ELSEVIER

Physiology & Behavior 74 (2001) 735–741

PHYSIOLOGY & BEHAVIOR

DIGESTIVO Interactions between gastric emptying and satiety, withspecial reference to glucagon-like peptide-1

P.M. Hellström[a,*], Erik Näslund[b]

[a]*Department of Internal Medicine, Unit of Gastroenterology Karolinska Hospital, Karolinska Institutet, Stockholm SE-171 76, Sweden*
[b]*Division of Surgery, Karolinska Institutet, Danderyd Hospital, Danderyd SE-182 88, Sweden*

Abstract

The slowing of gastric emptying is an important mechanism for the satiating effect of gut peptide signaling. After food intake, cholecystokinin (CCK), as well as glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2), are released from the gastrointestinal tract to mediate satiety. In humans, CCK and the GLP-1 have been found to cause satiety in both normal and obese subjects. This satiating effect may be caused by the peptides circulating as hormones with direct effects in the central nervous system, or indirect effects through signals mediated either via the vagus nerve or by activation of vagal afferent fibers due to slow gastric emptying. These peptides also cause gastric relaxation, considered an additional component in the satiating effect of the peptides. To conclude, after food intake, gut peptides may act in concert as neurohormonal satiety signals acting directly in the brain or indirectly via the vagus nerve, as well as through gastric sensory mechanisms to limit food intake.

Keywords: Food intake; Glucagon-like peptides; Gastrointestinal motility

1. Introduction

Food intake is a vital nutritional function and an essential component of normal life in any individual. For most people, weight is relatively constant throughout life. However, for an increasing number of people, weight gain is becoming an increasing problem. Diseases, such as non-insulin-dependent diabetes mellitus and cardiovascular diseases with myocardial infarction and hypertension, follow in the footsteps of obesity, but other disorders including osteoarthritis and infertility are also common in the population.

Our understanding of factors that regulate food intake is rapidly growing with the discovery of novel peptides that may influence ingestive behavior (Table 1). These peptides may be considered to act as neurohormonal agents because of their dual capability to act as hormones and transmitters in the periphery, as well as in the brain. These peptides have traditionally been described as having organ-specific effects in the brain, gastrointestinal tract, on the vascular bed and more recently, also adipose tissue. However, most peptides are multifunctional with considerable redundancy and overlap, which seems to be of vital significance for the nutritional balance of the living organism. Sophisticated surveillance systems of neuropeptide circuitries serve to monitor signals of adequate substrate levels in the brain, liver, adipose tissue and blood. At the cognitive level, these signals are experienced as "hunger" or "satiety," which form the basis for our ingestive behavior.

There is a close relationship between the gut and the brain. Peptides originally believed to exist only in hypothalamic feeding control centers have also recently been found in the gut [1], and gut peptides have been found to exert important functions in the brain and nervous tissue [2–4]. Hence, these findings, along with the complex interaction pattern between different nervous functions in the gut and in the brain, have led to the evolution of the concept of the gut as a minibrain.

The alimentary tract is the portal of entry of all nutrients and has a fundamental role in the regulation of food intake. The aim of this review is to describe the current status of knowledge about the relationship between the function of the gut and regulation of food intake, with focus on signals from the upper gastrointestinal tract. These signals are mostly mediated via the vagus nerve and interact with the recognized satiating peptides cholecystokinin (CCK) from

* Corresponding author. Tel.: +46-8-5177-3877; fax: +46-8-5177-2058.
E-mail address: per.hellstrom@medks.ki.se (P.M. Hellström).

0031-9384/01/$ – see front matter
PII: S0031-9384(01)00618-7

Table 1
Peptide implicated in the control of food intake

Stimulated food intake	Inhibited food intake
AGRP	Amylin
Dynorphin	Bombesin
β-endorphin	Calcitonin
β-casomorphine	Calcitonin gene-related peptide (GGRP)
Galanin	CART
Growth hormone-releasing hormone (GHRH)	CCK
Orexin A; orexin B	Enterostatin
NPY	GRP
Peptide YY (PYY)	Glucagon
	GLP-1
	GLP-2
	Insulin
	Leptin (ob protein)
	α-MSH
	Neurotensin (NT)
	Oxytocin
	Somatostatin
	Thyrotropin-releasing hormone (TRH)
	Urocortin
	Vasopressin

the upper gut, and glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2) from the lower gut.

