

Effects of glucagon-like peptide 1 on appetite and body weight: focus on the CNS

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Abstract

The delivery of nutrients to the gastrointestinal tract after food ingestion activates the secretion of several gut-derived mediators, including the incretin hormone glucagon-like peptide 1 (GLP-1). GLP-1 receptor agonists (GLP-1RA), such as exenatide and liraglutide, are currently employed successfully in the treatment of patients with type 2 diabetes mellitus. GLP-1RA improve glycaemic control and stimulate satiety, leading to reductions in food intake and body weight. Besides gastric distension and peripheral vagal nerve activation, GLP-1RA induce satiety by influencing brain regions involved in the regulation of feeding, and several routes of action have been proposed. This review summarises the evidence for a physiological role of GLP-1 in the central regulation of feeding behaviour and the different routes of action involved. Also, we provide an overview of presently available data on pharmacological stimulation of GLP-1 pathways leading to alterations in CNS activity, reductions in food intake and weight loss.

Key Words

- ▶ glucagon-like peptide 1
- ▶ CNS
- ▶ feeding behaviour
- ▶ obesity
- ▶ type 2 diabetes

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Introduction

Obesity and type 2 diabetes mellitus (T2DM), also termed 'diabesity', are major public health problems due to their pandemic occurrence (Whiting *et al.* 2011, Flegal *et al.* 2012) and their association with adverse consequences, such as cardiovascular disease and cancer (Stratton *et al.* 2000, Field *et al.* 2001). Obesity is the result of a long-term positive energy balance whereby energy intake surpasses expenditure. The CNS plays a major role in the maintenance of body weight and energy balance within a narrow range by regulating energy intake and energy expenditure. To regulate energy intake, signals, both neuronal and humoral, arising from peripheral organs involved in food intake, – digestion and – storage, such as the gut, pancreas, and adipose tissue, convey information on hunger and/or satiety to the brain. Gut-derived hormones, such as the

orexigenic hormone ghrelin and the prandially secreted anorexigenic hormones cholecystokinin (CCK), peptide YY (PYY), oxyntomodulin (OXM) and glucagon-like peptide 1 (GLP-1), have been identified as players in the regulation of feeding by relaying meal-related information on nutritional status to the brain.

Based on more than three decades of experimental evidence from rodent models and humans, GLP-1 was shown to lower blood glucose by stimulating insulin secretion and production and suppressing glucagon secretion in a glucose-dependent manner. Also GLP-1 decelerates gastric emptying, reduces body weight and induces satiety (Holst 2007). As native GLP-1 is quickly inactivated by the ubiquitous enzyme dipeptidyl peptidase 4 (DPP-4), requiring continuous parenteral

administration, degradation-resistant GLP-1 receptor agonists (GLP-1RA) have been developed that can be injected s.c. once daily (QD) or twice daily (BID) or even once weekly (QW) (Fineman *et al.* 2012). These agents are currently successfully being employed in the treatment of T2DM (Drucker & Nauck 2006). GLP-1RA improves glycaemic control and stimulates satiety, leading to reductions in food intake and body weight. The presence of GLP-1 receptors in the CNS and findings from animal and human studies indicate that the GLP-1RA-induced satiety and weight effects may be, at least in part, mediated by their actions on the brain. This review focuses on current evidence for a physiological role of GLP-1 in the central regulation of feeding behaviour. Also, we provide an overview of presently available data on pharmacological stimulation of GLP-1 pathways leading to CNS activation, changes in food intake and weight loss.

CNS regulation of feeding

Food intake is regulated by complex interactions between nutrients, hormones, neuropeptides and several different brain areas. The regulation of feeding can be divided in homeostatic and non-homeostatic feeding (Lutter & Nestler 2009). Homeostatic feeding controls energy balance by adjusting food intake to promote stability in the amount of energy stores. However, non-homeostatic or hedonic feeding can override this homeostatic pathway resulting in overeating. It has been postulated that this is caused by the rewarding (palatable) properties of food (Wang *et al.* 2004, Volkow & Wise 2005, Trinko *et al.* 2007).

Homeostatic control of feeding consists of the sensing and integration within the CNS of changes in nutrients, hormones and neuropeptides, reflecting changes in energy balance and the ensuing alterations in food intake. The brainstem and hypothalamus are important CNS structures within the regulatory pathways of homeostatic feeding as they receive, convey and integrate peripheral signals. The area postrema (AP) and nucleus tractus solitarius (NTS) in the brainstem convey these peripheral signals, consisting of nutrients, hormones and vagal afferent activation, to the arcuate nucleus (ARC) of the hypothalamus (Bailey 2008). The ARC consists of orexigenic neurons (expressing neuropeptide Y and agouti-related peptide) and anorexigenic neurons (expressing pro-opiomelanocortin), which collectively regulate homeostatic control of eating (Gao & Horvath 2008). In this process, the hypothalamus acts as a gatekeeper, as it additionally controls body temperature, energy

expenditure and glucose metabolism. In normal physiology, the integration of all peripheral signals will result in energy intake matching the organism's energy expenditure.

The homeostatic signals arising from peripheral organs convey different aspects of the energy regulatory process to the CNS: long-term ('static') information about energy stores and acute, meal-related ('dynamic') information (Schwartz *et al.* 2000, Havel 2001). Adipose-tissue-derived leptin, which is secreted in proportion to adipose mass, conveys 'static' information to the CNS about long-term energy stores. In normal physiology, central leptin signalling has an anorectic effect (Cohen *et al.* 2001), and central leptin resistance has been postulated to be a contributing factor to the development of obesity (Considine *et al.* 1996, Levin & Dunn-Meynell 2002, Enriori *et al.* 2007). Insulin secreted from pancreatic β -cells displays both tonic (basic) 24 h and meal-related secretion (Polonsky *et al.* 1988). Thus, insulin may relay both long-term and acute information and was shown to act in the brain to reduce food intake (Woods *et al.* 1979, Bruning *et al.* 2000, Benedict *et al.* 2008). In obesity and over-nutrition, peripheral insulin resistance results in chronic hyperinsulinaemia. Interestingly, a study using 18-fluoro-deoxy-glucose (^{18}F FDG) positron-emission tomography (PET) indicated the existence of central insulin resistance in obese individuals with the metabolic syndrome, which is compatible with the generally greater caloric intake in these individuals (Anthony *et al.* 2006). The above-mentioned meal-related gut-derived hormones (ghrelin, CCK, PYY, OXM and GLP-1) signal dynamic information about the changes in nutritional status to the CNS.

