Anorexigenic Effects of GLP-1 and Its Analogues

Baptist Gallwitz

Contents

Abstract GLP-1 receptors are expressed in the brain, especially in the regions responsible for the regulation of food intake, and intracerebroventricular injection of GLP-1 results in inhibition of food intake. Peripheral administration of GLP-1 dose-dependently enhances satiety and reduces food intake in normal and obese subjects as well as in type 2 diabetic patients. So far, the mechanisms by which GLP-1 exerts its effects are not completely clear. Interactions with neurons in the gastrointestinal tract or possibly direct access to the brain through the blood–brain barrier as observed in rats are possible and discussed in this chapter as well as a novel hypothesis based on the finding that GLP-1 is also expressed in taste cells. Finally, the role of GLP-1 receptor agonists as a possible treatment option in obesity is discussed as well as the role of GLP-1 in the effects of bariatric surgery on adiposity and glucose homeostasis.

B. Gallwitz (✉)
Medizinische Klinik IV, Otfried-Müller-Str. 10, 72076 Tübingen, Germany
e-mail: baptist.gallwitz@med.uni-tuebingen.de

H.-G. Joost (ed.), *Appetite Control*, Handbook of Experimental Pharmacology 209,
DOI 10.1007/978-3-642-24716-3_8,

Keywords Bariatric surgery • GLP-1 • GLP-1 receptor agonists • Gut-brain axis • Incretins • Obesity

1 Incretin Hormones

Upon stimulation by nutrients after a meal, the intestinal mucosa secretes the gastrointestinal hormones GLP-1 and GIP (*g*astric *i*nhibitory *p*olypeptide or *g*lucose-dependent *i*nsulinotropic *p*olypeptide) from the endocrine L and K cells, respectively (Wellendorph et al. 2009). Both hormones are responsible for approximately 60% of the postprandial insulin secretion and contribute to the so-called incretin effect. This effect describes the phenomenon that orally ingested glucose leads to a much larger insulin response than an isoglycemic, intravenous glucose load (Creutzfeldt 1979; Nauck et al. 1986).

Exogenous GLP-1 application either by subcutaneous or intravenous injection resulting in supraphysiological GLP-1 plasma concentrations restores the incretin effect with an adequate insulin response under hyperglycemic conditions (Nauck et al. 1993).

2 Biosynthesis of GLP-1 and Overview on Its Pleiotropic Actions

The glucagon gene encodes a large peptide sequence of 158 amino acids that contains not only the sequence of glucagon but also that of other peptides that are formed posttranslationally by organ-specific and cell-specific processing (Bell et al. 1983; Holst et al. 2007; Ørskov et al. 1987). In the neuroendocrine L cells of the intestinal mucosa and in the central nervous system, preproglucagon is cleaved mainly to generate GLP-1. In the pancreatic alpha cells of the islets, glucagon is the major biologically active peptide generated from preproglucagon. Figure 1 shows the schematic tissue-specific posttranslational processing of GLP-1.

GLP-1 binds to highly specific GLP-1 receptors that belong to the G protein coupled seven-transmembrane-spanning (7TM) receptors (Drucker and Nauck 2006). After binding to its receptor, adenylate cyclase is activated, and GLP-1 effects are mediated mainly via the cAMP and protein kinase A pathways (Gromada et al. 1996; Reimer 2006). GLP-1 shows numerous physiological actions in various tissues and a broad therapeutic potential (see Fig. 2 for details).

The two most important metabolic actions of GLP-1 are that it stimulates insulin secretion of the pancreatic beta cells and additionally inhibits glucagon secretion from the alpha cells. These two actions on the islet occur in a strictly glucose-dependent manner and lead to a normalization of hyperglycemia. Under hypoglycemic conditions, the counter-regulation by glucagon is not affected, and insulin secretion is not stimulated. GLP-1 is therefore not able to elicit hypoglycemia by

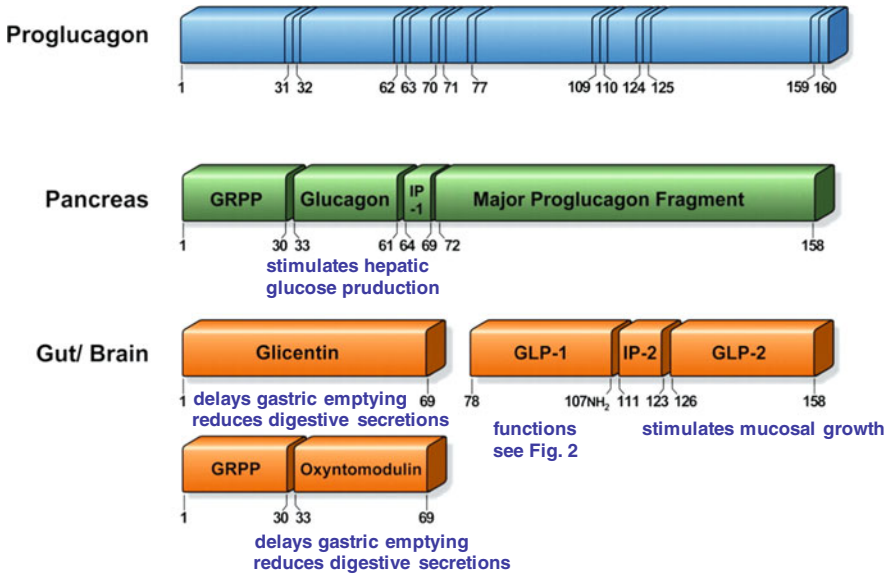

Fig. 1 *Posttranslational processing of proglucagon in different tissues*. Differential posttranslational processing of proglucagon in the pancreas and in the gut and brain. The *numbers* indicate amino acid positions in the 160-amino acid proglucagon sequence. The *vertical lines* indicate positions of basic amino acid residues, typical cleavage sites. *GRPP* glicentin-related pancreatic polypeptide, IP-1 *intervening peptide-1*, IP-2 *intervening peptide-2*. The major known biological actions of the peptides resulting from proglucagon processing are also shown (adapted from Holst 2007 and Pellissier et al. 2004)

itself. These physiological properties of GLP-1 later translated into the pharmacotherapy of type 2 diabetes with incretin-based therapies (Drucker and Nauck 2006).

Like other gastrointestinal regulatory peptides, GLP-1 has multiple further actions. In the gastrointestinal tract, GLP-1 slows gastric emptying after a meal. This effect also contributes to a normalization of postprandial hyperglycemia, promotes a feeling of fullness and possibly a secondary reduction of appetite (Meier et al. 2003a; Holst et al. 2008). In addition, GLP-1 binds to its receptor on hypothalamic neurons and stimulates satiety by direct actions described in detail in this chapter. These two satiety-promoting effects explain that long-term treatment with GLP-1 receptor agonists leads to long-term weight loss that persists as long as GLP-1 is given (Drucker and Nauck 2006).

Animal studies in different rodent species and studies in isolated human islets showed beneficial long-term actions of GLP-1: insulin synthesis is stimulated, and beta-cell mass is restored in rodent models of type 2 diabetes (Brubaker and Drucker 2004; Drucker and Nauck 2006; Fehmann and Habener 1992). Presently, it is not known whether these findings reflect an additional benefit in type 2 diabetes therapy in that GLP-1 slows or even stops disease progression. Long-term study data from clinical studies or clinical use of GLP-1 receptor agonists (GLP-1 RA) in type 2 diabetes with a sufficient observation time are still not yet available.

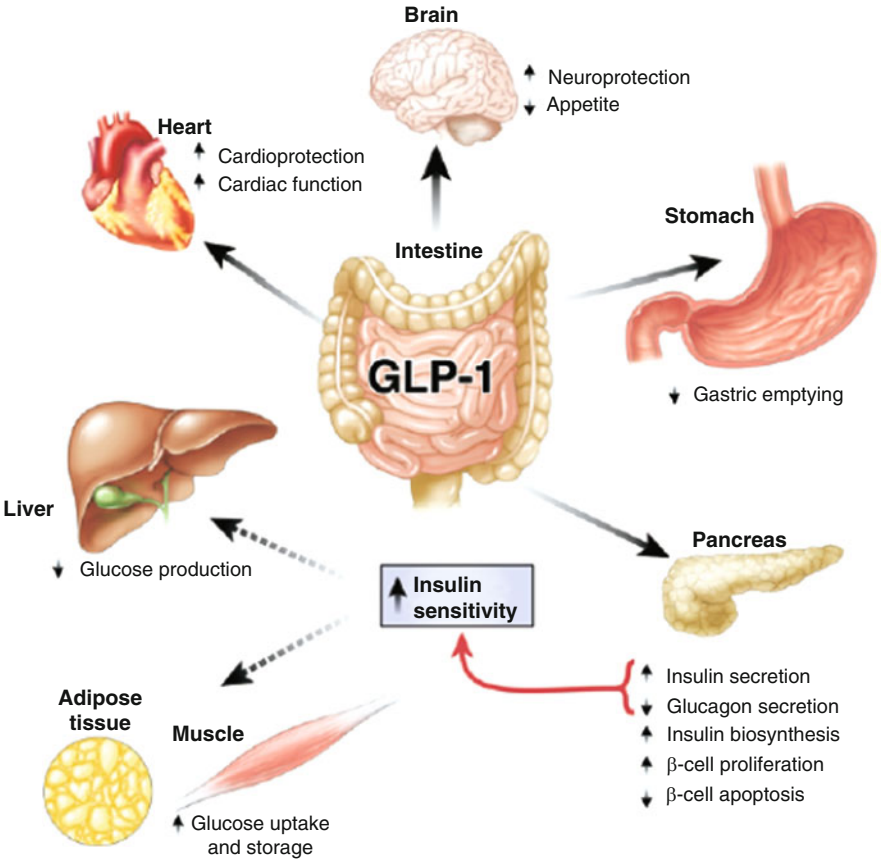

Fig. 2 *GLP-1 actions in peripheral tissues*. The majority of the effects of GLP-1 are mediated by direct interaction with GLP-1Rs on specific tissues. However, the actions of GLP-1 in liver, fat, and muscle most likely occur through indirect mechanisms (adapted from Baggio and Drucker 2007)

Furthermore, there are presently no reliable, validated methods to quantify beta cell mass in humans in a clinical setting.

