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Glucagon-like peptide 1 as a regulator of food intake and body weight: therapeutic perspectives

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Abstract

After ingestion of carbohydrate- and fat-rich meals, the incretin hormone glucagon-like peptide 1 (GLP-1) is secreted from the L-cells in the distal put into the circulation. Its major physiological effect lies in a strongly glucose-dependent stimulation of insulin secretion from pancreatic B-cells. Furthermore, GLP-1 suppresses glucagon secretion, stimulates B-cell neogenesis as well as proinsulin biosynthesis and inhibits gastric emptying and acid secretion. Recently, GLP-1 could be shown to reduce caloric intake and to enhance satiety, most likely via specific receptors within the central nervous system, resulting in reduced weight gain in experimental animals. In nondiabetic and Type 2 diabetic human subjects, exogenous GLP-1 reduces hunger, caloric intake and body weight. Therefore, in addition to its well-characterized antidiabetogenic effect, the anorectic effect may offer GLP-1 a potential in the pharmacotherapy of obesity. It is still unknown whether the GLP-1 effect on caloric intake is sustained after long-term treatment. Furthermore, the exact mechanisms by which the peptide exerts its biological effects have not yet been clarified. Due to the rapid degradation of native GLP-1, its therapeutic application is limited by the short half-life. Therefore, suitable modes of administration are needed in order to reach stable plasma concentrations. The present review aims to describe the role of GLP-1 in the central regulation of feeding and to discuss its possible application in the pharmacotherapy of obesity.

Keywords: (GLP-1) glucagon-like peptide 1; Obesity; Satiety; Food intake

1. Introduction

After an oral glucose load, insulin secretion from pancreatic B-cells exceeds the insulin response after intravenous infusion, leading to a similar glucose rise (Elrick et al., 1964). The postprandial enhancement of insulin secretion by humoral factors from the gut (Elrick et al., 1964; Creutzfeldt, 1979; Creutzfeldt et al., 1978; Nauck et al., 1986) is called the incretin effect. Two gastrointestinal hormones, (a) gastric inhibitory polypeptide (GIP), which is secreted from the K-cells in the duodenum, and (b) glucagon-like peptide 1 (GLP-1), which stems from L-cells mainly located in the jejunum, ileum and colon (Buffa et al., 1975; Buchan et al., 1978; Ørskov et al., 1989; Eissele et al., 1992), are predominantly involved in the mediation of this effect (Pederson et al., 1975; Schmidt et al., 1985). In contrast to the pancreas, where posttranslational processing of proglucagon results in the formation of glucagon and the major proglucagon fragment (MPGF), proteolytic cleavage in the L-cells of the gut yields the peptides glicentin, GLP-1 and GLP-2 (Bell et al., 1983; Holst et al., 1994). Interestingly, and different from GIP, which has lost most of its insulinotropic potency in Type 2 diabetic patients (Nauck et al., 1993b; Meier et al., 2001), GLP-1 still effectively stimulates insulin secretion in these patients (Nathan et al., 1992; Gutniak et al., 1992; Nauck et al., 1993c, 1998; Ritzel et al., 1995) (Fig. 1). Therefore, GLP-1 has a promising potential in the pharmacotherapy of Type 2 diabetes (Nauck et al., 1997a; Holst, 2000). In contrast to other insulinotropic agents, e.g. the sulfonylureas, the insulinotropic effect of GLP-1 depends even more closely on the actual glucose concentration providing the possibility of glucose normalisation without the risk of hypoglycemias (Nauck et al., 1993c, 1998; Nathan et al., 1992; Vilsbøll et al., 2001). In addition, the peptide has been shown to suppress glucagon secretion, thereby even enhancing the glucose-lowering effect (Ørskov et al., 1988; Kawai et al., 1989; Nauck et al., 1993b).

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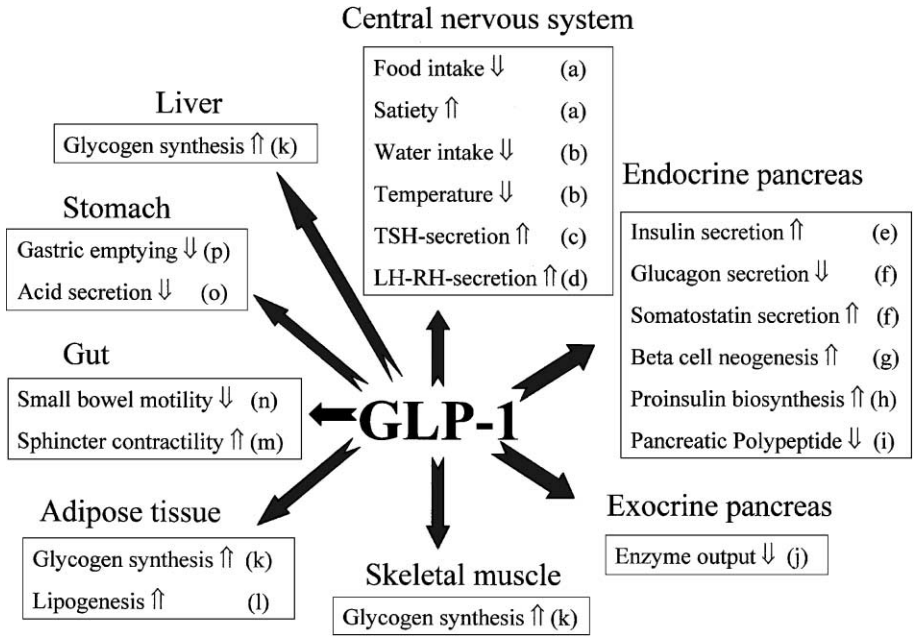