In contrast to homeostatic control of feeding behaviour, non-homeostatic feeding behaviour is not regulated by hunger and satiety signals but rather by the rewarding properties and motivation related to foods, and involves reward, cognitive and emotional factors. Thus, corticolimbic circuits in humans (including the striatum, amygdala, insula, nucleus accumbens (NAc) and orbitofrontal cortex) are implicated in non-homeostatic eating. Within the CNS, pathways for homeostatic and non-homeostatic control of feeding comprise multiple interconnected brain regions. The above-described hormonal regulators of homeostatic feeding may also influence brain reward systems and may increase or decrease the rewarding value of food depending on energy requirements (Berthoud 2011, Kenny 2011). Palatable food can activate brain reward circuits, and these rewarding effects can be a

powerful motivation for food consumption and may overrule signals regulating homeostatic feeding.

The studies summarised above show that both homeostatic and non-homeostatic factors influence feeding behaviour and that there is an extensive cross-modulation of signals within these pathways. Leptin and gut-derived hormones have been studied in the search for therapeutic targets for the treatment of obesity, but these attempts were not successful (Crawley & Beinfeld 1983, Jordan *et al.* 2008, Costantini *et al.* 2011, Moon *et al.* 2011, Cummings 2013), except for GLP-1RA. Although not approved for the treatment of obesity, administration of GLP-1RA consistently results in body weight loss in humans.

GLP-1RA treatment and body weight in humans

The incretin system: from physiology to pharmacology

Following meal ingestion, GLP-1 is secreted into the circulation by enteroendocrine L-cells located in the distal jejunum and ileum and contributes to postprandial glucose regulation, as it augments meal-related insulin secretion from the pancreas (Kreymann *et al.* 1987, Mojsov *et al.* 1987). Also GLP-1 promotes insulin gene transcription (Drucker *et al.* 1987). Also, GLP-1 improves pancreatic β -cell glucose responsiveness (Holz *et al.* 1993). Other glucose-lowering mechanisms of GLP-1 involve inhibition of glucagon secretion and deceleration of gastric emptying and gut motility. In addition to pancreatic islets, GLP-1 receptors have been demonstrated in the gut, heart, vasculature, kidney, muscle and lung (Sivertsen *et al.* 2012), indicating so-called pleiotropic effects of GLP-1, i.e. effects beyond glucose lowering. Many excellent reviews have been published describing the physiological role of GLP-1 in glucose regulation and the pleiotropic effects (Baggio & Drucker 2004, Drucker 2006, Holst 2007, van Genugten *et al.* 2009, Vilsboll & Garber 2012).

Exenatide, the first GLP-1RA developed for human use, is a synthetic form of exendin-4, a 39-amino acid peptide isolated from the salivary secretions of the Gila monster (*Heloderma suspectum*). Exendin-4 shares 53% sequence identity with GLP-1. Substitution of alanine by glycine at the second position of the NH₂-terminus makes exendin-4 resistant to DPP-4-mediated degradation (Nielsen *et al.* 2004). Exendin-4 has greater effective receptor affinity than native GLP-1 and is therefore a potent GLP-1RA (Raufman *et al.* 1992, Young *et al.* 1999).

Exenatide is currently available in two formulations for the treatment of T2DM, i.e. a short-acting compound for BID s.c. injection (half-life 2.4 h, to be administered before breakfast and dinner) and a long-acting extended-release formulation for QW administration. Exenatide BID was approved by the US Food and Drug Administration (FDA) in 2005 and by the European Medicines Agency (EMA) in 2006. Exenatide QW was approved by the FDA and EMA in 2012 and 2011 respectively. Liraglutide is a GLP-1RA, which, due to its 97% amino acid homology to native GLP-1, in contrast to exenatide, is a true GLP-1 analogue (Knudsen *et al.* 2000). Addition of a C16 fatty acid chain prolongs absorption from the subcutaneous depot and promotes albumin binding, collectively resulting in a prolonged (13 h) circulating half-life after s.c. injection. Consequently, liraglutide is suitable for QD administration. Liraglutide was approved in 2009 by the EMA and in 2010 by the FDA. Lixisenatide is a GLP-1RA based on exendin-4 that is DPP-4-resistant due to C-terminal modification with six lysine residues and deletion of one proline (Barnett 2011). Lixisenatide was approved by EMA in 2013 and will be submitted to the FDA in the near future. Although the half-life of lixisenatide is similar to that of exenatide BID, and lixisenatide is regarded as a short-acting GLP-1RA, it has fourfold higher affinity for the GLP-1 receptor than GLP-1 and therefore can be administered QD (Werner *et al.* 2010).

Short-acting GLP-1RA are more effective in lowering postprandial hyperglycaemia, while long-acting GLP-1RA rather reduce basal hyperglycaemia (Fineman *et al.* 2012). An important determinant of postprandial hyperglycaemia is the rate of gastric emptying. Rapid tachyphylaxis of gastric emptying deceleration, resulting from continuous stimulation of the GLP-1 receptor by long-acting (but not short-acting) GLP-1RA, may explain their lack of efficacy with respect to meal-related hyperglycaemia (Nauck *et al.* 2011). Inasmuch as gastric emptying delay also promotes the most common side effect of GLP-1RA, i.e. nausea and occasional vomiting, these side effects are more frequently observed with short-acting GLP-1RA than long-acting GLP-1RA (Drucker *et al.* 2008, Buse *et al.* 2009). The occurrence of these side effects may limit the possibility of higher dosing of GLP-1RA and possible greater improvement of glycaemic control and body weight reduction. The effects of GLP-1RA on gastric emptying and nausea and their possible influence on GLP-1RA-induced satiety will be discussed in more detail later in this review.

Several other GLP-1RA, mainly long-acting GLP-1RA, including albiglutide, semaglutide and dulaglutide are

currently under advanced clinical development (Fineman *et al.* 2012), but the preliminary clinical data are beyond the scope of this review.