Additionally, recent studies demonstrated that therapeutic application of GLP-1 or GLP-1 RA improved cardiovascular parameters. Systolic blood pressure is lowered by GLP-1 RA treatment for type 2 diabetes, and beneficial effects of GLP-1 on myocardial ischemia were observed in animal models as well as positive effects on left ventricular function in heart failure. These promising effects may also have important clinical implications for type 2 diabetes therapy with GLP-1 RA (Courreges et al. 2008; Klonoff et al. 2008; Sokos et al. 2006).

GLP-1 receptors are also expressed in the brain, especially in the regions responsible for the regulation of food intake (Göke et al. 1995), and intracerebroventricular injection of GLP-1 results in inhibition of food intake (Tang-Christensen

et al. 1996; Turton et al. 1996). Peripheral administration of GLP-1 dose-dependently enhances satiety and reduces food intake in normal subjects (Flint et al. 1998; Verdich et al. 2001), obese subjects (Näslund et al. 1999), and type 2 diabetic patients (Gutzwiller et al. 1999; Zander et al. 2002). The mechanisms by which GLP-1 exerts its effects are not completely clear yet. Interactions with neurons in the gastrointestinal tract or possibly direct access to the brain through as observed in rats (Ørskov et al. 1996) are possible and discussed in this chapter as well as other novel hypothesis based on the finding that GLP-1 is also expressed in taste cells. Finally, the role of GLP-1 receptor agonists as possible treatment options in obesity is discussed as well as the role of GLP-1 in the weight losing and metabolic effects after various methods of bariatric surgery.

3 Central Effects of GLP-1

3.1 Direct Dentral Effects of GLP-1 in the Hypothalamus

As early as in 1988, it was shown that GLP-1 is also synthesized in the CNS in the caudal part of the nucleus of the solitary tract (Jin et al. 1988) in addition to its peripheral synthesis in the intestinal L cell. Receptors for GLP-1 are expressed throughout the brain widely, with highest levels in the paraventricular nucleus (Larsen et al. 1997b; Van Dijk et al. 1996; Turton et al. 1996). The presence of both, the peptide GLP-1 and the GLP-1 receptor, in the CNS points toward important physiological actions of GLP-1 in the CNS in addition to its actions on the peripheral system.

The first report that GLP-1 exerted effects in the central nervous system (CNS) came from Turton and colleagues. This group gave intracerebroventricular (icv) injections of GLP-1 to rats. The injections reduced the food intake of the animals compared to saline-treated control rats (Turton et al. 1996). The group also demonstrated the presence of GLP-1-containing neurons in the rat brain in hypothalamic areas that are known to be responsible for regulating satiety and food intake.

Since then, there has been a great interest in understanding the role of GLP-1 in the regulation of food intake and satiety. In the rat, other groups confirmed the findings of Turton by using either GLP-1 or exendin-4, a naturally occurring GLP-1 RA (Meeran et al. 1999; Turton et al. 1996; Tang-Christensen et al. 1996). In humans, subcutaneous or intravenous application of GLP-1 also reduced hunger and food intake, prandial injections in obese subjects led to a reduction in food intake (Näslund et al. 2004). Blocking GLP-1 action in the CNS by using the GLP-1 receptor antagonist exendin(9–39) increased food intake in rats that had had icv injections with exendin(9–39), and additionally facilitated weight gain in these animals after long-term administration (Turton et al. 1996).

Icv injections of GLP-1 receptor agonists inhibit food intake in rodents (Turton et al. 1996; Meeran et al. 1999). Repeated icv administration of GLP-1 in rats leads to weight loss (see Fig. 3). Conversely, icv injection of the GLP-1 receptor antagonist exendin(9–39) promoted weight gain in the animals, and exendin(9–39) administered simultaneously with the central orexigenic agent neuropeptide Y (NPY) resulted in an increased food intake and weight gain compared with that observed with neuropeptide Y alone (Meeran et al. 1999; Abu-Hamdah et al. 2009). In this respect, it is important that the intestinal L cells cosecrete GLP-1 and peptide YY (PYY). Immunohistological studies demonstrated that these peptides are

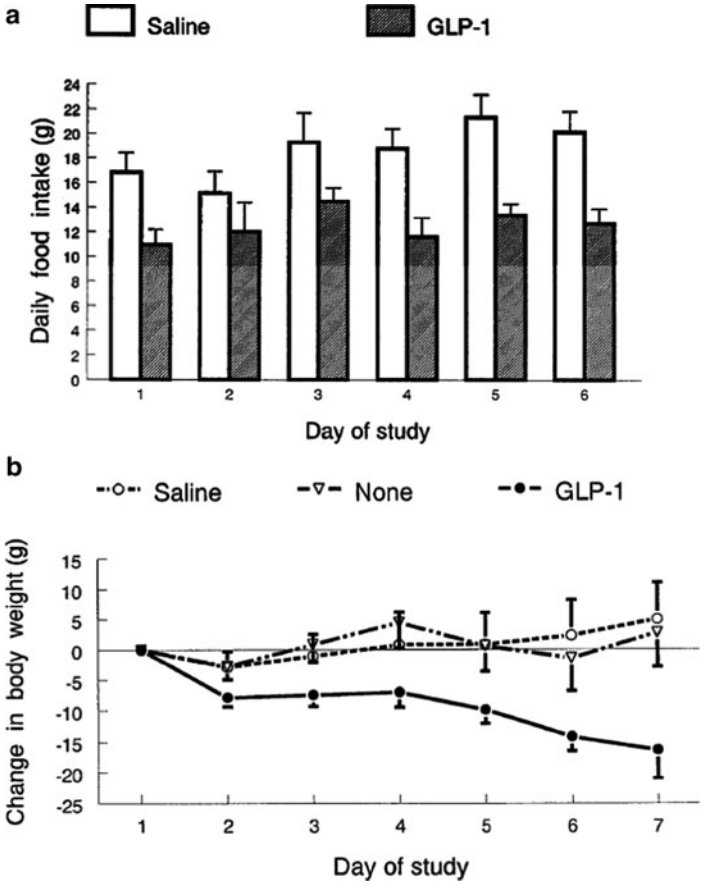

Fig. 3 *Effect of multiple icv injections of GLP-1 on food intake and body weight*. Food intake (**a**) and body weight (**b**) after daily icv injection of GLP-1 or saline as control are shown. The *hatched bars* and *filled circles* represent animals given 3 nmol GLP-1, and the *open bars* and *open circles* represent control animals that received saline. Food intake and body weight were significantly decreased through the study period in animals receiving GLP-1 ($P < 0.05$ for both groups). Body weight was similar in noninjected controls (*open triangles*) and those given icv normal saline (from Meeran et al. 1999 with permission)

colocalized and coreleased from these cells. The truncated PYY(3–36), comprising the major circulating form of PYY, has been reported to be a potent anorexigenic agent in rats as well as in man (Batterham et al. 2002, 2003). Although these effects have not been reproduced by others (Tschöp et al. 2004; Boggiano et al. 2005), it was suggested that the corelease of GLP-1 and PYY has an important roles in the mediation of satiety (Abu-Hamdah et al. 2009).

It has further been demonstrated that GLP-1 may play a role in the regulation of the hypothalamic pituitary axis via effects on CRH, LH, TSH, oxytocin, and vasopressin secretion (Beak et al. 1996, 1998). The available evidence suggests that taste and/or food aversion induced by GLP-1 is mediated by different CNS pathways (Kinzig et al. 2002; Seeley et al. 2000; Tang-Christensen et al. 1996).

The GLP-1 receptor is widely expressed in the rodent brain in the hypothalamic arcuate nucleus (ARC), the paraventricular nucleus (PVN), and supraoptic nuclei (Shughrue et al. 1996). Furthermore, GLP-1 neurons of the solitary tract predominantly project into the PVN (Larsen et al. 1997a). The food-intake decreasing effect of GLP-1 in rodents is associated with an increase in c-Fos expression in the ARC (Larsen et al. 1997b). In rats treated with monosodium glutamate, the inhibitory effect of GLP-1 on hunger-induced feeding was completely abolished (Tang-Christensen et al. 1998). Additionally, GLP-1 stimulates the electrical activity of proopiomelanocortin (POMC) neurons via the protein kinase A pathway and a consecutive increase of L-type calcium currents (Ma et al. 2007). These findings suggest that the hypothalamic ARC may play a role in GLP-1-induced inhibition of food intake.