Fig. 1. Actions of GLP-1 in various organs and tissues in vivo. Small letters indicate references documenting the quoted effect: (a) Flint et al. (1998); (b) Tang Christensen et al. (1996); (c) Beak et al. (1996); (d) Beak et al. (1998); (e) Holst et al. (1987); (f) Ørskov et al. (1988); (g) Xu et al. (1999); (h) Fehmann and Habener (1992); (i) Dupré et al. (1995); (j) Wettergren et al. (1993); (k) Valverde et al. (1994); (l) Oben et al. (1991); (m) Schirra et al. (2000); (n) Tolessa et al. (1998); (o) Schjoldager et al. (1989); (p) Wettergren et al. (1993). Modified according to Nauck (1997).

Recently, further evidence was gathered that GLP-1 exerts beneficial effects on B-cell regeneration and on the differentiation of pancreatic ductal cells into insulin-secreting cells (Xu et al., 1999; Hui et al., 2001). Possibly, this argues for a lasting therapeutic effect of GLP-1 in contrast to that of other insulin secretagogues, which are known to become

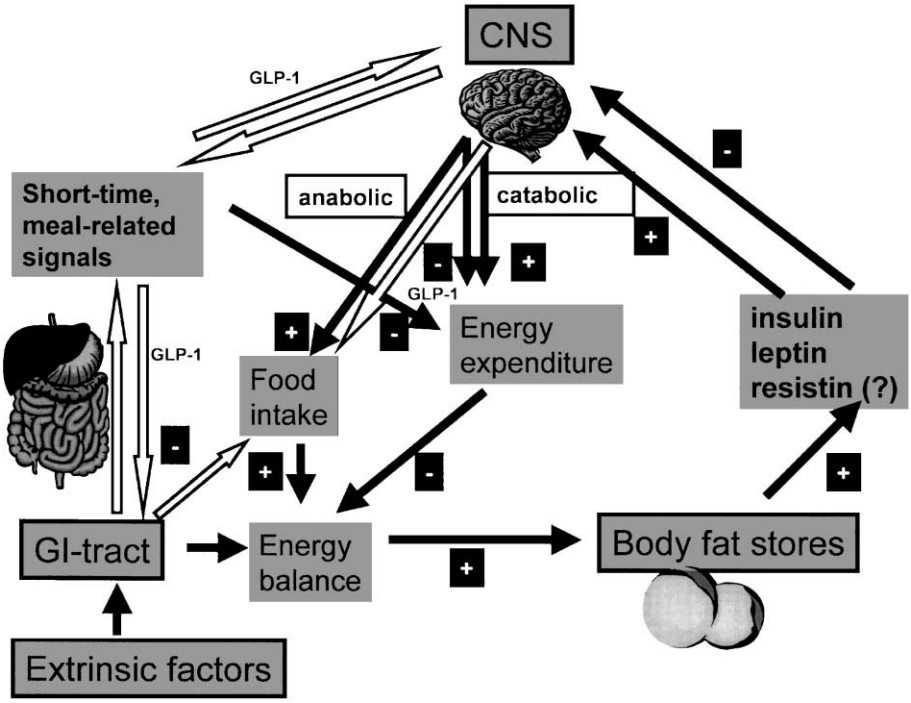

Fig. 2. Regulation of energy balance and obesity: neural systems and hormonal signals of energy balance represent major controllers of food intake. Anabolic effector pathways promote feeding and suppress energy expenditure, whereas catabolic effector pathways have the opposite effect. Short-term, meal-related hormonal (e.g. GLP-1, cholecystokinin) and neuronal (e.g. via distension of the stomach) signals from the gut exert further effects on central nervous regulation of feeding and energy balance. In addition, various interactions exist between adipose tissue and the central nervous system (e.g. via leptin, insulin and, possibly, resistin). Biological effects of GLP-1 are shown by open arrows (modified according to (Schwartz et al., 1999, 2000).

ineffective after several years of treatment (secondary failure) (Groop et al., 1989).

GLP-1 also acts as a physiological mediator of various gastrointestinal functions (Schirra et al., 2000). These actions include a delay of gastric emptying after liquid as well as after solid meals, thereby further contributing to the lowering effect on the postprandial rise in glucose concentrations (Wettergren et al., 1993; Schirra et al., 1996; Nauck et al., 1997b). In addition, GLP-1 has been shown to inhibit meal- and pentagastrin-stimulated gastric acid secretion (O'Halloran et al., 1990; Wettergren et al., 1993), as well as pancreatic enzyme secretion (Wettergren et al., 1993; Schirra et al., 1997). A summary of the various effects of GLP-1 in different tissues is shown in Fig. 1.