GLP-1RA and their effect on body weight

GLP-1RA are approved for the treatment of T2DM because of their glucose-lowering effects. As an additional benefit, treatment with GLP-1RA is associated with sustained dose-dependent weight loss. A meta-analysis of 21 trials (6411 participants) showed a weighted mean difference in body weight of -2.9 kg (95% CI, -3.6 to -2.2) achieved with the highest dose of GLP-1RA compared with the control treatment (Vilsboll *et al.* 2012). Mean weight changes in trials comparing exenatide BID or liraglutide at the highest dose to placebo as add-on treatment to oral blood-glucose-lowering agents during 20–30 weeks ranged from -3.1 to -0.2 kg in the treatment group compared with -1.4 to $+0.6$ kg in the placebo group (Table 1). In trials comparing exenatide BID, exenatide QW or liraglutide with basal or biphasic insulin, thus achieving similar glycaemic control in both intervention groups, the weight differences were even more prominent. Weight loss during GLP-1RA treatment ranged from 1.8 to 4.1 kg, while weight gain with insulin therapy varied between 1.0 and 4.1 kg (Table 1). In phase-3 trials, weight loss effects of lixisenatide were relatively modest (up to a mean of 1.0 kg vs placebo; Petersen & Christensen 2013; Table 1).

The observed GLP-1RA-related weight loss was associated with reduction in total body fat, particularly trunk or visceral fat (Jendle *et al.* 2009, Bunck *et al.* 2010). When on treatment, the achieved weight loss with GLP-1RA persisted over 52 weeks (Nauck *et al.* 2007, Bunck *et al.* 2009, Garber *et al.* 2009) and in open-label extension trials up to 2–3 years (Bunck *et al.* 2011, Garber *et al.* 2011, Macconell *et al.* 2013). Although open-label extension trials with GLP-1RA may be flawed by selection bias towards responders, the observed sustained weight loss over time seems different to weight loss through dietary restriction, where only a small minority of obese individuals maintain weight loss in the long term (Anderson *et al.* 2001). It is worthy of note, however, that when exenatide BID was discontinued after 3 years of exposure, patients started to regain weight during the 12-week washout period (Bunck *et al.* 2011). Thus, no durable effects are present unless patients are on active GLP-1RA treatment.

In non-diabetic obese individuals, placebo-adjusted weight loss after 20-week treatment with liraglutide, at doses of 1.2, 1.8, 2.4 and 3.0 mg QD, ranged from a mean of 2.1–4.4 kg, which persisted through 2 years of treatment

(Astrup *et al.* 2009, 2012). These seemingly more robust weight effects may be due to the higher doses of liraglutide used and higher BMI (~ 35 kg/m²) at baseline as compared with the phase-3 trials in T2DM populations (BMI ~ 32 – 33 kg/m²). A small-sized study in severely obese non-diabetic individuals with impaired glucose metabolism (baseline BMI ~ 40 kg/m²) showed a mean placebo-adjusted weight reduction of 3.3 kg after 24 weeks of exenatide 10 µg BID (Rosenstock *et al.* 2010). It is worth noting that, currently, GLP-1RA have not been officially approved for the treatment of obesity.

Taking all these clinical results together, GLP-1RA are associated with weight loss. This has consistently been shown during treatment with short-acting and long-acting GLP-1RA in both T2DM and obese individuals.

Effects of GLP-1 and GLP-1RA on energy balance

To attain body weight loss, achieving long-term negative energy balance by reduction in appetite and energy intake, or by an increase in energy expenditure or both is required.

Preclinical data indeed show an inhibiting effect of GLP-1 administration on food intake. Acute i.p. or s.c. administration of GLP-1 and exendin-4 resulted in a dose-dependent inhibition of food intake in rodents (Rodriguez de Fonseca *et al.* 2000, Abbott *et al.* 2005, Talsania *et al.* 2005), which also persisted during prolonged administration of i.p. exendin-4 BID (Szayna *et al.* 2000). The reductions in food intake with GLP-1 and exendin-4 are attributed to decreases in meal size (Scott & Moran 2007, Ruttimann *et al.* 2009). However, GLP-1 infusion during a 3 h period reduced the cumulative food intake not only by reducing meal size but also meal frequency (Chelikani *et al.* 2005).

Also in humans, GLP-1 was shown to reduce food intake, appetite, and hunger and to promote fullness and satiety (Flint *et al.* 1998, 2001, Naslund *et al.* 1998, Gutzwiller *et al.* 1999, Verdich *et al.* 2001). It is noteworthy that satiation and satiety are commonly used as synonyms, but need to be distinguished (Mithieux 2013). Satiation is the increasing sensation of fullness that occurs during digestion and absorption of a meal. Satiety is a state of no-hunger that occurs some time after the last meal and moderates the initiation of the following meal. A placebo-controlled study in healthy normal-weight individuals investigating the effects of i.v. administration of GLP-1 during a 5 h period showed that GLP-1 at pharmacological levels decreased hunger and enhanced satiety and fullness

Table 1 Weight changes during GLP-1RA treatment for 20–30 weeks compared with placebo or insulin. Weight changes from baseline to 20–30 weeks during phase-3 trials (no extension trials) comparing approved GLP-1RA with placebo or insulin in T2DM patients and obese (non-diabetic) individuals