The regulation of energy balance involves the interaction of numerous regulatory peptides and neurotransmitters in the hypothalamus. The orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide (AgRP) as well as the anorexigenic peptides POMC and cocaine- and amphetamine-related transcripts (CART) are produced in the ARC of the hypothalamus and play an important role in the regulation of energy intake and energy expenditure (Schwartz et al. 2000). The hypothalamic neurons are sensitive to satiety and hunger signals such as cholecystokinin (CCK) and ghrelin. These hypothalamic neurons are also sensitive to signals of long-term energy stores such as insulin and leptin (Schwartz et al. 2000). However, the effect of GLP-1 on the expression of these hypothalamic mediators is not completely known. NPY and AgRP expression as measured by mRNA concentrations is increased during fasting. These hunger-induced increases are significantly diminished by icv injections of GLP-1. Conversely, the expressions of POMC and CART are decreased during fasting, and again, these changes are attenuated by the icv injection of GLP-1. Additionally, when determining mRNA concentrations of AMP-activated kinase (AMPK), a stimulation of hypothalamic AMPKα2 could be observed during fasting that was also inhibited by GLP-1 application. In summary, these findings suggest that the decreased food intake mediated by GLP-1 is facilitated by the above mentioned changes of orexigenic and anorexigenic hypothalamic neurotransmitter expression changes (Seo et al. 2008).

Another regulatory system most likely to be involved is a GLP-1-mediated activation of the hypothalamo–pituitary–adrenocortical (HPA) axis (Larsen et al. 1997a; Larsen et al. 1997b). This mechanism primarily involves the stimulation of corticotropin-releasing factor (CRF) neurons by GLP-1, and this activation may also be responsible for the inhibition of feeding behavior. There seem to be species differences regarding this regulatory mechanism: in rats, plasma concentrations of corticosterone were rapidly increased after central administration of GLP-1, whereas icv injections of GLP-1 did not alter plasma corticosterone concentrations in the neonatal chick (Furuse et al. 1997).

In neonatal chicks, a noradrenergic mechanism was shown to contribute to the anorexigenic effect of GLP-1 (Bungo et al. 2001a). Icv administration of norepinephrine (NE) suppressed food intake and produced narcolepsy comparable to the effect of GLP-1 in chicks. Although dopamine (DA) did not alter food intake, the coadministration of inhibitors of dopamine-b-hydroxylase (DBH) or fusaric acid (FA) attenuated the suppressive effect of GLP-1 on feeding behavior. Thus, it is suggested that there may be interactive relationships between GLP-1 and noradrenergic regulatory systems in chicks (Bungo et al. 2001b), and that additionally, there may be species differences in GLP-1-mediated appetite control.

3.2 GLP-1 in Taste Cells

GLP-1 and PYY are secreted not only from L cells in the small intestine but also from mammalian taste cells. Both cell types, human duodenal L cells and taste cells of the tongue, express the sweet taste receptor G protein gustducin that may additionally be involved in the regulation of GLP-1 release (Jang et al. 2007). In many L cells, GLP-1, gustducin, and PYY are colocalized (Jang et al. 2007). Furthermore, GLP-1 is produced in two subsets of mammalian taste cells (type 2 and type 3).The corresponding GLP-1 receptors are present on adjacent intragemmal afferent nerve fibers (Shin et al. 2008). It is therefore hypothesized that GLP-1 (and PYY) activates anorexigenic CNS events prior to stimulating islet hormones (Egan and Margolskee 2008).

3.3 Central Effects of GLP-1 Influencing Gastrointestinal Functions

It has also been demonstrated already in 1997 that icv injections of GLP-1 cause a retardation of liquid gastric emptying (Imeryüz et al. 1997). Nakade and his group showed that the peripheral sympathetic nervous system and the central CRF receptors are involved in the central GLP-1-mediated delay of solid gastric emptying in rats (Nakade et al. 2006).

4 Peripheral Effects of GLP-1 Affecting Satiety

GLP-1 exerts potent and important inhibitory effects on gastric emptying and gastric acid secretion. It is primarily responsible for the "ileal break," a tightly regulated process under neural and hormonal control that regulates the passage of nutrients through the digestive tract. GLP-1 enhances satiety and reduces food intake (Pitomobo 2008). GLP-1 inhibits these proximal events of the gastrointestinal tract in a negative feedback manner (Ahren 2004). Nauck and colleagues were able to inhibit gastric emptying after a liquid meal by icv administration of GLP-1 in healthy, normoglycemic volunteers (Nauck et al. 1997). The observed effect of GLP-1 on gastric emptying was dose dependent and highly significant with physiological GLP-1 plasma concentrations (Nauck et al. 1997; Meier et al. 2002, 2003a) (see Fig. 4). Another study in healthy volunteers investigated the effect of two different doses of GLP-1 (0.125-nmol/kg or 0.25-nmol/kg body weight) administered subcutaneously 5 min prior to a mixed test meal (Schirra et al. 1997). The pattern of gastric emptying of the mixed meal as well as pancreatic secretion, antroduodenal motility, and the glycemic response and the release of insulin, C-peptide, and glucagon were quantified. The lag period or the time to reach maximal velocity of gastric emptying was dose-dependently prolonged in response to the subcutaneous application of GLP-1. However, the maximal emptying velocity, the total emptying rate, and the exponential emptying rate were unaltered (Schirra et al. 1997). The subcutaneous infusion of GLP-1 resulted in a dose-dependent inhibition of antral and duodenal motility, and both doses of GLP-1 led to coordinated antroduodenal contractions. GLP-1 initially reduced and then transiently stimulated the secretion of pancreatic enzymes. Both doses of GLP-1 delayed the postprandial insulin peak and enhanced total insulin release. The postprandial response of pancreatic polypeptide and glucagon was diminished (Schirra et al. 1997).

In another study, the same group investigated the antropyloroduodenal motility in humans and the actions of endogenously released GLP-1 on endocrine pancreas secretion (Schirra et al. 2006). In this study, the GLP-1 receptor antagonist exendin (9–39) was used to test whether GLP-1 acts as an incretin and/or as an enterogastrone in humans. The endogenously secreted GLP-1 significantly enhanced postprandial insulin secretion and suppressed the secretion of glucagon (Schirra et al. 2006). During the fasting and postprandial state, antroduodenal motility was inhibited by GLP-1, which qualifies GLP-1 as an enterogastrone. The stimulation of pyloric motility that is induced by intestinal glucose was mediated by GLP-1. The presence of nutrients in the small intestine stimulates the L cells to release GLP-1 into the circulation. The rise in GLP-1 concentrations not only stimulates the beta cells to produce insulin but also slows gastric emptying and may lead to a decrease in appetite and a sensation of fullness (Näslund et al. 1999; Flint et al. 2001; Meier et al. 2003b; Silvestre et al. 2003; Ling et al. 2001; Nagai et al. 2004).

The mechanisms by which GLP-1 inhibits gastric emptying appear to be complex and to involve communication with the central and peripheral nervous systems

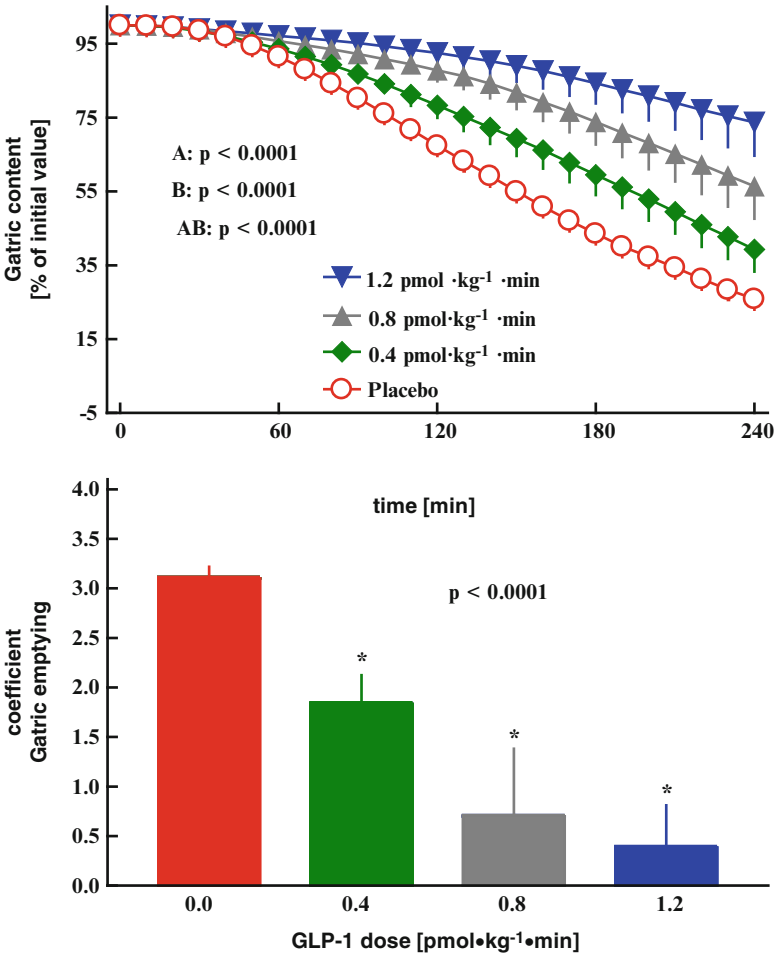

Fig. 4 *Time and dose dependency of GLP-1 on gastric emptying in humans*. Panel A: Time pattern of gastric emptying of a solid meal (250 kcal) during icv administration of different doses of GLP-1 (0.4, 0.8, and 1.2 pmol/kg/min; *filled symbols*) or placebo (*open symbols*) in patients with type 2 diabetes ($n = 12$). Gastric emptying was determined from the measurement of $^{13}CO_2$ in breath samples collected after the ingestion of the test meal labeled with [^{13}C] octanoic acid using infrared absorptiometry. Data are expressed as the mean + SE. *P* values were calculated using repeated measures ANOVA and denote: A, differences between the doses tested; B, differences over time; and AB, differences due to the interaction of experiment and time. Panel B: Gastric emptying coefficients. Data are expressed as the mean + SE. Asterisks indicate significant differences ($P < 0.05$) versus placebo. (from Meier et al. 2003a with permission)