Despite its promising characteristics, therapeutic administration of GLP-1 is limited by the short half-life of the peptide in vivo. After subcutaneous or intravenous injections, GLP-1 (7–36) is N-terminally degraded by the enzyme dipeptidyl-peptidase IV within 2 min, yielding the biologically inactive fragment GLP-1 (9–36) (Mentlein et al., 1993; Deacon et al., 1995a).

Within the last decade, various groups have reported a role of GLP-1 in the regulation of feeding behaviour leading to increased satiety, reduced caloric intake and weight loss (Turton et al., 1996; Flint et al., 1998; Gutzwiller et al., 1999a; Zander et al., 2001). However, the regulation of feeding and energy balance is complex and involves a number of neural and hormonal signals (Fig. 2). The physiological relevance of GLP-1 within this system is not completely understood yet.

The present review will focus on the evidence that GLP-1 has a role in the central nervous system regulation of feeding, the mechanisms involved and the therapeutic potential for the treatment of obesity that can be derived from such actions

2. Distribution of GLP-1 and its binding sites in the central nervous system

In addition to their main distribution on pancreatic islet cells and gastric glands (Uttenthal and Blazquez, 1990; Fehmann and Habener, 1991; Ørskov and Poulsen, 1991), GLP-1 receptors have been identified in various regions of the central nervous system (Drucker and Asa, 1988; Kanse et al., 1988). A role of gastrointestinal peptides in the regulation of central nervous functions was postulated even before the exact peptide structure and function of GLP-1 had been discovered. Along this line, glucagon-like material had been detected immunohistochemically in canine and rat brain in 1979/1980 (Lorén et al., 1979; Conlon et al., 1979; Tager et al., 1980). The glucagon-like immunoreactive material was preferentially distributed in the hypothalamus, but could also be identified in the cortex, thalamus, cerebellum and brain stem (Conlon et al., 1979; Tager et al., 1980). As the concentrations of these peptides in the central nervous system exceeded those measured in the peripheral circulation, a specific function in the brain was anticipated. However, the exact biological function of these peptides remained unexplained. Not long after the amino acid sequence of GLP-1 and its formation from the proglucagon gene had been described (Bell et al., 1983), the identification of GLP-1 binding sites in the rat brain and an increase in the cellular cAMP content of hypothalamic cells after incubation with various concentrations of GLP-1 implied a role for the peptide as a central neurotransmitter (Hoosein and Gurd, 1984). Sequence identity of GLP-1 across different mammalian species supported the idea of an important physiological function (Lund et al., 1982). In the late 1980s, various groups added to the knowledge about the distribution of GLP-1 and its binding sites in the central nervous system using more sensitive techniques (Shimizu et al., 1987; Drucker and Asa, 1988; Kanse et al., 1988; Kreymann et al., 1989). A wide distribution of GLP-1 receptors was identified throughout the rostro-caudal extent of the hypothalamus with a dense accumulation in the supraoptic, paraventricular and arcuate nuclei (Shughrue et al., 1996). Tissue-specific cloning provided evidence for a structural and sequence homology of the GLP-1 receptors in pancreas and brain (Thorens, 1992; Wei and Mojsow, 1996). The GLP-1 receptor belongs to the G-protein-coupled, 7-membrane-spanning family of receptors also including receptors for glucagon, vasoactive intestinal peptide (VIP), secretin, GIP and calcitonin (Thorens, 1992; Fehmann et al., 1995). The N-terminus of the peptide was identified as the domain important for receptor binding, whereas the C-terminus seems to be important for the induction of biological effects (Gallwitz et al., 1990, 1993, 1994, 1995; Wilmen et al., 1997). In the hypothalamus, GLP-1 is released in a Ca^{2+}-dependent manner after K^{+}-induced depolarisation (Kreymann et al., 1989).

The appearance of a mRNA-transcript of the glucagon gene in the central nervous system led Drucker and Asa (1988) to conclude that GLP-1 was probably locally produced and released in certain brain areas, independent of transport from the general circulation across the blood–brain barrier (Drucker and Asa, 1988). However, in addition to this local production, GLP-1 released into the circulation may also reach areas of the brain not equipped with a typical blood–brain barrier such as the subfornical organ and the area postrema (Ørskov et al., 1996). These brain areas are characterized by fenestrated capillaries and lack endothelial tight junctions, allowing larger peptides to reach the brain (Ørskov et al., 1996). Both the area postrema and the subfornical organ are known to be involved in the regulation of feeding and drinking behaviour via efferent projections to the hypothalamus (Shapiro and Miselis, 1985).

The detection of central coexpression of GLP-1 receptors together with glucokinase and GLUT-1 (a glucose transporter), both known to act as glucose sensors in pancreatic B-cells (Meglasson et al., 1983), prompted Navarro et al. (1996) to suggest that the secretion of GLP-1 in the central nervous system is regulated in a glucose-dependent manner as is insulin secretion from the islets of Langerhans. A further

dense accumulation GLP-1 receptors was detected on the posterior lobe of the pituitary gland (Göke et al., 1995).