Study	No. of patients	Duration (weeks)	Study populations	Compound/dosing	Mean (S.E.M.) weight changes in kg from baseline	P value	
Add-on GLP-1RA treatment vs placebo							
Buse <i>et al.</i> (2004)	377	30	T2DM	Exenatide 5 µg BID	−0.9 (0.3)	NS	
				Exenatide 10 µg BID	−1.6 (0.3)	<0.05	
				Placebo	−0.6 (0.3)	–	
DeFronzo <i>et al.</i> (2005)	137	30	T2DM	Exenatide 5 µg BID	−1.6 (0.4)	<0.05	
				Exenatide 10 µg BID	−2.8 (0.5)	<0.001	
				Placebo	−0.3 (0.3)	–	
Kendall <i>et al.</i> (2005)	733	30	T2DM	Exenatide 5 µg BID	−1.6 (0.2)	<0.01	
				Exenatide 10 µg BID	−1.6 (0.2)	<0.01	
				Placebo	−0.9 (0.2)	–	
Moretto <i>et al.</i> (2008)	232	24	T2DM	Exenatide 5 µg BID	−2.8 (0.3)	0.004	
				Exenatide 10 µg BID	−3.1 (0.3)	<0.001	
				Placebo	−1.4 (0.3)	–	
Astrup <i>et al.</i> (2009)	371	24	Obese, non-diabetic	Liraglutide 1.2 mg QD	−4.8 (0.5)	0.003	
				Liraglutide 1.8 mg QD	−5.5 (0.5)	<0.0001	
				Liraglutide 2.4 mg QD	−6.3 (0.5)	<0.0001	
				Liraglutide 3.0 mg QD	−7.2 (0.5)	<0.0001	
				Placebo	−2.8 (0.5)	–	
Marre <i>et al.</i> (2009)	1041	26	T2DM	Liraglutide 0.6 mg QD	+0.7 (0.0)	<0.05	
				Liraglutide 1.2 mg QD	+0.3 (0.0)	NS	
				Liraglutide 1.8 mg QD	−0.2 (0.0)	<0.05	
				Placebo	−0.1 (0.1)	–	
Nauck <i>et al.</i> (2009)	1091	26	T2DM	Liraglutide 0.6 mg QD	−1.8 (0.2)	NS	
				Liraglutide 1.2 mg QD	−2.6 (0.2)	<0.01	
				Liraglutide 1.8 mg QD	−2.8 (0.2)	<0.01	
				Placebo	−1.5 (0.3)	–	
Russell-Jones <i>et al.</i> (2009)	581	26	T2DM	Liraglutide 1.8 mg QD	−1.8 (0.3)	0.0001	
Zinman <i>et al.</i> (2009)	533	26	T2DM	Placebo	−0.4 (0.4)	–	
				Liraglutide 1.2 mg QD	−1.0 (0.3)	<0.0001	
Rosenstock <i>et al.</i> (2010)	163	24	Obese, non-diabetic	Liraglutide 1.8 mg QD	−2.0 (0.3)	<0.0001	
				Placebo	+0.6 (0.3)	–	
Bollig <i>et al.</i> (2011)	482	24	T2DM	Exenatide 10 µg BID	−5.1 (0.5)	<0.001	
				Placebo	−1.6 (0.5)	–	
Seino <i>et al.</i> (2012) ^a	311	24	T2DM	Lixisenatide 20 µg QD	−2.7 (0.3)	0.0025	
				Placebo	−1.6 (0.3)	–	
Pinget <i>et al.</i> (2013)	484	24	T2DM	Lixisenatide 20 µg QD	−0.4 (0.3)	0.086	
				Placebo	+0.1 (0.3)	–	
Riddle <i>et al.</i> (2013) ^a	446	24	T2DM	Lixisenatide 20 µg QD	−0.2 (0.3)	NS	
				Placebo	+0.2 (0.3)	–	
Add on GLP-1RA vs insulin treatment	Heine <i>et al.</i> (2005)	551	26	T2DM	Lixisenatide 20 µg QD	+0.3 (0.3)	0.0012
					Placebo	+1.2 (0.3)	–
Heine <i>et al.</i> (2005)	551	26	T2DM	Exenatide 10 µg BID	−2.3 (0.2)	<0.0001	
				Insulin glargine, titrated QD	+1.8 (0.2)	–	
Bergenstal <i>et al.</i> (2009)	372	24	T2DM	Exenatide 5 µg BID	−2.0 (0.3)	<0.001	
				Insulin BIAsp 70/30 12 U QD	+2.9 (0.3)	–	
				Insulin BIAsp 70/30 6 U BID	+4.1 (0.9)	–	
Davies <i>et al.</i> (2009)	49	20	T2DM	Exenatide 10 µg BID	−2.7 (0.3)	<0.001	
				Insulin glargine, titrated QD	+3.0 (0.3)	–	
Russell-Jones <i>et al.</i> (2009)	581	26	T2DM	Liraglutide 1.8 mg QD	−1.8 (0.3)	<0.0001	
				Insulin glargine, titrated QD	+1.6 (0.3)	–	
Diamant <i>et al.</i> (2010)	456	26	T2DM	Exenatide 2 mg QW	−2.6 (0.2)	<0.05	
				Insulin glargine, titrated QD	+1.4 (0.2)	–	
Gallwitz <i>et al.</i> (2011)	363	26	T2DM	Exenatide 10 µg BID	−4.1 (0.2)	<0.001	
				Insulin BIAsp 70/30, titrated	+1.0 (0.2)	–	

BIAsp, biphasic insulin aspart; BID, twice daily; NS, not significant; T2DM, type 2 diabetes mellitus; QD, once daily; QW, once weekly.

^aThese studies added GLP-1RA to insulin therapy.

scores after an energy-fixed breakfast, measured by visual analogue scale (VAS) questionnaires, and reduced caloric intake by 12% during a subsequent *ad libitum* lunch (Flint *et al.* 1998). However, there were no differences in the subjective ratings of taste, visual appeal, smell, aftertaste and overall palatability of the meal. Similar reductions in hunger and increases in satiety scores were described in studies with a similar design in obese and T2DM individuals (Naslund *et al.* 1998, Gutzwiller *et al.* 1999). In a meta-analysis of studies in humans evaluating acute effects of GLP-1 infusion on food intake, a mean decrease of 11.7% was reported in the amount of *ad libitum* energy intake compared with saline (Verdich *et al.* 2001). Interestingly, reductions in VAS-score hunger ratings were not only present with pharmacological levels, but also with infusions attempting to achieve physiological postprandial GLP-1 levels (~50 pmol/l; Flint *et al.* 2001). However, at the latter GLP-1 concentration, there were no statistically significant effects on *ad libitum* food intake.

Studies observing prolonged GLP-1 administration over more than one day are limited. Two small studies, using a continuous s.c. infusion pump, showed tendencies towards reduced hunger and enhanced fullness and satiety scores measured with VAS questionnaires. In a small study with six T2DM patients, GLP-1 administration over 48 h resulted in an average tendency towards a decrease in hunger and increase in satiety throughout the days, but this effect only reached statistical significance just before the start of the next meal (lunch and dinner; Toft-Nielsen *et al.* 1999). Furthermore, a hallmark proof-of-concept study, during which GLP-1 was administered via continuous s.c. infusion for 6 weeks in seven T2DM patients reported a trend towards reduction in overall appetite scores measured 2 h after the meal (Zander *et al.* 2001).

Taken together, these observations regarding food intake in humans show that GLP-1 administration has consistent acute effects on hunger, fullness and satiety measures. Longer-term studies in small groups indicate that a persistent reduction in appetite and food intake may mediate the effects of GLP-1RA treatment on body weight.