2. Gastric signaling

The stomach has an obvious role in the regulation of food intake, yet the mechanisms involved are only partly understood. The mechanisms related to stimulation of gastric mechanoreceptors involved in the capacity and propulsive functions of the stomach are best recognized where the gastric distension in association with a meal is an adequate stimulus that affects all types of gastrointestinal motor activity. In addition, gastric chemoreceptors have a major role in regulation of motility. The pyloric area senses the energy content of the food and thereby permits a fixed energy load to be emptied into the duodenum at a constant rate, regardless of the composition of the food [5]. In addition, multiple other endogenous or exogenous factors can influence the emptying rate, of which peptides with satiating effect are of primary importance.

Gastric distension causes a feeling of satiety in humans [6–8]. With balloon distension, an unpleasant feeling of fullness occurs. Intragastric balloons may reduce food intake in obese subjects, but only with a short-lasting effect [9]. Viscous distending substances may also delay gastric emptying and hence food intake. Again, the effect on food intake is short-lived [10,11].

Hunger and fullness are often interpreted as opposites although they are mediated through different pathways. After a fat-containing meal, postprandial fullness, but not hunger ratings, was related to intragastric volume [12]. After ingestion of a meal with high-calorie olive oil and low-calorie beef soup, postprandial fullness was related to gastric volume achieved, whereas hunger feelings were related to gastric fatty content [7,8]. Furthermore, postprandial fullness, but not hunger, was found to be related to antral distension after a glucose load [13]. Thus, these findings suggest that gastric distension by food may play a major role in eliciting satiety, whereas reduction of hunger feelings after a meal more likely results from an interaction between nutrients and receptors in the upper gut and postabsorptive signals from the liver or brain. In extension to this, infusion of food into the denervated rat stomach decreased food intake, implying a hormonal effect to be in operation independent of a neural network [14]. Gastrin-releasing peptide (GRP) and somatostatin are released from the antrum after food intake. Both peptides have been shown to have a satiating effect in animals and humans [15,16]. Recently, leptin has been demonstrated in gastric mucosa from where it may be released after a meal [17] and exert a paracrine effect, perhaps activating vagal afferents. It is not yet known if this leptin source may be of importance in food-taking.

3. Vagal signaling

With its extensive projections, both afferent and efferent, throughout the gastrointestinal tract, the vagus nerve has an important impact on functions of gastrointestinal organs. Information from the gut to the brain is relayed through vagal afferents projecting to the nucleus tractus solitarius (NTS). Nerve fibers from the NTS project further to the appetite-regulating nuclei of the hypothalamus. Gut peptides circulating in the bloodstream, and insulin and leptin signaling information about the size of the adipose tissue, are believed to enter the brain substance at the arcuate nucleus, which projects fibers to the paraventricular nucleus (PVN) of the hypothalamus and the lateral hypothalamus (LH). The neurons of the arcuate nucleus, the PVN and LH contain a multitude of neuropeptides known to effect food intake. These include neuropeptide Y (NPY), orexins, cocaine–amphetamine regulated transcript (CART), α-melanocyte-stimulating hormone (α-MSH), GLP-1, CCK and agouti-related peptide (AGRP) [2,18–21].

Gastric distension causes increased firing rate in vagal afferents [22]. The reception areas of these fibers are localized to small regions of less than 3 mm in the stomach. These fibers show a short response latency, suggesting involvement in the feedback control of propulsive and retropulsive grinding contractions needed to achieve the small particle size required for passage of macronutrients through the pylorus [22]. After gastric distension in rats, expression of c-*fos* is increased in the NTS and dorsal motor nucleus [23]. After feeding, c-*fos*-like immunoreactivity is increased in the dorsal motor ganglion and hypoglossal

nucleus in the rat [24]. These data indicate vagal afferent signaling from the stomach to the brain during and after food intake. One possible mediator is CCK since local administration of the peptide stimulates firing in vagal afferent mechanosensitive fibers [22]. Furthermore, the newly discovered peptide, urocortin, of the corticotropin-releasing factor (CRF) family has recently been shown to inhibit food intake and gastric emptying in lean and *ob/ob* mice when given peripherally [25]. Taken together, data indicate the stomach as having a key role in our control of food intake.

4. Gut peptide signaling

4.1. CCK

After food intake, CCK is released into the bloodstream from endocrine I-cells of the duodenum and the jejunum [26,27]. CCK exists in several bioactive molecular forms ranging from 4 to 58 amino acid residues. All forms of CCK have retained the bioactive C-terminal portion, and the molecular forms CCK-8, -33 and -58 have all been shown to have biological effects in association with food intake [28–30]. The receptors for CCK have been subdivided into CCK-A and CCK-B on the basis of structurally and functionally related peptide sequences [31,32].