A physiological role of GLP-1 in the regulation of feeding was inferred from the appearance of c-*fos* exclusively in the paraventricular nucleus of the hypothalamus and the central nucleus of the amygdala following intracerebroventricular GLP-1 injection (Turton et al., 1996). However, neither has coupling of these receptors to a specific second messenger system been described, nor could the biological function of these receptors be clarified (Göke et al., 1995; Satoh et al., 2000).

In conclusion, the broad distribution of GLP-1 binding sites in the central nervous system and peptide concentrations exceeding those in the circulation, especially in the area postrema that is involved in nutrient homeostasis, provide a basis for possible actions of GLP-1 on feeding behaviour.

3. Studies on the physiology of GLP-1 and the control of feeding behaviour

3.1. Central actions of GLP-1 in animals

With the detection of comparably high GLP-1 concentrations and a widespread distribution of binding sites in the central nervous system with a dense accumulation in areas responsible for the control of food ingestion, the idea of a central role for GLP-1 in the regulation of appetite and satiety had arisen already in the beginning of the 1990s (Schick et al., 1992; Lambert et al., 1993; Turton et al., 1996). Along these lines, Schick et al. (1992) first reported a significant reduction of food ingestion after intracerebroventricular injection of the peptide in rats in 1992. In addition, immunoblockade of endogenous GLP-1 by intracerebroventricular injection of monoclonal antibodies directed against GLP-1 led to an about 40% increase in food consumption (Lambert et al., 1993).

The function of GLP-1 as a potential satiety factor received wide attention with the description of effects on feeding behaviour in rats reported by Turton et al. (1996). These authors found a significant reduction of food intake after intracerebroventricular administration of GLP-1 in rats, whereas the simultaneous injection of the GLP-1 receptor antagonist, exendin-(9–39), completely abolished this effect and increased neuropeptide Y-mediated food ingestion. Antagonizing endogenous GLP-1 with the injection of exendin-(9–39) alone doubled food ingestion in ad libitum fed, but not in fasted rats. These data provided the first evidence of a central role for GLP-1 as a satiety factor (Schick et al., 1992; Lambert et al., 1993; Turton et al., 1996). In addition, GLP-1 was shown to inhibit angiotensin II-mediated drinking behaviour as well, implying a further role in fluid homeostasis (Tang Christensen et al., 1996).

It was still debated whether the reduced food intake observed in rats reflected a central satiating effect (Turton et al., 1996) or whether it was the consequence of a conditioned food aversion evoked by GLP-1 (Thiele et al., 1997). The interpretation of GLP-1 as an emetic agent was based on a delayed latency of rejection of a saccharin-solution following the intracerebroventricular infusion of GLP-1 in rats with a dose–response relationship similar to the quantitative satiating effect (Thiele et al., 1997).

In mice with a targeted disruption of the GLP-1 receptor, intracerebroventricularly injected GLP-1 failed to inhibit food ingestion, suggesting an identical structure and function of GLP-1 receptors in the central nervous system and on pancreatic B-cells (Scrocchi et al., 1996). However, in these mice, neither feeding behaviour nor body mass index was altered compared to those in wild type mice, indicating that GLP-1 might act as a short-time regulator of satiety, whereas long-term control of feeding behaviour appears to be unaffected (Scrocchi et al., 1996). Accordingly, Donahey et al. (1998) found the effect of intracerebroventricularly injected GLP-1 on food ingestion lasting for at least 2 h, whereas neither total food ingestion over 24 h, nor body weight was affected by once daily GLP-1 bolus injections. A continuous intracerebroventricular infusion via an osmotic mini-pump also failed to alter body weight or caloric intake (Donahey et al., 1998). In contradiction to these data, Meeran et al. (1999) reported a significant reduction of food intake and body weight in rats after 6 days of repeated intracerebroventricular GLP-1 treatment. In turn, daily administration of the GLP-1 receptor antagonist, exendin-(9–36), resulted in an increased food intake and body weight (Meeran et al., 1999). The authors suggested that methodological problems (e.g. differences in the preparation of the GLP-1 solution) were responsible for differences from previous studies (Scrocchi et al., 1996; Donahey et al., 1998). Recently, a significant reduction of total food intake, leading to lower weight gain could also be shown with the administration of a GLP-1 analogue in rhesus monkeys, *db/db* mice and in Zucker diabetic fatty rats (Hansen et al., 2001; Larsen et al., 2001; Sturis et al., 2001).

Similar results were obtained with the application of the GLP-1 receptor agonist, exendin-4, a 39-amino acid peptide produced in the salivary gland of *heloderma suspectum* venom that shares 53% sequence homology with GLP-1 and has an in vivo half-life of several hours (Eng et al., 1992). This peptide led to a significant reduction of food ingestion and reduced body weight when given to obese diabetic (*ob/ob*, *db/db*)-mice over a 6-week period (Young et al., 1999). More recent data indicated that the effect of exendin-4 given once daily is attenuated after 5 days, whereas its twice daily injection results in a sustained reduction of food intake and body weight after 56 days of treatment (Szayna et al., 2000). These data lead to the conclusion that in order to achieve a sustained reduction of body weight over a long-term period of treatment, a constantly elevated plasma concentration of GLP-1 or a GLP-1 receptor agonist is required.