(D'Alessio 2008; Drucker 2006). Gastric distension increases the expression of c-Fos in brain stem neurons that produce GLP-1 (Vrang et al. 2003). Furthermore, icv administration of GLP-1 resulted in reduction of food intake (Kinzig et al. 2002), which is accompanied with increased expression of c-Fos in the brain stem of the rat (Larsen et al. 1997b; Dakin et al. 2004). The denervation of afferent vagal

fibers abolishes the effects of GLP-1 on gastric emptying in the rat (Imeryüz et al. 1997). The stimulation to the CNS is most likely responsible for the reduction in food intake, inhibition of gastric emptying, as well as inhibitory action on gastric motor function (Kinzig et al. 2002; Imeryüz et al. 1997). These actions are most likely mediated by increased action potential and calcium influx in neurons of the nodose ganglion (Kakei et al. 2002).

Although small peptides such as GLP-1 and exendin-4 are capable of rapidly crossing the blood–brain barrier and directly accessing the CNS, GLP-1 receptor agonists with a larger molecule size and a higher molecular weight, such as albumin-bound GLP-1, that do not cross the blood–brain barrier, are still capable of inhibiting gastric emptying and food intake (Baggio et al. 2004). These findings underline the importance of ascending vagal afferents for the GLP-1 receptor-dependent control of gastrointestinal motility. Interestingly, studies by Meier and his group (Meier et al. 2005) showed that antagonizing the delaying effects of GLP-1 on gastric emptying by a prokinetic agent such as erythromycin resulted in an augmentation of the insulin secretory response after meal ingestion. GLP-1 receptors are also directly expressed in the stomach on gastric parietal cells, where GLP-1 may directly regulate gastric acid secretion (Schmidtler et al. 1994). However, the effects of GLP-1 on gastric acid secretion were found to be absent in vagotomized human subjects (Wettergren et al. 1997). Hence, considerable evidence supports the importance of vagal innervation for GLP-1 regulation of gastric secretion and motility.

These observed effects of delayed gastric emptying have been generally demonstrated with at least physiological or, as in most studies, supraphysiological doses of exogenously administered GLP-1 (Delgado-Aros et al. 2002; Schirra et al. 1996). Therefore, it remains unclear whether endogenously released GLP-1 has a significant effect on gastric emptying. Studies in healthy baboons have shown that with intragastric infusion of glucose and D-xylose (a marker for rate of emptying of glucose from stomach), plasma levels of D-xylose were similar when the effects of GLP-1 were blocked with exendin(9–36) amide or with a specific monoclonal antibody to GLP-1 (D'Alessio et al. 1996; D'Alessio 2008). These findings suggest that gastric emptying is not increased when the effects of GLP-1 are blocked, at least in the baboon. The use of a DPP-4 inhibitor, which increases plasma concentrations of endogenous GLP-1, might be expected to delay gastric emptying, but a study in patients with type 2 diabetes and DPP-4 inhibitor treatment did not reveal any changes in the gastric emptying of a solid meal (Vella et al. 2007). Most recently, an iv-oral hyperglycemic clamp study in humans was reported during which 75-g glucose-containing D-xylose was ingested. During the entire clamp, plasma glucose levels were held at a steady level despite the ingestion of glucose. Two studies were conducted, with blockade of GLP-1 receptor in one. The rate of appearance of ingested D-xylose was not different between the two studies, indicating that endogenously released GLP-1 has at best only a modest effect on gastric emptying (Salehi et al. 2008).

In a variety of endocrine regulatory systems, a negative feedback mechanism regulates the secretion of the hormone, e.g., the reproductive hormone regulation by

the hypothalamus. Exogenous infusion of a hormone may also exert negative feedback regulation of the endogenously released hormone. An example of this is the documented suppression of C-peptide plasma concentrations when insulin is infused (Elahi et al. 1982). In this context, it is presently still not known whether exogenously administered GLP-1 really has a significant impact on the regulation of endogenously released GLP-1.

5 Effects of GLP-1 Receptor Agonists on Body Weight in Humans

Native GLP-1 cannot be used in a feasible way for treatment of type 2 diabetes or obesity due to its very short biological half-life of 1–2 min. For this reason, long-acting GLP-1 receptor agonists were developed. In 1992 exendin-4, a reptilian peptide isolated from the lizard *Heloderma suspectum* was identified as a long-acting GLP-1 receptor agonist (Raufman et al. 1992; Göke et al. 1993). Exendin-4 has a 53% sequence homology with GLP-1 and has a biological half-life of approximately 3.5 h. The synthetic form of exendin-4, exenatide, was the first GLP-1 receptor agonist that was approved for type 2 diabetes therapy in patients not sufficiently controlled on a therapy with metformin or sulfonylureas or a combination of both (Klonoff et al. 2008). Exenatide (Byetta®, Eli Lilly Pharmaceuticals, Indianapolis, USA and Amylin Pharmaceuticals, San Diego, USA) is given subcutaneously twice daily.

Liraglutide (Victoza®, Novo Nordisk Pharmaceuticals, Copenhagen, Denmark) was the first human GLP-1 analogue that was developed for once daily subcutaneous application. Liraglutide has a half-life of 13.5 h. It has a fatty acid side chain that allows heptamer formation of the molecule that prevents direct DPP-4 action as well as fast dissociation from the subcutaneous tissue into the circulation. Furthermore, the fatty acid side chain allows albumin binding that further protracts degradation and prolongs biological availability (Garber et al. 2009; Madsbad et al. 2011).

Presently, even longer-acting GLP-1 receptor analogues are being developed in order to reduce the frequency of injections, to reduce fasting glucose more efficiently, and to reduce the gastrointestinal side effects (mainly fullness and nausea) that are associated with the fluctuation of GLP-1 receptor agonist plasma concentrations. Compounds with an exendin-4/exenatide backbone are exenatide once weekly (Bydureon®, Eli Lilly Pharmaceuticals, Indianapolis, USA and Amylin Pharmaceuticals, San Diego, USA) that has just received a positive opinion by the regulatory agencies in the United States and Europe and is expected to be marketed later in 2011 (Madsbad et al. 2011).

Lixisenatide (Sanofi-Aventis Pharmaceuticals, Paris, France) is an exendin-4 analogue for once daily application, presently in phase III of the clinical study program (Christensen et al. 2011; Madsbad et al. 2011).

Albiglutide, an albumin-bound-human GLP-1 fusion protein (GlaxoSmithKline Pharmaceuticals, London, UK) is feasible for once weekly dosing and is also presently in phase III of the clinical study program (Madsbad et al. 2011; St Onge and Miller 2011).

Another human GLP-1 receptor agonist in earlier development for once weekly dosing is LY2189265 (Dulaglutide, Eli Lilly Pharmaceuticals, Indianapolis, USA) (Glaesner et al. 2010; Madsbad et al. 2011). Table 1 gives an overview on the GLP-1 receptor agonists available and in development and their respective characteristics.

Chronic peripheral administration of GLP-1 RA agonists (exendin-4/exenatide and liraglutide) has consistently been associated with reductions in food intake and weight loss in animal studies and in humans (Szayna et al. 2000; Young et al. 1999; Schnabel et al. 2006; Garber et al. 2009). Also, weight loss was documented in a pivotal study in which a continuous 6-week infusion of GLP-1 was given to obese type 2 diabetic patients (Zander et al. 2002). Conversely, a continuous subcutaneous administration study of a lower dose of GLP-1 (1.5 pmol·kg^{-1}·min^{-1}) for 12 weeks

Table 1 *GLP-1 receptor agonists and their characteristics*. The available GLP-1 receptor agonists as well as substances advanced in clinical development are shown

Substance	Chemical backbone	Dosing interval	Approval/ developmental status
Exenatide (Byetta®, Eli Lilly and Amylin)	Exendin-4	Twice daily	Approved 2005
Liraglutide (Victoza®, NovoNordisk)	Human GLP-1 with two amino acid exchanges and a c-16 fatty acid side chain	Once daily	Approved 2009
Exenatide QW (Bydureon®, Eli Lilly and Amylin)	Exendin-4, incorporated into a matrix of poly(D,L-lactide-co-glycolide) (PLG) to prolong action	Once weekly	Approved 2011
Lixisenatide (Sanofi-Aventis)	Exendin-4, 44 amino acids with C-terminal extension (C-terminal with six Lys residues and one Pro deleted)	Once daily	Phase III clinical investigation
Albiglutide (Syncrea®, GlaxoSmithKline)	Human GLP-1 receptor agonist consisting of two copies of a 30-amino acid sequence of a dipeptyl peptidase-4-resistant human GLP-1 (as a tandem repeat) coupled to serum human albumin	Once weekly (planned)	Phase III clinical investigation
LY2189265 (Dulaglutide®, Eli Lilly)	DPP-4-protected GLP-1 analogue is fused to a modified immunoglobulin G4 (IgG4) Fc fragment	Once weekly (planned)	Phase III clinical investigation

produced no significant weight loss (Meneilly et al. 2003). This study most likely demonstrates that weight loss with exogenous GLP-1 administration is only possible, when much larger doses are given.