Studies in humans have repeatedly shown that CCK inhibits food intake [33–36]. However, a gastric preload is generally necessary to achieve a satiating effect with CCK. Thus, CCK-33 given at physiologically relevant concentrations to fasting humans had no effect on satiety or food intake [37], while the same infusion rate after a banana preload decreased food intake in both obese and normal subjects [38]. A common problem in the interpretation of data with CCK is that the peptide, in addition to its direct satiating effect, also causes gastric relaxation that may confound the understanding of the mechanism for its satiating effect. The temporal relationship between the peptide's satiating and relaxing effect on the stomach has not been clarified. The combination of a gastric distending load and CCK seems, however, to act synergistically to evoke greater discharge rates than that of either stimulus alone [39].

Administration of CCK antibodies and receptor antagonists increases food intake, suggesting that CCK may be a physiological inhibitor of food intake [40–42]. Peripherally administered CCK acts on CCK-A receptors in the gastric antrum, which are involved in the inhibition of gastric emptying after administration of CCK [43]. CCK-A receptors have also been demonstrated in the subdiaphragmatic vagus nerve [44] and vagotomy abolishes the satiating effect of the peptide [3]. Feeding also results in a local release of CCK in the brain to act on CCK-B receptors, indicating additional pathways for the action of CCK in relation to food intake [3]. A relationship between decreases in plasma levels of CCK and hunger as well as decreased fullness has also been reported in man [45] and strengthens the data pointing at CCK as a mediator of satiety.

4.2. GLP-1 and GLP-2

GLP-1 and GLP-2 are produced in endocrine L-cells mainly found in the mucosa of the ileum and colon, and arise as the result of proteolytic cleavage of proglucagon in the gut. Both peptides are released in equimolar amounts after food intake [46,47]. Interestingly, the amino acid sequence of GLP-1 and GLP-2 is highly conserved through the evolution, indicating physiologically important functions of the peptides [48,49].

The GLP-1 receptor is known to exist as a single receptor type in the brain, lung, stomach, skeletal muscle and adipose tissue [50–53]. In the brain, GLP-1-immunoreactive cell bodies are found in the caudal portion of the solitary tract and in the dorsal and ventral parts of the medullary reticular nucleus, corresponding to regions that receive vagal afferent fibers from the gut [2]. GLP-1-immunoreactive nerve fibers are found in the PVN and periventricular strata [2,54,55], as well as in thalamic nuclei and brainstem [54,56]. GLP-1 binding sites are found in the sensory circumventricular organs including the subfornical organ and area postrema. Since the different regions of the circumventricular organs lack an efficient perivascular blood–brain barrier, free exchange of molecules between the blood and cerebrospinal fluid is possible [57–59].

Physiologically, GLP-1 exerts dual actions in metabolic control. Through its insulinotropic and glucagonostatic mechanisms, blood glucose concentrations are regulated [48]. In addition, GLP-1 slows gastric emptying of liquid as well as solid meals [60,61] (Fig. 1), thereby reducing the

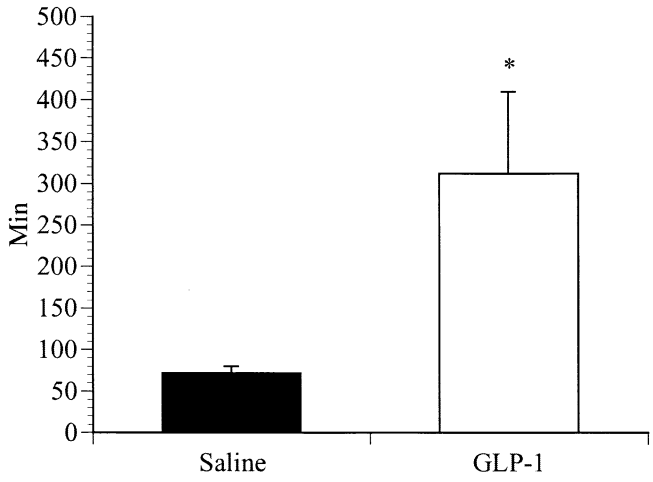

Fig. 1. Gastric half-emptying time (T_{50}; mean ± S.E.M.) in eight male subjects during scintigraphic gastric emptying test with saline or GLP-1 (0.75 pmol/kg/min) infusion for 120 min. * $P < .05$; Wilcoxon rank-signed test for matched pairs.

metabolic demand in association with food intake [62] and a concomitant decrease in food intake (Fig. 2). There is evidence that the effects of GLP-1 on gastric functions are mediated via the vagus nerve both in animals and humans [63–65], and data defy any direct action of the peptide on denervated gastrointestinal musculature [66].