3.2. Effects of intravenous or subcutaneous administration in human subjects

For humans, the first data concerning the GLP-1 effects on the regulation of feeding behaviour were obtained by Flint et al. (1998) (Table 1). These authors found a significantly increased feeling of satiety and fullness as well as a reduced total caloric intake and reduced feeling of hunger following the intravenous infusion of pharmacological GLP-1 doses in healthy subjects (Flint et al., 1998). Gutzwiller et al. (1999b) found the effects on feeding behaviour to be dose-dependent with a maximum inhibition of food intake of 32%. In Type 2 diabetic patients, intravenous infusion of GLP-1 caused a reduction of caloric intake and appetite as well (Gutzwiller et al., 1999a). A recent meta-analysis with data from 115 subjects revealed a reduction of energy intake by 727 kJ or 11.7% during GLP-1 infusion (Verdich et al., 2001). Toft-Nielsen et al. (1999) could demonstrate that similar effects on appetite and satiety could be obtained by continuous subcutaneous GLP-1 infusion in Type 2 diabetic patients. More recent data suggest that longer term subcutaneous infusion of GLP-1 for 6 weeks even reduces body weight (Zander et al., 2001). Therefore, the anorexigenic effect seems to be preserved after longer periods of treatment, even though further long-term studies are required. A summary of satiety-related effects with intravenous and subcutaneous administration of GLP-1 or exendin-4 in humans is presented in Table 1.

3.3. Importance of gut-derived versus centrally released GLP-1

Although it is established that GLP-1 exerts specific functions in the central nervous system (Turton et al., 1996), the exact mechanisms by which the peptide influences feeding behaviour have not been completely clarified yet. The wide distribution of GLP-1-receptors in the *area postrema* (Shimizu et al., 1987; Drucker and Asa, 1988; Kanse et al., 1988; Shughrue et al., 1996) implies that central effects may be involved in the reduction of food ingestion following GLP-1 infusion (Flint et al., 1998). However, an additional inhibition of gastrointestinal motility by GLP-1 (Wettergren et al., 1997; Nauck et al., 1997b; Schirra et al., 1997) may reduce the feeling of hunger and, in turn, increase satiety (Fig. 3).

In humans, with peripheral-venous as well as subcutaneous administration of GLP-1, a significant reduction of appetite and body weight has been observed (Flint et al., 1998; Gutzwiller et al., 1999a; Zander et al., 2001) (Table 1). However, in rats, intracerebroventricular, but not intraperitoneal, injection of GLP-1 caused a reduction of total body weight (Turton et al., 1996; Tang Christensen et al., 1996). One explanation for this loss of effect after peripheral application is the rapid degradation of the peptide, particularly in rats (Kieffer et al., 1995). After subcutaneous GLP-1 administration, Rodriguez de Fonseca et al. (2000) recently found increased satiety in rats. These authors suspected methodological reasons to be responsible for the failure of intraperitoneal GLP-1 to reduce food intake (Rodriguez de Fonseca et al., 2000).

It is still incompletely understood, how peripherally secreted or injected GLP-1 can evoke central effects, although most of the GLP-1 binding sites in the hypothalamic and extrahypothalamic nuclei are separated from the circulation by the blood–brain barrier. It is conceivable that peripherally injected or secreted GLP-1 could stimulate peripheral vagal afferent nerve fibres that project to central nuclei in the hypothalamus. Involvement of the vagus nerve

Table 1
Effects of GLP-1 on appetite, feeding behaviour and body weight in humans

References	Dose (pmol kg min^{-1})	Duration (hours)	Route	Subjects	Effects	*p*-value
Flint et al., 1998	0.7	4	i.v.	20 healthy subjects	reduction of energy intake: 21%	0.0002
					decreased feeling of hunger	0.012
					enhanced fullness	0.028
					enhanced satiety	0.013
Gutzwiller et al., 1999b	0–1.5	2	i.v.	16 healthy subjects	maximal reduction of food intake: 35%	<0.001
					maximal reduction of caloric intake: 32%	<0.001
					maximal reduction of fluid intake: 18%	<0.01
Gutzwiller et al., 1999a	1.5	2	i.v.	12 Type 2 diabetic patients	enhanced satiety	0.026
					enhanced fullness	0.028
					reduction of energy intake: 27%	0.034
					enhanced satiety	<0.05
Toft-Nielsen et al., 1999	2.4	48	s.c.	6 Type 2 diabetic patients	decreased feeling of hunger	<0.05
					decreased prospective food consumption	<0.05
					fullness not affected	–
Hellerström and Näslund, 1999	0.75	8	i.v.	obese subjects	reduced caloric intake	–
					reduced feeling of hunger	–
Zander et al., 2001	2.4	6 weeks	s.c.	10 Type 2 diabetic patients	reduction of body weight: 1.9%	0.02
					reduction of appetite: 21%	0.01