In most phase 3 studies with exenatide and liraglutide, the weight loss was in the range of 2–3 kg after 26 weeks of treatment compared with placebo, and greatest when added to metformin (Madsbad 2009). In studies with a longer duration, a plateau of the weight loss is seen in the same range (Garber et al. 2009, 2011).

Presently, long-acting GLP-1 receptor agonists that require a single weekly dose only, or other long-range dosing regimens, are in clinical development (Madsbad et al. 2011). Summarizing the known effects on body weight, there does not seem to be a difference between the short-acting, established GLP-1 RA and the novel long-acting ones. The weight loss in a study comparing the novel, once weekly GLP-1 RA albiglutide with exenatide did not reveal a significant difference in the body weight development. The weight loss amounted from −1.1 to −1.7 kg in the albiglutide groups compared with −0.7 kg in the placebo group and −2.4 kg in the exenatide group (Rosenstock et al. 2009).

Exenatide once weekly (exenatide QW) is a new dosage form of the active drug exenatide. Exenatide QW's microsphere technology enables very slow release due to the use of a slowly biodegradable polymer as the exenatide carrier. This changes both the effect and adverse effect profiles versus the short-acting receptor stimulation produced by the established, unretarded exenatide for twice daily application. Long-term stimulation of GLP-1 receptors results in superior lowering of fasting blood glucose levels and HbA1c (Kim et al. 2007). In subjects on first-line treatment with metformin, exenatide QW produced a superior HbA1c reduction. Because of the weaker inhibition of gastric emptying, gastrointestinal side effects are reduced by about one-third (20% with exenatide QW versus 35% with exenatide) (Linnebjerg et al. 2008; Wang et al. 2008). In addition, a relevant loss in mean weight (ranging from 2.3 kg to 3.7 kg) was seen in all studies (Drucker et al. 2008; Buse et al. 2010; Bergenstal et al. 2010; Diamant et al. 2010; Kim et al. 2007).

Another GLP-1 RA in development is CJC-1134-PC (ConjuChem, Montreal, Quebec, Canada), which consists of an exendin-4 molecule covalently linked to human recombinant albumin. Its half-life of approximately 8 days corresponds to that of circulating albumin (Thibaudeau et al. 2006; Baggio et al. 2008). At present, it is unclear whether the modest effect on body weight is explained by a reduced efficacy in engaging the central nervous system regions regulating appetite and body weight, because large proteins like albumin are not expected to cross the blood–brain barrier (Chuang et al. 2002). Alternatively, the compound can still regulate feeding and body weight via the vagus nerve (Abbott et al. 2005; Imeryüz et al. 1997).

With respect to weight control, no clinically significant differences seem to exist within the entire group of GLP-1 receptor agonists, although it remains possible that the CJC-1134-PC is less effective (Chuang et al. 2002; Wang et al. 2009).

With the short-acting GLP-1 RA liraglutide, a clinical study was performed in obese, nondiabetic subjects to investigate the efficacy and safety as a weight-loss-promoting drug. In a placebo-controlled 20-week trial, with an open-label

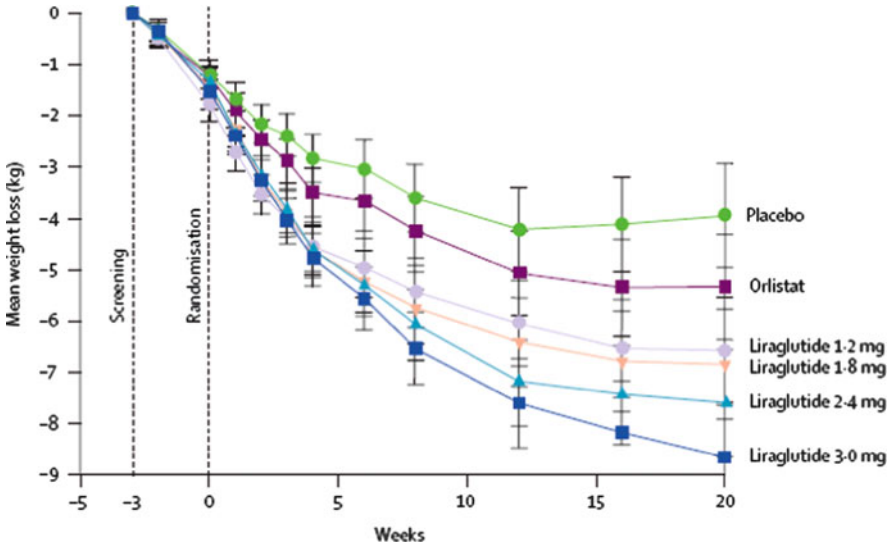

Fig. 5 *Dose dependent effects of the GLP-1 RA liraglutide on body weight in obese subjects*. Five hundred sixty-four individuals (age range 18–65 years, BMI 30–40 kg/m) were randomized to one of four liraglutide doses (1·2 mg, 1·8 mg, 2·4 mg, or 3·0 mg, $n = 90$–95) or to placebo ($n = 98$) administered once a day subcutaneously, or orlistat (120 mg, $n = 95$) three times a day orally. Weight change was analyzed by intention to treat. Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward (from Astrup et al. 2009 with permission)

orlistat (120 mg t.i.d.) comparator arm, study participants were assigned to arms of four liraglutide doses (1.2 mg/d, 1.8 mg/d, 2.4 mg/d, or 3.0 mg/d) or to placebo. Participants on liraglutide lost significantly more weight than did those on placebo and orlistat. The mean weight loss caused by liraglutide was dose dependent and amounted to 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg for the respective liraglutide doses (1.2 mg/d, 1.8 mg/d, 2.4 mg/d, or 3.0 mg/d) and was 2.1 kg greater than that in the placebo group. The weight loss with placebo amounted to 2.8 kg and with orlistat 4.1 kg (Astrup et al. 2009) (see Fig. 5).

6 GLP-1 and Bariatric Surgery

The mechanisms involved in weight loss and metabolic improvements after bariatric surgery are dependent on the type of surgery performed and are not yet completely understood. They are presently under thorough investigation. Changes in the size of the gastric pouch and the length and parts of the intestinal surfaces after bariatric surgery determine the contact of food with enteroendocrine cells and consequently also the gut hormonal response. Each type of bariatric surgery has

a different effect on hormonal secretion and thus may play a significant role in the mechanism of weight loss (Vetter et al. 2009).

Rubino and colleagues evaluated the early effects of Roux-Y gastric bypass (RYGB) on glucose, insulin, glucagon, insulin-like growth factor-1, GIP, GLP-1, CCK, adrenocorticotropic hormone (ACTH), corticosterone, and neuropeptide Y (Rubino et al. 2004; Thomas and Schauer 2010). RYGB led to a decrease in BMI paralleled by a significant decrease in glucose, insulin, leptin, and an increase in ACTH levels 3 weeks after surgery. The other hormones, especially GLP-1, did not change significantly. However, of the six diabetic patients in the study, all had normal glucose and insulin levels after surgery and did not require any diabetic medications.

It has been observed that the initial weight loss observed with either laparoscopic sleeve gastrectomy (LSG) as a restrictive surgical method or RYGB as a diversion method of surgery leads to similar results (Thomas and Schauer 2010). There are metabolic differences however, demonstrating that patients with RYGB show a rapid normalization of fasting glucose and an improvement of insulin clearance and sensitivity, but these changes do not occur in patients with LSG. Testing the different cohorts of patients after RYGB or LSG with a mixed meal tolerance test, the dramatic increase in insulin secretion and an increase in GLP-1 are only observed in the RYGB group (Thomas and Schauer 2010).

In obese patients with coexisting type 2 diabetes, both types of bariatric procedures were associated with an improvement of hyperglycemia. RYGB was associated with an insulinotropic response with an oral mixed meal but not with intravenous glucose, consistent with an incretin effect. These data suggest a different effect of the two procedures on pancreatic beta-cell function. The improvement may be due to insulin sensitivity and therefore a reduced insulin response following gastric restriction only (Thomas and Schauer 2010). It is still not known, however, whether the portion that is bypassed causes this effect or whether this effect is due to nutrients that rapidly reach the distal ileum and release insulinotropic and beta-cell-enhancing hormones (Kashyap et al. 2010). The limitations of the study are the small sample size and the sample being a nonrandomized convenience sample.

To evaluate the potential role of the exclusion of the proximal small intestine in the improvement of diabetes mellitus after gastric bypass surgery, Peterli and his group conducted a prospective, randomized, controlled trial comparing RYGB and LSG. Patients were evaluated 1 week and 3 months after surgery before and after a standard test meal. At 3 months, body weight and BMI decreased significantly and comparably in both groups with markedly increased postprandial plasma insulin and GLP-1 levels (Dirksen et al. 2010). RYGB patients had increased insulin responses as early as 1 week after the surgery; however, no significant differences were seen at 3 months in insulin or GLP-1 levels. Thus, both procedures improved glucose homeostasis, insulin, and GLP-1 and PYY levels (Peterli et al. 2009).