The body-weight-reducing effects of GLP-1RA treatment could also be due to increased energy expenditure, leading to a negative energy balance. However, the reported effects of GLP-1 on energy expenditure from animal data are not consistent. Energy expenditure depends on oxidation of substrates and consists of different elements, such as resting metabolic rate, physical activity and thermogenesis. Both i.v. and i.c.v. administration of GLP-1 in rats increased oxygen consumption,

although the later had smaller effects (Hwa *et al.* 1998, Osaka *et al.* 2005), indicating that peripheral effects of GLP-1 are also important. In contrast, acute i.c.v. exendin-4 administration in mice resulted in a rapid decrease in oxygen consumption (Baggio *et al.* 2004b), but vehicle administration also resulted in a large decrease in oxygen consumption, making the results difficult to interpret. Furthermore, 4 week i.c.v. treatment with a selective GLP-1 receptor antagonist (exendin 9–39) in mice resulted in a higher oxygen consumption (~22%) compared with vehicle, but the exendin 9–39-induced increase in food consumption (~83%) (Knauf *et al.* 2008) could contribute to the observed increase in oxygen consumption. More specifically, GLP-1 seems to affect thermogenesis. I.v. administration of GLP-1 in rats increased body temperature by 0.3 °C. The effect of GLP-1 on body temperature was not altered by decerebration, whereas cervical spinal transection attenuated the thermogenic response to GLP-1 (Osaka *et al.* 2005), indicating involvement of the lower brainstem but not forebrain areas in this mechanism. Moreover, i.c.v. GLP-1 administration in mice resulted in an increase in brown adipose tissue (BAT) thermogenesis (Lockie *et al.* 2012). Interestingly, BAT thermogenesis changes did correlate with an increased activity of sympathetic fibres innervating BAT. As peripherally administered GLP-1 did not alter BAT thermogenesis, it is likely that the thermogenic effects of GLP-1 are mediated by the brain. Taken together, these preclinical findings indicate that GLP-1 might have effects on the central regulation of energy balance by affecting energy expenditure and specifically thermogenesis, but the results are not fully conclusive.

In humans, the reported effects of GLP-1 on energy expenditure are more inconsistent. During acute GLP-1 infusion, energy expenditure caused by diet-induced thermogenesis was decreased in both healthy lean and obese individuals (Flint *et al.* 2000, 2001). After treatment of 4 weeks with liraglutide in T2DM patients, the estimated 24 h resting energy expenditure tended to increase (Horowitz *et al.* 2012), but this effect was not confirmed in trials with a treatment duration of 8–10 weeks with liraglutide or exenatide (Harder *et al.* 2004, Bradley *et al.* 2012).

Given the lack of consistency in the effects of GLP-1 and GLP-1RA on energy expenditure in humans, it has been concluded that the treatment-related body weight loss can rather be attributed to a decrease in energy intake. Various mechanisms and routes of action of GLP-1 are involved and contribute to the inhibitory effect on food intake.

GLP-1 effects on the regulation of appetite: the role of delayed gastric emptying

An important factor in the regulation of appetite and satiation during food intake is gastric mechanosensation. Distension of the stomach induces satiation signals by activation of gastric mechanoreceptors, which relay information via vagal nerves to the NTS in the brainstem. The amount of gastric distension due to food intake is partly influenced by the rate of gastric emptying, which affects postprandial glycaemic excursions. The role of gastric motility in appetite and satiation regulation and the effects of GLP-1/GLP-1RA on gastric and gut motility has been extensively reviewed (Janssen *et al.* 2011, Marathe *et al.* 2011). GLP-1 delays gastric emptying and gut motility not only in healthy lean but also in obese subjects and patients with T2DM (Nauck *et al.* 1997, Naslund *et al.* 1998, Schirra *et al.* 2002, Meier *et al.* 2003, Little *et al.* 2006). Delayed gastric emptying affects the extent of gastric distension, the rate of nutrient exposure of the gut and, consequently, gut hormones secretion, which in turn influences postprandial glucose excursions.

Although usually transient, gastrointestinal symptoms, most notably nausea and occasional vomiting, are the most commonly reported side effects during GLP-1RA treatment. One might speculate that changes in signalling due to delayed gastric emptying and nausea are the sole cause of GLP-1-induced changes in appetite and satiation and of GLP-1RA treatment-induced weight loss. In rodents, acute infusion with GLP-1RA induced a delay in gastric emptying, associated with a decrease in food intake. However, after 14 days of continuous GLP-1RA infusion, gastric emptying was similar to that of animals receiving a vehicle infusion, but food intake was still reduced (Jelsing *et al.* 2012). Also in humans, the inhibitory effect of GLP-1 on gastric emptying is subject to tachyphylaxis (Nauck *et al.* 2011). In spite of the observed tachyphylaxis of delayed gastric emptying, the weight-lowering effect of GLP-1RA treatment persists over periods up to 3 years (Macconell *et al.* 2013). Other observations making it less likely that GLP-1RA effects on gastric emptying are the only cause of appetite and weight loss include the observed weight reduction during GLP-1RA treatment in the absence of nausea (Buse *et al.* 2004, DeFronzo *et al.* 2005, Nauck *et al.* 2009, Russell-Jones *et al.* 2009, Garber *et al.* 2011, Shyangdan *et al.* 2011); similar or even greater weight loss with long-acting GLP-1RA, despite their reduced effect on gastric emptying relative to short-acting GLP-1RA (Jelsing *et al.* 2012); and the reported reduction in appetite after GLP-1

