** Well, GLP-1 does have a variety of effects. First of all, it stimulates insulin release much more than does glucose alone, so it’s one of the incretins in the GI tract, but then it also inhibits gastric emptying and with that it inhibits appetite. Now it’s unclear at the moment whether the inhibition of meal intake or calorie intake is entirely due to the effect of GLP-1 on gastric emptying. So as you delay gastric emptying, you induce higher satiety. But there are some pieces of evidence, which would suggest that GLP-1 could have an effect on satiety independent of its effect on gastric emptying. If you look at infusion studies during the pre-meal period, subjects experience less hunger and have higher fullness feelings with GLP-1 compared to the control studies—therefore, implying that indeed the risk and effect of GLP-1 on food intake is independent of its effect on gastric emptying.

**Dr. Ravindra Chittal:** My question is about satiety in newborns. Essentially, breastfed newborns have a very poor intake of long-chain fatty acids, because breast milk is indeed...
rich in medium-chain fatty acids. What difference would there be in their satiety, if they started having no fatty acids?

Dr. Christoph Beglinger: I have no idea. I don’t have any experience with children, and I don’t know of any studies, which have looked at this particular question in small children. Therefore I cannot give you an answer.

Dr. B. S. Ramakrishna: My question relates to the regulation of the CCK receptors. We know that in mucosal disease of the small intestine, for instance tropical sprue, CCK release from the small bowel is affected, in fact it’s markedly reduced and you can have exocrine pancreatic insufficiency secondary to that. Now do we know how the CCK receptors are regulated? Is it just a lack of these receptors, or is it inflammation in the mucosa that affects them?

Dr. Christoph Beglinger: Well, actually it’s not the receptor, it’s the CCK cell, which is decreased. So in patients with celiac disease, there’s clear evidence that they have a reduced CCK response if they are active; I’ve recently reviewed a paper from the Liverpool group, which documented that people with Giardia infection do have an increase in CCK release; the authors suggested that the inflammation is responsible for an increased CCK response. So if you have diseases of the mucosa of the small intestine, you clearly have a change in CCK release with reduced CCK secretion in atrophies such as celiac disease and perhaps an increase in CCK release in situations of inflammation.

Dr. Narendra Kumar Arora: We conducted a randomized trial feeding nine-month children. In one group we gave 20% calories as fat, using groundnut oil, which is long-chain, and in the other group we gave 45% calories as fat, and we found that the children receiving extra fat continued to consume the same volume and fat has often reissued in at least 85% of the low-fat group to 93% of the high fat group. And obviously as they continued to eat at least the same volume the net calorie intake was higher, in the high fat group. How would you explain that?

Dr. Christoph Beglinger: Well, as I said in the beginning, we are looking at individual meals and again, it’s a clear model situation. The volunteers who receive the fat had a feeding tube in the small intestine in order to diffuse the fat into the small intestine. Under normal circumstances, you would not like to have a feeding tube into your small intestine, and therefore it’s a model situation. Number two, we only use males, because male subjects are much less influenced by other factors apart from what they receive. Therefore I would not apply our conclusions to the general situation, and I think it tells you again that the regulation of appetite is a very complex story. So the only thing I could say from our model situations with feeding tubes in the small intestine is that if you give fat, you reduce the intake of individual meals, an effect that can be blocked by CCK antagonists. I think that’s the limitation of the models we use, and it would be dangerous to extrapolate that to other situations or the general clinical situation.

Dr. M. S. Westerterp-Plantenga: Do you know of any exogenous factors like perhaps nutrients or something else that would affect GLP-1 release?

Dr. Christoph Beglinger: Well the most potent secretagogue for GLP-1 release is glucose, and it is generally assumed that 2 calories per minute emptied from the stomach into the small intestine are sufficient to stimulate GLP-1 release. But if you increase the caloric load of carbohydrates into the small intestine, you can increase the amount of GLP-1 release. But we have shown that free fatty acids also can stimulate GLP-1 release, but to a much lesser extent than the carbohydrates, but they are able to stimulate GLP-1 release.