Two different hypotheses have been proposed to explain these conflicting data. One offered is the "hindgut explanation," suggesting that the rapid transit of nutrients to the distal intestine improves glucose metabolism by stimulating secretion of GLP-1 and other appetite-suppressing gut peptides such as PYY. Insulin

secretion is increased and glucose tolerance improves, affecting body weight and food intake (Cummings et al. 2007; Patrita et al. 2007). On the other hand, Rubino and his group proposed the "foregut hypothesis." They propose that there is a yet-unknown factor that promotes insulin resistance and type 2 diabetes. When food bypasses the duodenum and proximal jejunum after bariatric surgery, this so-called anti-incretin or decretin factor is inhibited, and thus insulin resistance is decreased and glucose tolerance improves. Other factors may help to explain the differences seen among the various types of procedures (Vetter et al. 2009; Cummings et al. 2008). Likewise, because GLP-1, PYY, and GIP are secreted by the small intestine, differences in the length of the roux limb may contribute to the secretion of these gut hormones and thus the results seen. Finally, as this is a relatively new, evolving field of research, there are most likely unknown factors to be considered (Thomas and Schauer 2010).

References

Abbott CR, Monteiro M, Small CJ, Sajedi A, Smith KL, Parkinson JR, Ghatei MA, Bloom SR (2005) The inhibitory effects of peripheral administration of peptide YY(3–36) and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal-brainstem-hypothalamic pathway. Brain Res 1044:127–131

Abu-Hamdah R, Rabiee A, Meneilly GS, Shannon RP, Andersen DK, Elahi D (2009) Clinical review: the extrapancreatic effects of glucagon-like peptide-1 and related peptides. J Clin Endocrinol Metab 94:1843–1852

Ahren B (2004) GLP-1 and extra-islet effects. Horm Metab Res 36:842–845

Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, Madsen J, Rasmussen MF, Lean ME, NN8022-1807 Study Group (2009) Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 374:1606–1616

Baggio LL, Drucker DJ (2007) Biology of incretins: GLP-1 and GIP. Gastroenterology 132:2131–2157

Baggio LL, Huang Q, Brown TJ, Drucker DJ (2004) A recombinant human glucagon-like peptide (GLP)-1-albumin protein (albugon) mimics peptidergic activation of GLP-1R-dependent pathways coupled with satiety, gastrointestinal motility, and glucose homeostasis. Diabetes 53:2492–2500

Baggio LL, Huang Q, Cao X, Drucker DJ (2008) An albumin-exendin-4 conjugate engages central and peripheral circuits regulating murine energy and glucose homeostasis. Gastroenterology 134:1137–1147

Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR (2002) Guthormone PYY(3–36) physiologically inhibits food intake. Nature 418:650–654

Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, Bloom SR (2003) Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med 349:941–948

Beak SA, Small CJ, Ilovaiskaia I, Hurley JD, Ghatei MA, Bloom SR, Smith DM (1996) Glucagon-like peptide-1 (GLP-1) releases thyrotropin (TSH): characterization of binding sites for GLP-1 on α-TSH cells. Endocrinology 137:4130–4138

Beak SA, Heath MM, Small CJ, Morgan DG, Ghatei MA, Taylor AD, Buckingham JC, Bloom SR, Smith DM (1998) Glucagon-like peptide-1 stimulates luteinizing hormone-releasing hormone secretion in a rodent hypothalamic neuronal cell line. J Clin Invest 101:1334–1341

Bell GI, Sanchez-Pescador R, Laybourn PJ, Najarian RC (1983) Exon duplication and divergence in the human preproglucagon gene. Nature 304:368–371

Bergenstal RM, Wysham C, Macconell L, Malloy J, Walsh B, Yan P, Wilhelm K, Malone J, Porter LE (2010) Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet 376:431–439

Boggiano MM, Chandler PC, Oswald KD, Rodgers RJ, Blundell JE, Ishii Y, Beattie AH, Holch P, Allison DB, Schindler M, Arndt K, Rudolf K, Mark M, Schoelch C, Joost HG, Klaus S, Thone-Reineke C, Benoit SC, Seeley RJ, Beck-Sickinger AG, Koglin N, Raun K, Madsen K, Wulff BS, Stidsen CE, Birringer M, Kreuzer OJ, Deng XY, Whitcomb DC, Halem H, Taylor J, Dong J, Datta R, Culler M, Ortmann S, Castaneda TR, Tschop M (2005) PYY3-36 as an anti-obesity drug target. Obesity Rev 6:307–322

Brubaker PL, Drucker DJ (2004) Minireview: glucagon-like peptides regulate cell proliferation and apoptosis in the pancreas, gut, and central nervous system. Endocrinology 145:2653–2659

Bungo T, Ando R, Kawakami S-I, Ohgushi A, Furuse M (2001a) The role of central catecholaminergic systems in regulation of food intake of chicks. J Poult Sci 38:35–40

Bungo T, Kawakami S-I, Ohgushi A, Sashihara K, Saito N, Sugahara K, Hasegawa S, Denbow DM, Furuse M (2001b) Intracerebroventricular injection of fusaric acid attenuates the anorexia by glucagon-like peptide-1 in the neonatal chick. Pharmacol Biochem Behav 70:251–255

Buse JB, Drucker DJ, Taylor KL, Kim T, Walsh B, Hu H, Wilhelm K, Trautmann M, Shen LZ, Porter LE (2010) DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes Care 33:1255–1261

Christensen M, Knop FK, Vilsbøll T, Holst JJ (2011) Lixisenatide for type 2 diabetes mellitus. Expert Opin Investig Drugs 20:549–557

Chuang VT, Kragh-Hansen U, Otagiri M (2002) Pharmaceutical strategies utilizing recombinant human serum albumin. Pharm Res 19:569–577

Courreges JP, Vilsboll T, Zdravkovic M, Le-Thi T, Krarup T, Schmitz O, Verhoeven R, Buganova I, Madsbad S (2008) Beneficial effects of once-daily liraglutide, a human glucagon-like peptide-1 analogue, on cardiovascular risk biomarkers in patients with Type 2 diabetes. Diabet Med 25:1129–1131

Creutzfeldt W (1979) The incretin concept today. Diabetologia 16:75–85

Cummings D, Overduin J, Foster-Schubert K, Carlson M (2007) Role of the bypassed proximal intestine in the anti-diabetic effects of bariatric surgery. Surg Obes Relat Dis 3:109–115

Cummings D, Foster-Schubert K, Carlson M, Shannon M, Overduin J (2008) Possible hormonal mechanisms mediating the effects of bariatric surgery. In: Pitomobo C, Jones K, Higa K, Pareja J (eds) Obesity surgery: principles and practice. McGraw-Hill, New York, NY, pp 137–147

D'Alessio D (2008) Intestinal hormones and regulation of satiety: the case for CCK, GLP-1, PYY, and Apo A-IV. JPEN J Parenter Enteral Nutr 32:567–568

D'Alessio DA, Vogel R, Prigeon R, Laschansky E, Koerker D, Eng J, Ensinck JW (1996) Elimination of the action of glucagon-like peptide 1 causes an impairment of glucose tolerance after nutrient ingestion by healthy baboons. J Clin Invest 97:133–138

Dakin CL, Small CJ, Batterham RL, Neary NM, Cohen MA, Patterson M, Ghatei MA, Bloom SR (2004) Peripheral oxyntomodulin reduces food intake and body weight gain in rats. Endocrinology 145:2687–2695

Delgado-Aros S, Kim DY, Burton DD, Thomforde GM, Stephens D, Brinkmann BH, Vella A, Camilleri M (2002) Effect of GLP-1 on gastric volume, emptying, maximum volume ingested, and postprandial symptoms in humans. Am J Physiol Gastrointest Liver Physiol 282: G424–G431

Diamant M, Van GL, Stranks S, Northrup J, Cao D, Taylor K, Trautmann M (2010) Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet 375:2234–2243