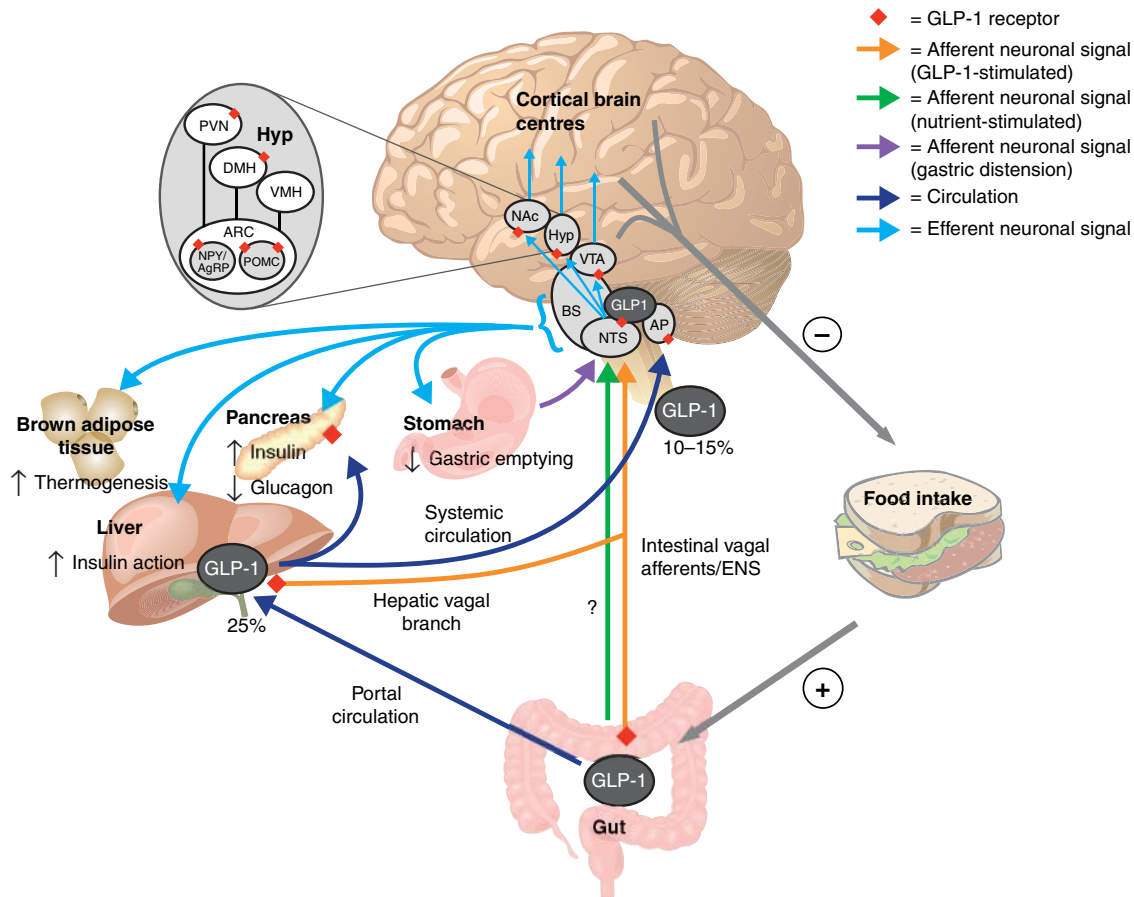
administration observed in fasting human subjects (with an empty stomach) (Gutzwiller *et al.* 1999). Taken together, other mechanisms than delayed gastric emptying alone contribute to the appetite-suppressing effect of GLP-1RA treatment. These effects may partly be mediated by actions of GLP-1 on CNS networks involved in the regulation of appetite.

GLP-1 effects on the CNS regulation of appetite and satiety

GLP-1/GLP-1RA exerts their effects on glucose homeostasis, feeding behaviour and body weight, both via direct and indirect pathways, which are largely mediated by the CNS (Fig. 1).

Experimental data indicate that GLP-1 may also exert actions in the brain beyond these well-established effects, by influencing neuronal health, cognition and neuroinflammation (During *et al.* 2003, Li *et al.* 2009, McClean *et al.* 2011, Tweedie *et al.* 2013). The latter CNS effects of GLP-1 are beyond the scope of this review.

A physiological role for GLP-1 in the central regulation of feeding was suggested when GLP-1 receptors were localised in many parts of the rat brain, including areas that are implicated in the control of food intake (including areas important for reward processing and motivated behaviour) and energy balance, such as the hypothalamus, NTS, AP, dorsal striatum and NAC (Shugrue *et al.* 1996, Merchenthaler *et al.* 1999). In addition, administration of GLP-1 into the lateral ventricle resulted in powerful inhibition of feeding when fasted male rats were refed, which was accompanied by *c-Fos* expression, a marker of neuronal activation, in both the paraventricular nucleus (PVN) of the hypothalamus and the central nucleus of the amygdala (Turton *et al.* 1996). This effect was dose-dependent and was blocked by i.c.v. administration of exendin 9–39, a highly selective antagonist of the GLP-1 receptor. Moreover, administration of GLP-1 into the third ventricle also significantly inhibited food intake in fasted male rats in a dose-dependent fashion (Schick *et al.* 2003). As i.c.v. GLP-1 administration in GLP-1 receptor knockout mice failed to reduce food intake, the GLP-1 receptor seems to be implicated in these GLP-1-induced effects. Interestingly, GLP-1-receptor deletion itself did not alter body weight or feeding behaviour (Scrocchi *et al.* 1996). Direct administration of GLP-1 into the PVN, lateral hypothalamus, dorsomedial hypothalamus and the ventromedial hypothalamus significantly reduced food intake, whereas injection of the GLP-1 receptor antagonist exendin 9–39 into the lateral hypothalamus augmented

**Figure 1**

Proposed routes of action of GLP-1 in the central regulation of feeding and glucose metabolism. Gut-derived GLP-1 may affect the brain by several routes of action, i.e. indirectly, via neural afferents, and directly, by entering the brain via the systemic circulation and by crossing the blood-brain barrier. Other potential mediators constituting the gut-brain axis include nutrients and signals arising from meal-related gastric distension. GLP-1 secreted from intestinal L-cells in response to meal-ingestion, diffuses across the basal lamina into the lamina propria, at which level the uptake by capillaries and the degradation by DPP-4 occurs. Subsequently, endogenous GLP-1 activates intestinal vagal afferents, located in the gut or portal circulation, partly belonging to the enteric nervous system (ENS), which may activate GLP-1-producing neurons in the nucleus tractus solitarius (NTS). Additional activation of intestinal or portal vagal afferents by nutrients, other gut-hormones or gastric distension may also activate these GLP-1-producing neurons. These neurons project to several food-regulating areas, most of which contain GLP-1 receptors. These areas include the ventral tegmental area (VTA), the nucleus accumbens (NAc) and the hypothalamus (Hyp). Throughout the hypothalamus, the GLP-1 receptor is present, particularly in the paraventricular nucleus (PVN), dorsomedial hypothalamus (DMH) and the arcuate nucleus (ARC), with a greater density on pro-opiomelanocortin (POMC) neurons (anorexigenic neurons) than on the agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons (orexigenic neurons). To date, no receptors have been found in the ventromedial hypothalamus (VMH). Less is known about the higher cortical centres that extend the circuitry beyond the hypothalamus, VTA and nucleus accumbens. Only 25% of the gut-derived GLP-1 reaches the portal circulation, where it can activate afferent hepatic vagal nerves, while merely 10–15% of gut-derived GLP-1 enters the systemic circulation and may access the brain through areas with a permeable blood-brain barrier, such as the area postrema (AP) and ARC. Efferent pathways, among others, originating in the brain stem (BS), subsequently signal to peripheral organs to close the loop of feeding behaviour and glucose metabolism regulation, both of which may be partly interlinked. Accordingly, GLP-1 lowers blood glucose by stimulating pancreatic insulin secretion and production, and by suppressing glucagon secretion from the pancreas and by enhancing hepatic insulin action in a glucose-dependent manner. Also, GLP-1-related effects promoting gastric emptying delay seem to be part of this regulatory loop. These actions may be due to direct effects of circulating gut-derived GLP-1 but, given the short circulating half-life of the incretin hormone, indirect, neurally mediated effects may contribute, even to a greater extent, to the efferent output to these organs.