GLP-1 also exerts dual actions as regards feeding behavior and satiety. Several reports have demonstrated that intracerebroventricular injection of GLP-1 in rats inhibits food and water intake [67–69] and induces c-*fos* expression in the PVN [69]. Administration of the GLP-1 receptor antagonist exendin (9–39) amide intracerebroventricularly to satiated, but not fasted, rats resulted in increased food intake [69]. Furthermore, exendin (9–39) amide given twice daily during 10 days not only increased food intake, but also resulted in significant weight gain [70]. No effect was seen after intraperitoneal injections of GLP-1 [69], suggesting a central mode of action for GLP-1 as regards food intake in the rat.

In humans, so far, seven studies have shown GLP-1 to increase satiety and decrease food intake in normal weight [71–73], diabetic [74,75] and obese subjects [76,77]. However, one study failed to demonstrate any effect of GLP-1 on food intake or appetite [78]. The studies range from 2 to 48 h in duration with either intravenous or subcutaneous infusions of GLP-1. In all studies, slightly supraphysiological concentrations of GLP-1 were achieved. No nausea or other side effects were noted. The physiological importance of GLP-1 as a satiating peptide may be revealed as GLP-1 receptor antagonists such as exendin (9–39) amide or des-His–Glu–exendin-4 become generally available for use in humans.

Commensurate with the findings above, indirect data indicate GLP-1 as a physiological regulator of food intake. It has been shown that the plasma increase of GLP-1 after a meal is attenuated in obese subjects [79–81]. As GLP-1 strongly inhibits gastric emptying by about 50% at 3 h after a meal [76,77], data imply that low postprandial GLP-1 concentrations in the obese may promote an earlier onset of the next anticipated meal. When obese individuals are subjected to jejuno-ileal bypass, the gastric emptying is slowed along with a restituted GLP-1 response to the ingested meal [80]. In this context, genetic studies of families with morbid obesity show a linkage with islet 1 locus (Isl-1) on chromosome 5q. As Isl-1 is a positive regulator of proglucagon gene transcription, it may influence GLP-1 elaboration and release [82]. Thus, a defect in this system may result in decreased plasma levels of GLP-1, rapid gastric emptying and short intermeal periods due to short postprandial satiety periods with increased food intake as a consequence.

The importance of GLP-2 in regulation of food intake is not as clearly characterized as for GLP-1. GLP-2 is known to exert trophic effects on the intestinal mucosa [83] and is investigated in the treatment of short bowel syndrome [84]. GLP-2 also affects gastric motor activity. In pigs, GLP-2 has been shown to inhibit antral motility [85]. Recently, a GLP-2-containing neuronal pathway connecting the NTS with the dorsomedial hypothalamic nucleus has been found in rats together with mRNA for the GLP-2 receptor in this hypothalamic nucleus. A functional aspect of this finding is that central administration of GLP-2 to rodents resulted in a 35% decrease of food intake compared to placebo [4].

Thus, in terms of gastric motor function, it would seem as if the concept of an "ileal brake" mechanism would be applicable to both GLP-1 and GLP-2 as these two distal gut peptides exert similar effects on food intake and gastric emptying.

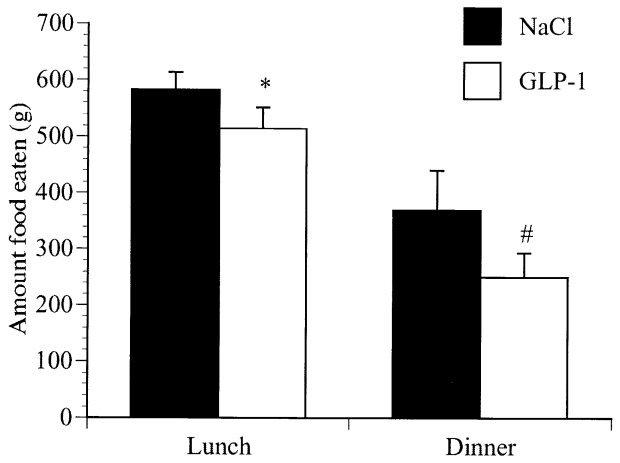

Fig. 2. Amount of food eaten at lunch (1200 h) and dinner (1600 h) in eight obese subjects with continuous intravenous saline or GLP-1 (0.75 pmol/kg/min) infusion over 8 h after an energy-fixed breakfast (at 0800 h). * $P < .05$, # $P = .06$; Wilcoxon rank-signed test for matched pairs.

5. Conclusion

Signals arising from the upper gastrointestinal tract seem to influence the intermeal appetite and primarily the food intake interval. These signals are initiated by mechanoreceptors and chemoreceptors in the stomach, and are relayed through the vagus nerve to the brain and its cognitive centers for food-taking. The gut peptides CCK, GLP-1 and GLP-2 are released in response to food intake and may act as direct satiating mediators, but also form the basis for gastric relaxation in response to a meal, which may act in concert with direct peptidergic signaling in order to achieve satiety.