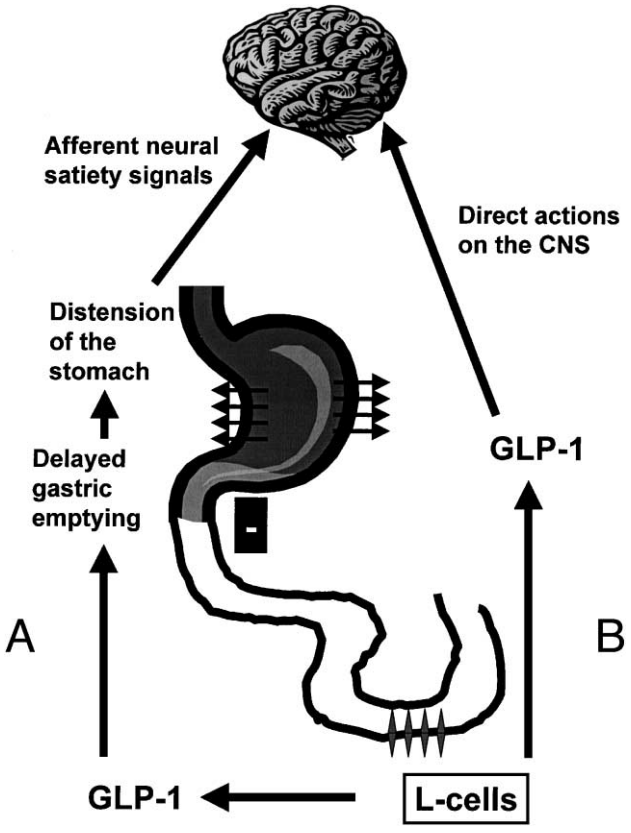

Fig. 3. Two possible explanations for the effect of peripherally secreted or injected GLP-1 on central nervous regulation of feeding: (A) indirect effects on fullness and satiety via distension of the stomach induced by delayed gastric emptying; (B) direct effects on GLP-1 receptors in the central nervous system with efferent projections to the hypothalamus.

in the GLP-1 effects on gastrointestinal functions was clearly demonstrated by various groups (Wettergren et al., 1997; Nakabayashi et al., 1996; Imeryuz et al., 1997). However, in vagally denervated rats, no suppression of feeding behaviour was observed after either subcutaneous or intracerebroventricular injection of GLP-1, although inhibitory effects on gastric emptying were completely abolished (Imeryuz et al., 1997). These data imply that different mechanisms of action are involved in the regulation of feeding behaviour and gastric emptying by GLP-1.

Furthermore, a delay in gastric emptying mediated by GLP-1 (Wettergren et al., 1993; Nauck et al., 1997b) could result in distension of the stomach, thereby increasing the feeling of fullness and leading to termination of meal ingestion (Flint et al., 1998) (Fig. 3). According to this hypothesis, GLP-1 is an endogenous signal for meal termination. Against this view is the fact that plasma concentrations of GLP-1 peak only approximately 60 min after meal ingestion, long after the end of the meal (Blundell and Naslund, 1999).

Another possible mode of action could be transport into the central nervous system via specific carriers or endothelial leaks, making peripheral GLP-1 accessible to central binding sites. Evidence for such transport mechanisms has been provided by Ørskov et al. (1996), who identified peripherally injected ^{125}I-GLP-1 in the subfornical organ and the periphery of the *area postrema*. Therefore, it is possible that GLP-1 injected intravenously or subcutaneously exerts its effects on feeding behaviour via binding sites in these areas of the brain stem, whence efferent projections are directed to major relay nuclei involved in nutrient and fluid homeostasis (Shapiro and Miselis, 1985). This hypothesis is supported by the loss of the GLP-1 effect on feeding behaviour in rats with excessive damage to the *nucleus arcuatus* and parts of the circumventricular organ caused by neonatal monosodium glutamate treatment (Tang-Christensen et al., 1998). This animal model emphasizes the importance of these central areas in the brain for the regulation of feeding behaviour by GLP-1. It is therefore likely that GLP-1 exerts its effect on the regulation of food intake via a specific interaction with binding sites in certain areas of the central nervous system from where efferent projections are directed to the hypothalamus. However, involvement of peripheral, possibly vagally mediated effects cannot be excluded. A model of the possible mechanisms involved in the central nervous actions of peripherally secreted or injected GLP-1 is presented in Fig. 3.

4. Modes of administration of GLP-1

Considering the antidiabetic use of the incretin hormone GLP-1, a number of problems have become obvious. As a peptide, after its oral ingestion, GLP-1 is immediately denaturated by gastric acid and consequently inactivated (Brown and Dryburgh, 1971). Therefore, GLP-1 must be administrated subcutaneously or intravenously in order to reach the circulation. Another problem is the extremely short half-life of the peptide. As early as 2 min after its subcutaneous or intravenous administration most of the peptide, GLP-1 (7–36) is cleaved by the enzyme dipeptidyl-peptidase IV at the N-terminus (Mentlein et al., 1993; Kieffer et al., 1995; Pauly et al., 1996; Deacon et al., 1995a,b), yielding the biologically inactive fragment GLP-1 (9–36). Therefore, the administration of native GLP-1 as a single subcutaneous injection is not suitable for reaching constantly elevated plasma concentrations of the intact peptide (Ritzel et al., 1995; Nauck et al., 1996).