food intake in satiated rats. Despite the reported presence of GLP-1 receptors, injections of GLP-1 directly into the ARC did not affect food intake (Sandoval *et al.* 2008). The effects of GLP-1 on food intake may not only be due to effects on hypothalamic and brainstem circuits regulating

homeostatic feeding, but also due to effects on the rewarding value of food that are exerted at the level of the mesolimbic reward system. Microinfusion of exendin-4 in key mesolimbic structures, ventral tegmental area and NAc, resulted in decreased motivated behaviour for

sucrose in rats (Dickson *et al.* 2012). Also, injection of exendin 9–39 into the NAc resulted in significant hyperphagia in rats, indicating a physiologic role of GLP-1 receptors in the NAc for the control of food intake (Dossat *et al.* 2011). Collectively, these preclinical data show that central GLP-1 induces satiety by affecting both homeostatic and reward-associated food intake and that these effects seem to be GLP-1 receptor-mediated.

Routes of action of GLP-1: direct and indirect effects on the CNS

The inhibitory effects of GLP-1 on food intake may be due to both direct and indirect effects on the CNS (Fig. 1), but the exact routes of action are largely unknown. Gut-derived GLP-1 may enter the brain through the AP, at the level of which the blood–brain barrier is permeable. A radiolabelled GLP-1 analogue has been demonstrated to easily cross the blood–brain barrier in mice (Kastin *et al.* 2002). But due to its short circulating half-life (Kieffer *et al.* 1995), it is likely that only a small amount of gut-derived GLP-1 reaches the brain. Therefore, it is unclear whether peripherally released GLP-1 needs to enter the brain to affect food intake, or whether other routes of action are involved in its effects on feeding behaviour. Based on *in situ* hybridisation experiments, preproglucagon-encoding mRNA was found in a single population of neurons in the caudal portion of the NTS, indicating that local GLP-1 synthesis in the brainstem which could serve to amplify peripherally generated GLP-1 signals (Larsen *et al.* 1997). However, more recent work has shown that after i.p. administration of exendin-4 in male rats the majority of GLP-1-containing neurons in the NTS were not c-Fos-positive (Gu *et al.* 2013). Interestingly, i.p. administration of exendin-4 resulted in extensive c-Fos expression in regions where a high density of GLP-1-immunoreactive terminals originating from the NTS were localised. Therefore, it remains undetermined whether the GLP-1-containing neurons in the NTS have a role in amplifying or relaying gut-derived GLP-1 signals to the central GLP-1 networks.

The relative importance of peripheral vs central GLP-1 networks for control of satiety was studied in mice by acute peripheral and central administration of exendin-4 and the large GLP-1–albumin fusion protein albiglutide (Albugon), which is unable to cross the blood–brain barrier (Baggio *et al.* 2004a). Exendin-4 and albiglutide both reduced glycaemic excursions, which inhibited food intake and gastric emptying after peripheral as well as

i.c.v. administration. Albiglutide, injected i.p., was more effective in lowering hyperglycaemia than inducing satiety. Although c-Fos activation in different CNS nuclei was similar after peripheral albiglutide administration, it was less robust compared with the pattern induced by exendin-4. These experiments indicated that both peripheral and central mechanisms are involved in the GLP-1 receptor-mediated effects on glucose and energy homeostasis.

Studies using the GLP-1 receptor antagonist exendin 9–39 provide further insights into the routes of action of GLP-1. Peripheral administration of exendin 9–39 increased food intake when given to satiated rats (Williams *et al.* 2009). To differentiate between central and peripheral pathways involved, exendin 9–39 was injected either centrally or peripherally before both central and peripheral injection of GLP-1. Anorexia induced by peripheral GLP-1 was totally blocked by peripheral, but not central i.c.v. pretreatment with exendin 9–39, whereas the opposite was true for the anorectic effect of central GLP-1, which was not blocked by peripheral exendin 9–39. These data indicate that GLP-1 released by the intestine acts as a physiological satiety signal by activating peripheral GLP-1 receptors, whereas central GLP-1 affects feeding through GLP-1 receptors in the brain. Interestingly, these findings also imply that the anorectic effects of peripheral GLP-1 do not depend on central GLP-1 receptors. However, given the previously mentioned data, it seems likely that the GLP-1 systems in the CNS and in the periphery work together in the regulation of feeding behaviour.

Because GLP-1 receptors have been observed on vagal fibres (Vahl *et al.* 2007), it has been suggested that the vagal nerve plays an important role in the communication between gut and brain. This hypothesis was supported by experiments with vagotomised animals. The effects of i.p. injected GLP-1 on food intake and activation of hypothalamic ARC feeding neurons were abolished after bilateral subdiaphragmatic total truncal vagotomy as well as after brainstem–hypothalamic pathway transectioning in rats (Abbott *et al.* 2005). However, these experiments did not allow the identification of the exact portion of the vagal nerve (intestinal or hepatic) involved in the GLP-1-mediated effects. Gut-derived GLP-1 diffuses across the basal lamina of the gut into the lamina propria, where the uptake by capillaries and the degradation by DPP-4 take place. Only 25% of the gut-derived GLP-1 reaches the portal circulation and 10–15% of the secreted amount leaves the liver and enters the systemic circulation (Holst & Deacon 2005). As the portal circulation has the highest GLP-1 levels, vagal afferents in the portal branch may be an

important site of action of GLP-1. Indeed, intraportal infusion of DPP-4 inhibitor was shown to suppress food intake in rats and to increase *c-Fos* expression in several areas of the brain and these responses were blocked by hepatic vagotomy (Fujiwara *et al.* 2012). Moreover, it was shown that food intake suppression induced by i.p. GLP-1 was blunted in rats with complete subdiaphragmatic vagal deafferentation, but not in rats with selective ablation of the common hepatic branch of the vagal nerve (Hayes *et al.* 2011). These results unlike that the hepatic branch of the vagus is not the only route via which GLP-1 induces effects on food intake. There may be paracrine-like GLP-1 signalling on GLP-1 receptors expressed on vagal afferents innervating the gastrointestinal tract and actions of GLP-1 in the portal area as well as on gastrointestinal vagal afferents may reduce food intake. Recently, truncally vagotomised male subjects showed no reduction in *ad libitum* food intake during exogenous i.v. GLP-1 administration, unlike healthy control subjects (Plamboeck *et al.* 2013). Similar to rodents, these findings indicate an involvement of vagal afferent signalling in peripheral GLP-1-mediated regulation of feeding in humans.