Acknowledgments

This work was supported by the Swedish Medical Research Council (7916, 13150) the Magnus Bergvall fund, the Ruth and Richard Juhlin fund, The Professor Nanna Svartz fund, the Åke Wiberg fund and the AMF

sjukförsäkringar Jubilee Foundation and funds of Karolinska Institutet.

References

[1] Kirchgessner AL, Liu M. Orexin synthesis and response in the gut. Neuron 1999;24:841–951.

[2] Jin SLC, Han VKM, Simmons JG, Towle AC, Lauder JM, Lund PK. Distribution of glucagon-like peptide-1 (GLP-1), glucagon, and glicentin in the rat brain. J Comp Neurol 1988;271:519–32.

[3] Geiselman PJ. Control of food intake. Endocrinol Metab Clin North Am 1996;25:815–29.

[4] Tang-Christensen M, Larsen PJ, Thulesen J, Rømer J, Vrang N. The proglucagon-derived peptide, glucagon-like peptide-2, is a neurotransmitter involved in the regulation of food intake. Nat Med 2000;6: 802–7.

[5] McHugh PR, Moran TH. Calories and gastric emptying: a regulatory capacity with implications for feeding. Am J Physiol 1979; 235:R29–34.

[6] Bergman JF, Chassany O, Petit A, Triki R, Caulin C, Segrestaa JM. Correlation between echographic gastric emptying and appetite: influences of psyllium. Gut 1992;33:1042–3.

[7] Horowitz M, Jones K, Edelbroek MA, Smout AJ, Read NW. The effect of posture on gastric emptying and intragastric distribution of oil and aqueous meal components and appetite. Gastroenterology 1993;105:382–90.

[8] Carney BI, Jones KL, Horowitz M, Sun WM, Penagini G, Meyer JH. Gastric emptying of oil and aqueous meal components in pancreatic insufficiency—effects on posture and on appetite. Am J Physiol 1995;268:G925–32.

[9] Rigaud D, Trostler N, Rozen R, Vallat T, Apfelbaum M. Gastric distention, hunger and energy intake after balloon implantation in severe obesity. Int J Obes 1995;19:489–95.

[10] Shafer RB, Levine AS, Marlette JM, Morley JE. Effects of xylitol on gastric emptying and food intake. Am J Clin Nutr 1987;45:744–7.

[11] French SJ, Read NW. The effect of guar gum on hunger and satiety following meals of differing fat content; relationship with gastric emptying. Am J Clin Nutr 1994;59:87–91.

[12] Benini L, Brighenti F, Castellani G. Gastric emptying of solids is markedly delayed when meals are fried. Dig Dis Sci 1994;1994: 2288–94.

[13] Jones KL, Doran SM, Hveem K, Bartholomeusz FDL, Morley JE, Sun WM, Chatterton BE, Horowitz M. Relation between postprandial satiation and antral area in normal subjects. Am J Clin Nutr 1997; 66:127–32.

[14] Koopmans HS. A stomach hormone that reduces food intake. J Auton Nerv Syst 1983;9:157–71.

[15] Gutzwiller JP, Dreuve J, Hildebrand P, Rossi L, Lauper JZ, Beglinger C. Effect of intravenous human gastrin-releasing peptide on food intake in humans. Gastroenterology 1994;106:1168–73.

[16] Lieverse RJ, Jansen JB, Masdee AM, Lamers CB. Effects of somatostatin on human satiety. Neuroendocrinology 1995;61:112–6.

[17] Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Le Marchand-Brustel Y, Lewin MJ. The stomach is a source of leptin. Nature 1998;394: 790–3.

[18] Flier JS, Maratos-Flier E. Obesity and the hypothalamus: novel peptides for new pathways. Cell 1998;92:437–40.

[19] Kristensen P, Judge ME, Thim L, Ribel U, Christjansen KN, Wulff BS, Clausen JT, Jensen PB, Madsen OD, Vrang N, Larsen PJ, Hastrup S. Hypothalamic CART is a new anorectic peptide regulated by leptin. Nature 1998;393:72–6.

[20] Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richarson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ. Orexin and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 1998;92: 573–85.

[21] Leibowitz SF. Neurochemical–neuroendocrine systems in the rat brain controlling macronutrient intake and metabolism. Trends Neurosci 1992;15:491–7.

[22] Schwartz GJ, McHugh PR, Moran TH. Integration of vagal afferent responses to gastric loads and cholecystokinin. Am J Physiol 1991;261:R64–9.