Presently, various modes of administration are now under consideration to overcome these problems (Table 2). One approach is a continuous subcutaneous infusion via a portable pump. Such an approach guarantees reliably constant plasma concentrations (Larsen et al., 1996; Toft-Nielsen et al., 1999; Zander et al., 2001), but the broad application of an infusion pump may be limited by patients' preferences for less invasive methods. In addition, a continuous subcutaneous infusion is associated with the risk of catheter infections, and the costs for pumps and catheter material are quite substantial. Nevertheless, for special clinical indications, for instance, metabolic control after acute myocardial infarcts,

Table 2
Routes of application of GLP-1 and analogues

Mode of application	References	Advantage	Disadvantage
Intravenous GLP-1 infusion	(Gutniak et al., 1992) (Nauck et al., 1993c)	stable plasma concentrations application of the native peptide possible	clinical setting required intravenous cannula required catheter infections reduced mobility of patients
Continuous subcutaneous GLP-1 infusion via portable pump	(Larsen et al., 1996) (Toft-Nielsen et al., 1999) (Zander et al., 2001)	sustained mobility stable plasma concentrations administration of the native peptide possible	high costs catheter infections
GLP-1 analogues	(Deacon et al., 1998b) (Siegel et al., 1999) (Gallwitz et al., 2000)	resistant to DDP IV degradation prolonged biological half-life subcutaneous injection possible	antibody formation (?) unknown toxicology anaphylactic reactions (?)
Exendin-4	(Edwards et al., 2001)	natural GLP-1 analogue prolonged biological half-life once/twice daily subcutaneous injection possible	antibody formation (?) unknown toxicology anaphylactic reactions (?)
Inhibition of dipeptidyl-peptidase IV	(Holst and Deacon, 1998) (Deacon et al., 1998a) (Pederson et al., 1998) (Pauly et al., 1999)	oral administration possible indirect elevation of biologically active GLP-1	unspecific enzyme inhibition possibly leading to reduced degradation of other hormones little effect in the interdigestive state long-term effects unknown

the application of GLP-1 via constant intravenous or subcutaneous infusion may be practical.

Another possibility for increasing plasma concentration of incretin hormones lies in the inhibition of their degradation (Holst and Deacon, 1998). This could be achieved in in vitro as well as animal studies, using specific inhibitors of the enzyme dipeptidyl-peptidase IV (Deacon et al., 1998a; Pederson et al., 1998; Pauly et al., 1999). Such an inhibitor could be taken orally together with the main meals. However, inhibition of dipeptidyl-peptidase IV affects mainly postprandial plasma concentrations of GLP-1 and GIP, whereas in the interdigestive state, these concentrations drop again. Therefore, considering the necessity for constantly elevated GLP-1 concentrations in order to evoke effects on feeding behaviour (Szayna et al., 2000), inhibition of dipeptidyl-peptidase IV only around mealtime does not seem to be appropriate to reduce body weight. In addition, many other physiologically important peptide hormones are also cleaved by dipeptidyl-peptidase IV, a rather nonspecific enzyme (Mentlein et al., 1993; Kieffer et al., 1995). The biological long-term effect of a general dipeptidyl-peptidase IV inhibition is not known yet.

A further approach is the generation of GLP-1 analogues resistant to degradation by dipeptidyl-peptidase IV with extended half-lives (Deacon et al., 1998b; Siegel et al., 1999; Gallwitz et al., 2000; Xiao et al., 2001). These analogues could be a suitable way to obtain constant GLP-1 receptor activation, leading to reduction of appetite and consequently of caloric intake. A number of companies and groups are presently examining the pharmacokinetic properties and biological activities of various GLP-1 analogues (Hansen et al., 2001; Larsen et al., 2001; Pascoe et al., 2000; Wargent et al., 2000; Rolin et al., 2000). However, it cannot be excluded that such analogues could induce antibody formation or lead to anaphylactic reactions. Long-term studies will be required to clarify these open questions.

Promising data, with a reduction of caloric intake by 19%, have been obtained with the clinical application of the natural GLP-1 analogue, exendin-4, in health volunteers (Edwards et al., 2001). The biological effects and possible adverse events after long-term administration of this peptide are yet to be evaluated as well.

A further conceivable approach to obtaining stimulation of central GLP-1 receptors could be the biochemical generation of small molecular GLP-1 receptor agonists that are absorbed from the gut after oral application. However, no such molecule is available yet. An overview of the various possible modes of administration is given in Table 2.