Dirksen C, Hansen DL, Madsbad S, Hvolris LE, Naver LS, Holst JJ, Worm D (2010) Postprandial diabetic glucose tolerance is normalized by gastric bypass feeding as opposed to gastric

feeding and is associated with exaggerated GLP-1 secretion: a case report. Diabetes Care 33:375–377
Drucker DJ (2006) The biology of incretin hormones. Cell Metab 3:153–165
Drucker DJ, Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 368:1696–1705
Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, Porter L (2008) Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 372:1240–1250
Egan JM, Margolskee RF (2008) Taste cells of the gut and gastrointestinal chemosensation. Mol Interv 8:78–81
Elahi D, Nagulesparan M, Hershcopf RJ, Muller DC, Tobin JD, Blix PM, Rubenstein AH, Unger RH, Andres R (1982) Feedback inhibition of insulin secretion by insulin: relation to the hyperinsulinemia of obesity. N Engl J Med 306:1196–1202
Fehmann HC, Habener JF (1992) Insulinotropic hormone glucagon-like peptide-I(7–37) stimulation of proinsulin gene expression and proinsulin biosynthesis in insulinoma beta TC-1 cells. Endocrinology 130:159–166
Flint A, Raben A, Astrup A, Holst JJ (1998) Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest 101:515–520
Flint A, Raben A, Ersbøll AK, Holst JJ, Astrup A (2001) The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. Int J Obes Relat Metab Disord 25:781–792
Furuse M, Matsumoto M, Saito N, Sugahara K, Hasegawa S (1997) The central corticotropin-releasing factor and glucagon-like peptide-1 in food intake of the neonatal chick. Eur J Pharmacol 339:211–213
Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B (2009) Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised,52-week, phase III, double-blind, parallel-treatment trial. Lancet 373:473–481
Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B, LEAD-3 (Mono) Study Group (2011) Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes Obes Metab 13:348–356
Glaesner W, Vick AM, Millican R, Ellis B, Tschang SH, Tian Y, Bokvist K, Brenner M, Koester A, Porksen N, Etgen G, Bumol T (2010) Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an Fc fusion protein. Diabetes Metab Res Rev 26:287–296
Göke R, Fehmann HC, Linn T, Schmidt H, Krause M, Eng J, Göke B (1993) Exendin-4 is a high potency agonist and truncated exendin-(9–39)-amide an antagonist at the glucagon-like peptide 1-(7–36)-amide receptor of insulin-secreting beta-cells. J Biol Chem 268:19650–19655
Göke R, Larsen PJ, Mikkelsen JD, Sheikh SP (1995) Distribution of GLP-1 binding sites in the rat brain: evidence that exendin-4 is a ligand of brain GLP-1 binding sites. Eur J Neurosci 7:2294–2300
Gromada J, Rorsman P, Dissing S, Wulff BS (1996) Stimulation of cloned human glucagon-like peptide 1 receptor expressed in HEK 293 cells induces cAMP-dependent activation of calcium-induced calcium release. FEBS Lett 373:182–186
Gutzwiller JP, Drewe J, Goke B, Schmidt H, Rohrer B, Lareida J, Beglinger C (1999) Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol 276:R1541–R1544
Holst JJ (2007) The physiology of glucagon-like peptide 1. Physiol Rev 87:1409–1439
Holst JJ, Deacon CF, Vilsbøll T, Krarup T, Madsbad S (2008) Glucagon-like peptide-1, glucose homeostasis and diabetes. Trends Mol Med 14:161–168
Imeryüz N, Yeden BC, Bozkurt A, Copkun T, Villanueva-Peñacarrillo ML, Ulusoy NB (1997) Glucagon-like peptide-1 inhibits gastric emptying via vagal afferent-mediated central mechanisms. Am J Physiol 273:G920–G927

Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, KimHH XuX, Chan SL, Juhaszova M, Bernier M, Mosinger B, Margolskee RF, Egan JM (2007) Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. Proc Natl Acad Sci USA 104:15069–15074

Jin SL, Han VK, Simmons JG, Towle AC, Lauder JM, Lund PK (1988) Distribution of glucagonlike peptide I (GLP-I), glucagon, and glicentin in the rat brain: an immunocytochemical study. J Comp Neurol 271:519–532

Kakei M, Yada T, Nakagawa A, Nakabayashi H (2002) Glucagon-like peptide-1 evokes action potentials and increases cytosolic Ca2+ in rat nodose ganglion neurons. Auton Neurosci 102:39–44

Kashyap SR, Daud S, Kelly KR, Gastaldelli A, Win H, Brethauer S, Kirwan JP, Schauer PR (2010) Acute effects of gastric bypass versus gastric restrictive surgery on beta-cell function and insulinotropic hormones in severely obese patients with type 2 diabetes. Int J Obes (Lond) 34:462–471

Kim D, Macconell L, Zhuang D, Kothare PA, Trautmann M, Fineman M, Taylor K (2007) Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. Diabetes Care 30:1487–1493

Kinzig KP, D'Alessio DA, Seeley RJ (2002) The diverse roles of specific GLP-1Rs in the control of food intake and the response to visceral illness. J Neurosci 22:10470–10476

Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, Wintle ME, Maggs DG (2008) Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin 24:275–286

Larsen PJ, Tang-Christensen M, Holst JJ, Ørskov C (1997a) Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem. Neuroscience 77:257–270

Larsen PJ, Tang-Christensen M, Jessop DS (1997b) Central administration of glucagon-like peptide-1 activates hypothalamic neuroendocrine neurons in the rat. Endocrinology 138:4445–4455

Ling Z, Wu D, Zambre Y, Flamez D, Drucker DJ, Pipeleers DG, Schuit FC (2001) Glucagon-like peptide 1 receptor signaling influences topography of islet cells in mice. Virchows Arch 438:382–387

Linnebjerg H, Park S, Kothare PA, Trautmann ME, Mace K, Fineman M, Wilding I, Nauck M, Horowitz M (2008) Effect of exenatide on gastric emptying and relationship to postprandial glycemia in type 2 diabetes. Regul Pept 151:123–129

Ma X, Bruning J, Ashcroft FM (2007) Glucagon-like peptide 1 stimulates hypothalamic proopiomelanocortin neurons. J Neurosci 27:7125–7129

Madsbad S (2009) Exenatide and liraglutide: different approaches to develop GLP-1 receptor agonists (incretin mimetics) - preclinical and clinical results. Best Pract Res Clin Endocrinol Metab 23:463–477

Madsbad S, Kielgast U, Asmar M, Deacon C, Torekov SS, Holst JJ (2011) An overview of once-weekly GLP-1 receptor agonists - available efficacy and safety data and perspectives for the future. Diabetes Obes Metab 13:394–407

Meeran K, O'Shea D, Edwards CM, Turton MD, Heath MM, Gunn I, Abusnana S, Rossi M, Small CJ, Goldstone AP, Taylor GM, Sunter D, SteereJ CSJ, Ghatei MA, Bloom SR (1999) Repeated intracerebroventricular administration of glucagon-like peptide-1-(7–36) amide or exendin-(9–39) alters body weight in the rat. Endocrinology 140:244–250

Meier JJ, Gallwitz B, Schmidt WE, Nauck MA (2002) Glucagon-like peptide 1 as a regulator of food intake and body weight: therapeutic perspectives. Eur J Pharmacol 440:269–279

Meier JJ, Gallwitz B, Salmen S, Goetze O, Holst JJ, Schmidt WE, Nauck MA (2003a) Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous glucagon-like peptide 1 in patients with type 2 diabetes. J Clin Endocrinol Metab 88:2719–2725

Meier S, Hücking K, Ritzel R, Holst JJ, Schmiegel WH, Nauck MA (2003b) Absence of a memory effect for the insulinotropic action of glucagon-like peptide 1 (GLP-1) in healthy volunteers. Horm Metab Res 35:551–556

Meier JJ, Kemmeries G, Holst JJ, Nauck MA (2005) Erythromycin antagonizes the deceleration of gastric emptying by glucagon-like peptide 1 and unmasks its insulinotropic effect in healthy subjects. Diabetes 54:2212–2218

Meneilly GS, Greig N, Tildesley H, Habener JF, Egan JM, Elahi D (2003) Effects of 3 months of continuous subcutaneous administration of glucagon-like peptide 1 in elderly patients with type 2 diabetes. Diabetes Care 26:2835–2841

Nagai K, Tsuchiya K, Ezaki T, Tsuchiya M, Ohgawara H (2004) Effect of GLP-1 (glucagon-like peptide 1:7–36 amide) on porcine pancreatic endocrine cell proliferation and insulin secretion. Pancreas 28:138–145

Nakade Y, Tsukamoto K, Pappas TN, Takahashi T (2006) Central glucagon like peptide-1 delays solid gastric emptying via central CRF and peripheral sympathetic pathway in rats. Brain Res 1111:117–121

Näslund E, Barkeling B, King N, Gutniak M, Blundell JE, Holst JJ, Rössner S, Hellström PM (1999) Energy intake and appetite are suppressed by glucagon-like peptide-1 (GLP-1) in obese men. Int J Obes Relat Metab Disord 23:304–311

Näslund E, King N, Mansten S, Adner N, Holst JJ, Gutniak M, Hellström PM (2004) Prandial subcutaneous injections of glucagon-like peptide-1 cause weight loss in obese human subjects. Br J Nutr 91:439–446

Nauck M, Stöckmann F, Ebert R, Creutzfeldt W (1986) Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia 29:46–52

Nauck MA, Kleine N, Ørskov C, Holst JJ, Willms B, Creutzfeldt W (1993) Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7–36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 36:741–744

Nauck MA, Niedereichholz U, Ettler R, Holst JJ, Ørskov C, Ritzel R, Schmiegel WH (1997) Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol 273:E981–E988

Ørskov C, Holst JJ, Poulsen SS, Kirkegaard P (1987) Pancreatic and intestinal processing of proglucagon in man. Diabetologia 30:874–881

Ørskov C, Poulsen SS, Moller M, Holst JJ (1996) Glucagon-like peptide I receptors in the subfornical organ and the area postrema are accessible to circulating glucagon-like peptide I. Diabetes 45:832–835

Patrita A, Aisa M, Annetti C, Sidoni A, Galli F, Ferri I, Gullà N, Donini A (2007) How the hindgut can cure type 2 diabetes. Ileal transposition improves glucose metabolism and β-cell function in Goto-kakizaki rats through enhanced proglucagon gene expression and L-cell number. Surgery 142:74–85

Pellissier S, Sasaki K, Le-Nguyen D, Bataille D, Jarrousse C (2004) Oxyntomodulin and glicentin are potent inhibitors of the fed motility pattern in small intestine. Neurogastroenterol Motil 16:455–463