[23] Willing AE, Berthoud HR. Gastric distention-induced c-*fos* expression in catecholaminergic neurons of rat dorsal vagal complex. Am J Physiol 1997;272:R59–67.

[24] Emond MH, Weingarten HP. Fos-like immunoreactivity in vagal and hypoglossal nuclei in different feeding states: a quantitative study. Physiol Behav 1995;58:459–65.

[25] Asakawa A, Inui A, Makino S, Fujino MA, Kasuga M. Urocortin reduces food intake and gastric emptying in lean and Ob/ob obese mice. Gastroenterology 1999;116:1287–92.

[26] Buchan AM, Polak JM, Solcia E, Capella C, Hudson D, Pearse AG. Electron immunohistochemical evidence for human intestinal I cells as the source of CCK. Gut 1978;19:403–7.

[27] Schultzberg M, Hökfelt T, Nilsson G, Terenius L, Rehfeld JF, Brown M, Elde R, Goldstein M, Said S. Distribution of peptide- and catecholamine-containing neurons in the gastro-intestinal tract of rat and guinea-pig: immunohistochemical studies with antisera to substance P, vasoactive intestinal polypeptide, enkephalins, somatostatin, gastrin/cholecystokinin, neurotensin and dopamine beta-hydroxylase. Neuroscience 1980;5:689–744.

[28] Liddle RA, Goldfine ID, Rosen MS, Taplitz RA, Williams JA. Cholecystokinin bioactivity in human plasma. Molecular forms, responses to feeding and relationship to gallbladder contractions. J Clin Invest 1985;75:1144–52.

[29] Walsh J, Lamers C, Valenzuela J. Cholecystokinin–octapeptide-like immunoreactivity in human plasma. Gastroenterology 1982;82: 438–44.

[30] Overduin J, Reeve JR, Gibbs J. Comparison of satiating actions of CCK-8 and CCK-58 (abstract). Annual Meeting of the Society for the Study of Ingestive Behavior, Dublin, Ireland 2000;53.

[31] Wank SA, Pisegna JR, de Weerth A. Brain and gastrointestinal cholecystokinin receptor family: structure and functional expression. Proc Natl Acad Sci USA 1992;89:8691–5.

[32] Mantyh CR, Pappas TN, Vigina SR. Localization of cholecystokinin A and cholecystokinin B/gastrin receptors in the canine upper gastrointestinal tract. Gastroenterology 1994;107:1019–30.

[33] Kissileff HR, Pi-Sunyer X, Thornton J, Smith GP. C-terminal octapeptide of cholecystokinin decreases food intake in man. Am J Clin Nutr 1981;34:154–60.

[34] Stacher G, Steinringer H, Schmierer C, Schneider C, Winklehner S. Cholecystokinin octapeptide decreases intake of solid food in man. Peptides 1982;3:133–6.

[35] West DB, Fey D, Woods SC. Cholecystokinin persistently suppresses meal size but not food intake in free-feeding rats. Am J Physiol 1984;246:R776–87.

[36] Ballinger A, McLoughlin L, Medback S, Clark M. Cholecystokinin is a satiety hormone in humans at physiological post-prandial concentrations. Clin Sci 1995;89:375–81.

[37] Lieverse RJ, Jansen JBMJ, Zwan A, Samson L, Masclee AAM, Lamers CBHW. Effects of a physiological dose of cholecystokinin on food intake and postprandial satiation in man. Regul Pept 1993;43: 83–9.

[38] Lieverse RJ, Jansen JBMJ, Zwan A, Samson L, Masclee AAM, Lamers CBHW. Satiety effects of a physiological dose of cholecystokinin in humans. Gut 1993;36:176–9.

[39] Schwartz GJ, Berkow G, McHugh PR, Moran TH. Gastric loads and cholecystokinin synergistically stimulate rat gastric vagal afferents. Am J Physiol 1993;265:R872–6.