In conclusion, effects of GLP-1 in the CNS may be due to both direct and indirect routes of action. However, it seems that GLP-1 more probably exerts its actions on the brain by indirect pathways, i.e. via vagal afferents originating in the intestine and portal circulation. However, additional information regarding the interaction between the various circuits involved is needed in future studies.

GLP-1 effects on food-related brain responses; neuroimaging studies

With the development of neuroimaging techniques, recent studies substantiate the effects of GLP-1 on brain areas related to feeding, in both animals but particularly in humans *in vivo*. An observational study using ¹⁵O-water PET for cerebral blood flow (CBF) measurement showed that the postprandial increase in GLP-1 concentration correlated with the postprandial regional CBF increments in the hypothalamus and left dorsolateral prefrontal cortex (Pannacciulli *et al.* 2007). Using ¹⁸FDG PET, GLP-1 infusion in lean individuals reduced glucose metabolism in the hypothalamus and brainstem (Alvarez *et al.* 2005). These findings demonstrate that exogenous GLP-1 is associated with altered cerebral glucose metabolism, but the relationship of these cerebral changes with food intake and appetite is not clear.

Functional magnetic resonance imaging (fMRI) is currently used to assess neuronal activation in a resting state, but also in response to different tasks or stimuli. Intra-gastric nutrient infusion in male rats reduced fMRI-measured activation in homeostatic (hypothalamus and NTS) and non-homeostatic (cortico-limbic) brain areas and these effects were inversely correlated with circulating GLP-1 plasma concentrations (Min *et al.* 2011). Injection of GLP-1 i.p. into fasted mice reduced fMRI signal intensity in the PVN, increased signal intensity in the VMH and resulted in no alterations in the ARC. *Ad libitum* fed rats (without exogenous GLP-1 administration) also showed a reduced activation in the PVN, but as well as in the ARC, and elicited no changes in the VMH (Chaudhri *et al.* 2006). Taken together, this indicates that feeding-induced changes in PVN activity may be related to GLP-1. *Ad libitum* feeding resulted in a decrease in ARC signal intensity that could not be replicated by exogenous GLP-1 infusions, indicating that changes in ARC activity during feeding probably result from other signals than GLP-1.

The effects of GLP-1 infusion on fMRI-measured neuronal activity have also been studied in humans (DeSilva *et al.* 2011). In healthy normal-weight individuals (11 males and five females), the mean fMRI signal change was described in *a priori* selected brain regions involved in reward processing and hedonic feeding (dorsal striatum, NAc, insula, amygdala and orbitofrontal cortex). Mean activity in these regions was attenuated when viewing food pictures in the fed as compared with the fasted state. Interestingly, GLP-1 infusion in the fasted state attenuated neuronal activity to an extent similar to that observed after feeding. The effect of exenatide vs saline infusion on hypothalamic connectivity was studied using fMRI in obese males and 'responders' (i.e. those who showed reduction in *ad libitum* food intake after exenatide infusion) vs 'non-responders' were compared (Schlogl *et al.* 2013). During scanning, different pictures (food and non-food) were presented and subjects were asked to rate the pictures for tastiness. While rating the food pictures, only the group of responders showed a higher connectivity of the hypothalamus during exenatide infusion compared with placebo. Connectivity is a proxy for the influence of this brain region on the rest of the brain. The effect of exenatide on connectivity was not observed in the non-responder group nor in the responder group while rating non-food pictures, supporting the hypothesis of a hypothalamic exenatide effect specific to states when networks of appetite and feeding control are active.

Taken together, these studies indicate that peripherally administered GLP-1 affects brain activity in areas

involved in the regulation of feeding. These effects could contribute to the appetite-suppressing effect of GLP-1 and the weight loss during GLP-1RA treatment.

Conclusions

Different signals from peripheral organs convey different aspects of nutritional status to the CNS. In the search of treatments for obesity, the potential therapeutic utility of these peripheral signals has been explored, but with no success. GLP-1RA are currently employed in the treatment of patients with T2DM and, in addition to their glucose-lowering effect, have shown consistent body weight loss in the majority of patients. These weight effects seem to be the result of combined central and peripheral actions of GLP-1RA, collectively promoting satiety, decreasing hunger sensation and ultimately leading to reductions in food intake. Possibly, GLP-1RA-induced deceleration of gastric emptying and occasional nausea could contribute to the weight reducing effects, but seem to play a minor and often temporary role. GLP-1/GLP-1RA-mediated inhibition of food intake was attributed to its direct central actions, based on the presence of GLP-1 receptors in brain regions implicated in the control of food intake and energy balance, the observations that GLP-1 and some GLP-1RA can cross the blood–brain barrier, and studies showing that i.c.v. administration of GLP-1 reduced food intake in rodents. However, currently, it seems that in addition to direct CNS effects of GLP-1, the incretin more probably exerts its actions on the brain by indirect pathways, i.e. via vagal afferents originating in the intestine and portal circulation. To date, it is unclear whether the GLP-1-producing neurons in the NTS, potentially acting to modify or amplify peripheral signals to the brain, that were previously described in rodents, also exist in humans. The role of this pathway and its interactions with the direct and indirect GLP-1 signalling circuits require extensive study to advance our understanding in the mechanisms underlying GLP-1-mediated regulation of feeding behaviour. State-of-the-art neuroimaging techniques have recently been employed which may help to further our knowledge of this field. Using PET and particularly fMRI, effects of peripherally injected GLP-1 on brain activity and connectivity of areas involved in the regulation of feeding could be demonstrated. Future research should determine which routes of action are involved in the effects of endogenous meal-related GLP-1 (physiology) as well as the actions of exogenously administered GLP-1RA (pharmacology) on the CNS to regulate feeding behaviour and body weight in humans.

These investigations may help to identify targets for future development of preventive and therapeutic strategies for the ‘diabesity’ pandemic.

Declaration of interest

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