5. Chances for GLP-1 in the pharmacotherapy of obesity

Approximately a decade after the first description of GLP-1 effects on the central regulation of feeding behaviour (Schick et al., 1992), further studies in various animal models as well as in humans provided evidence for a satiating effect of this peptide (Turton et al., 1996; Flint et al., 1998; Gutzwiller et al., 1999a) (Table 1). In addition, numerous groups found a significant reduction of body weight following the administration of GLP-1 (Meeran et al., 1999; Donahey et al., 1998; Zander et al., 2001). These data suggest that GLP-1 might, in addition to its well-characterized antidiabetogenic effects, also have a potential for the pharmacotherapy of obesity. However, some questions remain to be answered.

One important point is the duration of such an effect. Is the reduction of body weight by GLP-1 only a transitory phenomenon or does it persist during long-term treatment? Tachyphylaxis after continuous or repetitive treatment could theoretically attenuate the satiating effects of GLP-1. In rats, Donahey et al. (1998) reported a reduced food intake only for 2 h of treatment, whereas total food consumption over 4

days of GLP-1 administration was not altered. On the contrary, other groups reported a reduction of caloric intake and body weight also after long-term treatment with the peptide (Meeran et al., 1999). In humans, recent data for GLP-1 treatment over a period of 6 weeks in Type 2 diabetic patients indicated a sustained effect on insulin secretion as well as reduction of body weight by approximately 2 kg (Zander et al., 2001).

However, mice with a targeted disruption of the GLP-1 receptor showed normal weight gain compared to wild type mice, whereas disruption of the leptin receptor in the *ob/ob*-mouse led to a markedly increased weight gain (Scrocchi et al., 1996, 2000). From these data, the authors concluded that GLP-1 is not an essential regulator of feeding behaviour (Scrocchi et al., 2000). Another possible explanation is that even though in GLP-1-receptor knock-out mice, the loss of central functions of GLP-1 may be compensated for by other peptides, for instance, neuropeptide Y or leptin (Bouchard, 2000) (Fig. 2), GLP-1 might still influence long-term caloric intake by other mechanisms. However, regarding the role as an endogenous regulator of feeding, it is obvious that GLP-1 is less important than these other hormones.

Furthermore, continuously elevated peptide plasma concentrations seem to be necessary to obtain a consistent reduction of body weight. This is indicated by data from Szayna et al. (2000). These authors found a sustained effect on weight gain in rats following once daily injection of exendin-4 for only 4 days, whereas twice daily application of the peptide, leading to continuously elevated plasma concentrations, caused a permanent reduction of body weight (Szayna et al., 2000).

Considering an attenuated GLP-1 secretion in obese patients in response to oral carbohydrates (Ranganath et al., 1996), GLP-1 treatment in these patients could merit further discussion as a supplementation of unphysiologically low plasma concentrations. Therefore, GLP-1 therapy might ''repair'' a defect in obesity.

One major problem if GLP-1 is to be considered as an agent for the pharmacotherapy of obesity is the size of the maximal weight reduction that can be achieved with the application of GLP-1. In healthy subjects as well as in Type 2 diabetic patients, infusions of GLP-1 lead to a 12–35% maximal reduction of food intake (Flint et al., 1998; Gutzwiller et al., 1999a,b). After 6 weeks of subcutaneous GLP-1 infusion in patients with Type 2 diabetes, body weight decreased from 105.8 ± 6.2 to 103.8 ± 6.5 kg ($p = 0.02$) (Zander et al., 2001). This reduction of body weight by less than 2% appears to be comparably low. However, if this effect persists over longer periods of treatment, GLP-1 could become a beneficial agent for obese patients. Furthermore, it is still unknown whether a combination of GLP-1 treatment with so called ''lifestyle intervention'' could increase weight loss.

GLP-1 treatment seems to have a great potential in the treatment of obese Type 2 diabetic patients. A major problem in the pharmacotherapy of Type 2 diabetes with other insulinotropic agents is the unfavourable effect on body weight. A weight gain of 4–7 kg is typical for antidiabetic treatment with sulfonylureas as well as for insulin therapy because of antilipolytic insulin effects (UK Prospective Diabetes Study (UKPDS) Group, 1998). Therefore, GLP-1 is the only known antidiabetic agent that combines insulinotropic and anorectic effects. These characteristics make it very attractive for the pharmacotherapy of obese patients with Type 2 diabetes. In addition, hypoglycemic episodes do not occur due to the strictly glucose-dependent insulinotropic effect of GLP-1 in Type 2 diabetes (Kreymann et al., 1987; Nauck et al., 1993a). As a consequence of these beneficial effects, especially the reduction of body weight, one could hypothesize that GLP-1 therapy enhances patients' compliance with the antidiabetic treatment and dietary recommendations (Toft-Nielsen et al., 1999).

In conclusion, it is obvious that GLP-1 is effective to reduce food intake and appetite and, in turn, causes an increased feeling of satiety. These effects could be helpful in the reduction of body weight in obese patients. However, suitable modes of administration are needed to maintain constantly elevated plasma concentrations. Further studies will be required to characterize the long-term GLP-1 effect on body weight and to quantify the maximal reduction of body weight that can be achieved. GLP-1 has great potential in the pharmacotherapy of obese patients with Type 2 diabetes, as a combination of antidiabetogenic and anorectic effects could target two problems with a single agent.

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