[40] Peikin SR. Role of cholecystokinin in the control of food intake. Gastrointest Endocrinol 1989;18:757–75.
[41] Plata-Salaman CR. Regulation of hunger and satiety in man. Dig Dis Sci 1991;9:253–68.
[42] Reidelberger RD, O'Rourke MF. Potent cholecystokinin antagonist L 364718 stimulates food intake in rats. Am J Physiol 1989;257: R1512–8.
[43] Reubi JC, Waser B, Läderach U, Stettler C, Friess H, Halter F, Schmassmann A. Localization of cholecystokinin A and cholecystokinin B gastrin receptors in the human stomach. Gastroenterology 1997;112:1197–205.
[44] Mercer JG, Lawrence CB. Selectivity of cholecystokinin (CCK) receptor antagonists, MK-329 and L-365260, for axonally-transported CCK binding sites on the rat vagus nerve. Neurosci Lett 1992;137: 229–31.
[45] French SJ, Murry B, Rumsey RD, Sepple CP, Read NW. Is cholecystokinin a satiety hormone? Correlations of plasma cholecystokinin with hunger, satiety, and gastric emptying in normal volunteers. Appetite 1991;21:95–104.
[46] Bell GI, Santerre RF, Mullenbach GT. Hamster preproglucagon contains the sequence of glucagon and two related peptides. Nature 1983;302:716–8.
[47] Holst JJ. Enteroglucagon. Annu Rev Physiol 1997;59:257–71.
[48] Ørskov C. Glucagon-like peptide-1, a new hormone of the enteroinsular axis. Diabetologia 1992;35:701–11.
[49] Hartmann B, Johnsen AH, Ørskov C, Adelhorst K, Thim L, Holst JJ. Structure, measurement, and secretion of human glucagon-like peptide-2. Peptides 2000;21:73–80.
[50] Valverde I, Merida E, Delgado E, Trapote MA, Villanueva-Penacarrillo MC. Presence and characterisation of glucagon-like peptide-1 (7–36)amide receptors in solubilized membranes of rat adipose tissue. Endocrinology 1993;132:75–9.
[51] Lankat-Buttgereit B, Göke R, Fehmann HC, Richter G, Göke B. Molecular cloning of cDNA for GLP-1 the receptor expressed in the rat lung. Exp Clin Endocrinol 1994;102:341–7.
[52] Schmidtler J, Dehne K, Allescher HD, Schusdziarra V, Classen M, Holst JJ, Polack A, Schepp W. Rat parietal cell receptors for GLP-1-(7–36) amide: Northern blot, cross-linking and radioligand binding. Am J Physiol 1994;269:G423–32.
[53] Alvarez A, Roncero I, Chowen JA, Thorens B, Balzques E. Expression of the glucagon-like peptide-1 receptor gene in the rat brain. J Neurochem 1996;66:920–7.
[54] Shimizu I, Hirota M, Ohboshi C, Shima K. Identification and localization of the glucagon-like peptide-1 and its receptor in rat brain. Endocrinology 1987;121:1076–82.
[55] Kreymann B, Ghatei MA, Burnet P, Williams G, Kanse S, Diani AR, Bloom SR. Characterization of glucagon-like peptide-1 (7–36)amide in the hypothalamus. Brain Res 1989;502:325–31.
[56] Kanse SM, Kreymann B, Ghatei MA, Bloom SR. Identification and characterisation of glucagon-like peptide-1 7–36 amide-binding sites in the rat brain and lung. FEBS Lett 1988;241:209–12.
[57] Johnson AK, Gross PM. Sensory circumventricular organs and brain homeostatic pathways. FASEB J 1993;7:673–86.
[58] Göke R, Larsen PH, Mikkelsen JD, Sheikh SP. Identification of specific binding sites for glucagon-like peptide-1 on the posterior lobe of the rat pituitary. Neuroendocrinology 1995;62:130–4.
[59] Göke R, Larsen PH, Mikkelsen JD, Sheikh SP. Distribution GLP-1 of binding sites in the rat brain: evidence that exendin-4 is a ligand of GLP-1 brain binding sites. Eur J Neurosci 1995;7:2294–300.
[60] Wettergren A, Schjøldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 87–107-amide) inhibits gastric and pancreatic functions in man. Dig Dis Sci 1993;38:665–73.
[61] Näslund E, Bogefors J, Skogar S, Grybäck P, Jacobsson H, Holst JJ, Hellström PM. Glucagon-like peptide-1 slows solid gastric emptying with inhibition of insulin, C-peptide, glucagon and YY peptide release in humans. Am J Physiol 1999;277:R910–6.
[62] Nauck MA, Niedereichholz U, Ettler R, Holst JJ, Ørskov C, Ritzel R, Schmiegel WH. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol 1997;273:E981–8.
[63] Imeryüz N, Yegen BC, Bozkurt A, Coskun T, Villanueva-Penacarrillo NB, Ulusoy NB. Glucagon-like peptide-1 inhibits gastric emptying via vagal afferent-mediated central mechanisms. Am J Physiol 1997;273:G920–7.