Dr. Michael J. G. Farthing: There’s a lot of serotonin release after a standard meal, particularly a high carbohydrate meal, and we know it has post-secretory pro-motility effects in the distal gut. Do you think it could have any effects on satiety by effects on the gut?
Dr. Christoph Beglinger: Well, there is some evidence that serotonin interacts with CCK, so if you combine two things, yes you could expect an effect. We have never looked at this particular question, as we do not know which serotonin receptor would be the right one and then you would have to use different receptor antagonists to test that, so I don’t have any personal experience, but there is experimental evidence suggesting that serotonin interacts with CCK.

Dr. Vay Liang W. Go: Your GLP-1 story in relation to CCK makes a lot of sense, particularly related to gastric emptying of various nutrients after eating. We have previously found that glucose is emptied first, followed by fatty acid later, so the time sequence of the release of the hormones is important. GLP-1 is probably more important at the beginning, and CCK may be more important for the latter part of satiety, given that the fatty acid emptying from the stomach doesn’t really occur until about 5 or 10 minutes later on, while glucose is emptied immediately after eating.

Dr. Christoph Beglinger: Yes, actually the story can be even more complicated. We have an unpublished study, where we gave four different sequences to the volunteers. Number one, GLP-1, number two CCK, number three the combination of CCK-A and GLP-1 and number four, the control infusion (saline). CCK alone or GLP-1 alone inhibited food intake as expected, but the combination didn’t do anything. So you might be right that the time sequence might not have been the right one and therefore instead of having an additional effect, we didn’t have any effect at all.

Dr. Cecilia Albala: Is there any new relationship between this fatty acid-binding protein polymorphism and the CCK release?

Dr. Christoph Beglinger: So far there is no polymorphism for fatty acid-binding protein with repeat CCK release demonstrated.

Dr. Cecilia Albala: No, the fatty acid-binding protein for instance?

Dr. Christoph Beglinger: I don’t know. Free fatty acids alone stimulate CCK release, so only the free fatty acids stimulate the CCK in the small intestine. But we don’t have the receptor yet, so we do not know how the three fatty acids actually bind to the receptor and how they stimulate CCK release.

Dr. George Bray: CCK is an interesting prohibitor of food intake and the possibility of making drugs would be an intriguing one. The challenge would be to separate the pancreatic secretion from the food intake inhibition. Do you know of anything that does that or is there any way of doing that, or are we always stuck with having the food intake effect and the pancreatic secretory effect couple?

Dr. Christoph Beglinger: The acids of the pancreas do not have any CCK-A receptors, so our current thinking is that pancreatic secretion is stimulated by nerves and that CCK receptors, CCK-A receptors on pancreatic nerves actually account for the stimulation process. Even if you block CCK, you will still have a good stimulation of the exocrine pancreas as CCK-A receptors can only inhibit the pancreatic secretory response by perhaps 40-50%. I would be more concerned about the gallbladder. If you have a CCK agonist acting on CCK-A receptors, you would have a continuous stimulation or contraction of the gallbladder and that could be a problem; therefore I’m not sure whether it is a good idea to over-stimulate the CCK-A receptors by giving potent CCK analogues acting on CCK-A receptors.

Dr. Gareth Williams: Let us go back to the brain for a moment. CCK could be given as a nasal spray. This could get it into the CSF, as has been demonstrated for small ACTH cleavage peptides. They pass through the olfactory mucosa and across the cribriform plate into the CSF. If you did this in humans, what do you predict would happen?
Dr. Christoph Beglinger: It's a very tough question actually, because most of the data which were generated in humans indicate that the effect of CCK is a peripheral effect, and most of the effects are mediated by the alimentary receptors, the CCK-A receptors. Therefore, if you could give CCK by any route, which would reach the brain, I'm not convinced that it would do a lot because the importance of the CCK-A receptors in the brain is not clear. It is also not clear whether they have a role at all in regulating food intake and satiety.