Peterli R, Wölnerhanssen B, Peters T, Devaux N, Kern B, Christoffel-Courtin C, Drewe J, von Flüe M, Beglinger C (2009) Improvement in glucose metabolism after bariatric surgery: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: a prospective randomized trial. Ann Surg 250:234–241

Pitomobo C (2008) Central nervous system regulation and hormonal signaling. In: Pitomobo C, Jones K, Higa K, Pareja C (eds) Obesity surgery: principles and practice. McGraw-Hill, New York, NY

Raufman JP, Singh L, Singh G, Eng J (1992) Truncated glucagon-like peptide-1 interacts with exendin receptors on dispersed acini from guinea pig pancreas. Identification of a mammalian analogue of the reptilian peptide exendin-4. J Biol Chem 267:21432–21437

Reimer RA (2006) Meat hydrolysate and essential amino acid-induced glucagon-like peptide-1 secretion, in the human NCI-H716 enteroendocrine cell line, is regulated by extracellular

signal-regulated kinase1/2 and p38 mitogen-activated protein kinases. J Endocrinol 191:159–170
Rosenstock J, Reusch J, Bush M, Yang F, Stewart M (2009) Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. Diabetes Care 32:1880–1886
Rubino F, Gagner M, Gentileschi P, Kini S, Fukuyama S, Feng J, Diamond E (2004) The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. Ann Surg 240:236–242
Salehi M, Vahl TP, D'Alessio DA (2008) Regulation of islet hormone release and gastric emptying by endogenous GLP-1 following glucose ingestion. J Clin Endocrinol Metab 93:4909–4916
Schirra J, Katschinski M, Weidmann C, Schäfer T, Wank U, Arnold R, Göke B (1996) Gastric emptying and release of incretin hormones after glucose ingestion in humans. J Clin Invest 97:92–103
Schirra J, Kuwert P, Wank U, Leicht P, Arnold R, Göke B, Katschinski M (1997) Differential effects of subcutaneous GLP-1 on gastric emptying, antroduodenal motility, and pancreatic function in men. Proc Assoc Am Physicians 109:84–97
Schirra J, Nicolaus M, Roggel R, Katschinski M, Storr M, Woerle HJ, Göke B (2006) Endogenous glucagon-like peptide 1 controls endocrine pancreatic secretion and antro-pyloro-duodenal motility in humans. Gut 55:243–251
Schmidtler J, Dehne K, Allescher HD, Schusdziarra V, Classen M, Holst JJ, Polack A, Schepp W (1994) Rat parietal cell receptors for GLP-1-(7–36) amide: Northern blot, cross-linking, and radioligand binding. Am J Physiol 267:G423–G432
Schnabel CA, Wintle M, Kolterman O (2006) Metabolic effects of the incretin mimetic exenatide in the treatment of type 2 diabetes. Vasc Health Risk Manag 2:69–77
Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG (2000) Central nervous system control of food intake. Nature 404:661–671
Seeley RJ, Blake K, Rushing PA, Benoit S, Eng J, Woods SC, D'Alessio D (2000) The role of CNS glucagon-like peptide-1 (7–36) amide receptors in mediating the visceral illness effects of lithium chloride. J Neurosci 20:1616–1621
Seo S, Ju S, Chung H, Lee D, Park S (2008) Acute effects of glucagon-like peptide-1 on hypothalamic neuropeptide and AMP activated kinase expression in fasted rats. Endocr J 55:867–874
Shin YK, Martin B, Golden E, Dotson CD, Maudsley S, Kim W, Jang HJ, Mattson MP, Drucker DJ, Egan JM, Munger SD (2008) Modulation of taste sensitivity by GLP-1 signaling. J Neurochem 106:455–463
Shughrue PJ, Lane MV, Merchenthaler I (1996) Glucagon-like peptide-1 receptor (GLP1-R) mRNA in the rat hypothalamus. Endocrinology 137:5159–5162
Silvestre RA, Rodríguez-Gallardo J, Egido EM, Marco J (2003) Interrelationship among insulin, glucagon and somatostatin secretory responses to exendin-4 in the perfused rat pancreas. Eur J Pharmacol 469:195–200
Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP (2006) Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. J Card Fail 12:694–699
St Onge EL, Miller SA (2011) Albiglutide: a new GLP-1 analog for the treatment of type 2 diabetes. Expert Opin Biol Ther 10:801–806
Szayna M, Doyle ME, Betkey JA, Holloway HW, Spencer RG, Greig NH, Egan JM (2000) Exendin-4 decelerates food intake, weight gain, and fat deposition in Zucker rats. Endocrinology 141:1936–1941
Tang-Christensen M, Larsen PJ, Göke R, Fink-Jensen A, Jessop DS, Møller M, Sheikh SP (1996) Central administration of GLP-1-(7–36) amide inhibits food and water intake in rats. Am J Physiol 271:R848–R856
Tang-Christensen M, Vrang N, Larsen PJ (1998) Glucagon-like peptide 1(7–36) amide's central inhibition of feeding and peripheral inhibition of drinking are abolished by neonatal monosodium glutamate treatment. Diabetes 47:530–537

Thibaudeau K, Robitaille M, Wen S et al (2006) CJC-1134-PC: an exendin-4 conjugate with extended pharmacodynamic profiles in rodents. Diabetes 55(suppl 1):A103

Thomas S, Schauer P (2010) Bariatric surgery and the gut hormone response. Nutr Clin Pract 25:175–182

Tschöp M, Castaneda T, Joost HG, Thöne-Reineke C, Ortmann S, Klaus S, Hagan HH, Chandler PC, Oswald KD, Benoit SC, Seeley RJ, Kinzig KP, Moran TH, Beck-Sickinger AG, Koglin N, Rodgers RJ, Blundell JE, Ishii Y, Beattie AH, Holch P, Allison DB, Raun K, Madsen K, Wulff BS, Stidsen CE, Birringer M, Kreuzer O, Schindler M, Arndt K, Rudolf K, Mark M, Deng XY, Withcomb DC, Halem H, Taylor J, Dong J, Datta R, Culler M, Craney S, Flora D, Smiley D, Heiman ML (2004) Does gut hormone PYY3-36 decrease food intake in rodents? Nature 430:165–166

Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K, Choi SJ, Taylor GM, Heath MM, Lambert PD, Wilding JP, Smith DM, Ghatei MA, Herbert J, Bloom SR (1996) A role for glucagon-like peptide-1 in the central regulation of feeding. Nature 379:69–72

Van Dijk G, Thiele TE, Donahey JC, Campfield LA, Smith FJ, Burn P, Bernstein IL, Woods SC, Seeley RJ (1996) Central infusions of leptin and GLP-1-(7–36) amide differentially stimulate c-FLI in the rat brain. Am J Physiol 271:R1096–R1100

Vella A, Bock G, Giesler PD, Burton DB, Serra DB, Saylan ML, Dunning BE, Foley JE, Rizza RA, Camilleri M (2007) Effects of dipeptidyl peptidase-4 inhibition on gastrointestinal function, meal appearance, and glucose metabolism in type 2 diabetes. Diabetes 56:1475–1480

Verdich C, Flint A, Gutzwiller JP, Näslund E, Beglinger C, Hellström PM, Long SJ, Morgan LM, Holst JJ, Astrup A (2001) A meta-analysis of the effect of glucagon-like peptide-1 (7–36) amide on ad libitum energy intake in humans. J Clin Endocrinol Metab 86:4382–4389

Vetter ML, Cardillo S, Rickels MR, Iqbal N (2009) Narrative review: effect of bariatric surgery on type 2 diabetes mellitus. Ann Intern Med 150:94–103

Vrang N, Phifer CB, Corkern MM, Berthoud HR (2003) Gastric distension induces c-Fos in medullary GLP-1/2-containing neurons. Am J Physiol Regul Integr Comp Physiol 285: R470–R478

Wang GJ, Tomasi D, Backus W, Wang R, Telang F, Geliebter A, Korner J, Bauman A, Fowler JS, Thanos PK, Volkow ND (2008) Gastric distention activates satiety circuitry in the human brain. Neuroimage 39:1824–1831

Wang M, Matheson S, Picard J, Pezzullo J, Ulich T (2009) PC-DAC (TM): exendin-4 (CJC-1134-PC) significantly reduces HbA1c and body weight as an adjunct therapy to metformin: two randomized, double-blind, placebo-controlled, 12 week, phase II studies in patients with type 2 diabetes mellitus. Diabetes 58(suppl 1):A148

Wellendorph P, Johansen LD, Brauner-Osborne H (2009) Molecular pharmacology of promiscuous seven transmembrane receptors sensing organic nutrients. Mol Pharmacol 76:453–465

Wettergren A, Wøjdemann M, Meisner S, Stadil F, Holst JJ (1997) The inhibitory effect of glucagon-like peptide-1 (GLP-1) 7–36 amide on gastric acid secretion in humans depends on an intact vagal innervation. Gut 40:597–601

Young AA, Gedulin BR, Bhavsar S, Bodkin N, Jodka C, Hansen B, Denaro M (1999) Glucose-lowering and insulin-sensitizing actions of exendin-4: studies in obese diabetic (ob/ob, db/db) mice, diabetic fatty Zucker rats, and diabetic rhesus monkeys (Macacamulatta). Diabetes 48:1026–1034

Zander M, Madsbad S, Madsen JL, Holst JJ (2002) Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and β-cell function in type 2 diabetes: a parallel-group study. Lancet 359:824–830