[64] Wettergren A, Wøjdemann M, Meisner S, Stadil F, Holst JJ. The inhibitory effect of glucagon-like peptide-1 (GLP-1) 7–36 amide on gastric acid secretions in humans depends on an intact vagal innervation. Gut 1997;40:597–601.
[65] Wettergren A, Wøjdemann M, Holst JJ. Glucagon-like peptide-1 inhibits gastropancreatic function by inhibiting central parasympathetic outflow. Am J Physiol 1998;275:G984–92.
[66] Tolessa T, Gutniak M, Holst JJ, Efendic S, Hellstrom PM. Glucagon-like peptide-1 retards gastric emptying and small bowel transit in the rat: effect mediated through central or enteric nervous mechanisms. Dig Dis Sci 1998;43:2284–90.
[67] Lambert PD, Wilding PH, Ghatei MA, Bloom SR. A role for GLP-1-(7–36)-NH_2 in the central control of feeding behaviour. Digestion 1994;54:360–1.
[68] Tang-Christensen M, Larsen PJ, Göke R, FinkJensen A, Jessop DS, Møller M, Sheikh SP. Central administration of GLP-1 (7–36) amide inhibits food and water intake in rats. Am J Physiol 1996; 271:R848–56.
[69] Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CMB, Meeran K, Choi SJ, Taylor GM, Heath MM, Lambert PD, Wilding JP, Smith DM, Ghatei MA, Herbert J, Bloom SR. A role for glucagon-like peptide-1 in the central regulation of feeding. Nature 1996;385:69–72.
[70] Bloom SR. Glucagon-like peptide-1 and satiety. Nature 1997;385:214.
[71] Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide-1 promotes satiety and suppresses energy intake in humans. J Clin Invest 1998;101:515–20.
[72] Gutzwiller JP, Göke B, Drewe J, Hildebrand P, Ketterer S, Handschin R, Winterhalder R, Conen D, Beglinger C. Glucagon-like peptide-1: a potent regulator of food intake in humans. Gut 1999;44:81–6.
[73] Flint A, Raben A, Rehfeld JF, Holst JJ, Astrup A. The effect of glucagon-like peptide-1 on energy expenditure and substrate metabolism in humans. Int J Obes 2000;24:288–98.
[74] Gutzwiller JP, Drewe J, Göke B, Schmidt H, Rohrer B, Lareida J, Beglinger C. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol 1999;276:R1541–4.
[75] Toft-Nielsen MB, Madsbad S, Holst JJ. Continuous subcutaneous infusion of glucagon-like peptide-1 lowers plasma glucose and reduces appetite in type 2 diabetic patients. Diabetes Care 1999;22: 1137–43.
[76] Näslund E, Gutniak M, Skogar S, Rössner S, Hellström PM. Glucagon-like peptide-1 (GLP-1) increases the period of postprandial satiety and slows gastric emptying in obese humans. Am J Clin Nutr 1998; 68:525–30.
[77] Näslund E, Barkeling B, King N, Gutniak M, Blundell JE, Holst JJ, Hellström PM. Energy intake and appetite are suppressed by glucagon-like peptide-1 in obese men. Int J Obes 1999;23:304–11.
[78] Kong MF, Chapman I, Goble E, Wishart J, Wittert G, Morris H, Horowitz M. Effects of oral fructose and glucose on plasma GLP-1 and appetite in normal subjects. Peptides 1999;20:545–51.
[79] Ranganath LR, Beety JM, Morgan LM, Wright JW, Howland R, Marks V. Attenuated GLP-1 secretion in obesity: cause or consequence. Gut 1996;38:916–9.
[80] Näslund E, Grybäck P, Backman L, Jacobsson H, Holst JJ, Theodorsson E, Hellström PM. Small bowel gut hormones: correlation to fasting antroduodenal motility and gastric emptying. Dig Dis Sci 1998;43:945–52.
[81] Ranganath L, Norris F, Morgan L, Wright J, Marks V. Inhibition of carbohydrate-mediated glucagon-like peptide-1 (7–36)amide

secretion by circulating non-esterified fatty acids. Clin Sci 1999;96: 335–42.
[82] Clément K, Dina C, Basdevant A, Chastang N, Pelloux V, Lahlou N, Berlan M, Langin D, Guy-Grand B, Froguel P. A sib-pair analysis study of 15 candidate genes in French families with morbid obesity: indication for linkage with islet 1 locus on chromosome 5q. Diabetes 1999;48:398–402.
[83] Tsai CH, Hill M, Drucker DJ. Biological determinants of intestinotrophic properties of GLP-2. Am J Physiol 1997;272:G662–8.
[84] Lovshin J, Drucker DJ. New frontiers in the biology of GLP-2. Regul Pept 2000;90:27–32.
[85] Wøjdemann M, Wettergren A, Hartmann B, Holst JJ. Glucagon-like peptide-2 inhibits centrally induced antral motility in pigs. Scand J Gastroenterol 1998;33:828–32.