INTRODUCTION

The incretin hormones are gut hormones that amplify nutrient-induced insulin secretion in response to meal intake. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the two most important hormones and both are thought to contribute equally to the effect. GLP-1 is secreted from endocrine cells in the epithelium of the small intestine that express the proglucagon gene, the so-called L cells. Unlike in the pancreas, the gene product, (pre)proglucagon, is processed here to release the two glucagon-like hormones, GLP-1 and GLP-2, whereas the glucagon sequence is buried in an N-terminal fragment of proglucagon called glicentin. GLP-1 binds to a single GLP-1 receptor and possesses several physiological effects that contribute to the regulation of glucose (Figure 1). GIP is secreted from K cells in the proximal small bowel and binds to GIP receptors expressed by pancreatic islet β cells, as well as to receptors in adipose tissue and the brain. A large body of data indicate that GIP-1 has an important role in satiation signaling, but this does not appear to be the case for GIP. As a result, the remainder of this review focuses on GLP-1. On the other hand, GIP may be involved in the development of obesity, as mice with GIP receptor deletions are resistant to diet-induced obesity. This is thought to reflect an action of GIP on the adipose tissue promoting fat storage, although this is controversial.

GLP-1 AND REGULATION OF APPETITE

As outlined in Figure 1, GLP-1 has numerous targets that may also be established in the regulation of food intake. The widespread distribution of GLP-1 receptors in the brain12 suggested actions of GLP-1 on brain centers, and in early studies, Schick et al.13 demonstrated inhibition of food intake after intracerebroventricular (ICV) as well as direct hypothalamic administration of GLP-1 in rats. This was followed up by extensive studies by Burton et al.14 and Tang-Christensen et al.15 demonstrating powerful inhibition of food intake after ICV administration of GLP-1, an effect that could be blocked by the specific receptor antagonists exendin 9–39, which also enhanced spontaneous as well as neuropeptide Y-stimulated food intake. These experiments indicated that GLP-1 has an important role in satiation signaling,16–19 which has also been associated with enteroceptive stress.20,21 Cells positive for GLP-1 mRNA are widely expressed in the human brain in areas, including the frontal, parietal, temporal and occipital cortices; the basal ganglia; and the hypothalamus.22 Radioligand-binding studies have shown high densities of GLP-1 receptors in the lateral septum, the subfornical organ, the thalamus, the hypothalamus, the interpeduncular nucleus, the area postrema (AP), the inferior olive and the nucleus tractus solitarius (NTS).23 Recent studies provide a direct demonstration of actions of central GLP-1 and show projections from GLP-1–containing neurons in the NTS to the nucleus accumbens core and of satiation induced by injections of GLP-1 into this region of the accumbens.22,24 Furthermore, GLP-1 receptors in this region and in the ventral tegmental area appear to be responsible for an inhibitory effect of GLP-1 on the rewarding value of food in rats.24 GLP-1 receptors are also present in the floor of the fourth ventricle, notably the subfornical organ and the AP, areas not fully blocked from the peripheral circulation by the blood–brain barrier. These areas are accessible to circulating peripheral GLP-1 and thus may permit direct effects of this peptide in the central nervous system (CNS). It has also been claimed that GLP-1 may pass the blood–brain barrier even outside these leaks,25,26 but it is currently unknown to what extent this route may be involved in signaling from the gut to the brain.

The central GLP-1 system has been studied by several groups (reviewed in Vrang and Larsen27), and there is little doubt that it represents an important central appetite regulating mechanism, although its physiological role is currently uncertain. In rats, it may be activated by peripheral signals, such as distension of the stomach that activate the GLP-1–expressing neurons of the NTS, and it has also been associated with enteroceptive stress. However, its relation to food intake is unclear. Inconsistent...
findings in other species (mice) render the generality of these findings unclear. On the other hand, knock down of the GLP-1–producing neurons as well as chronic administration of the GLP-1 receptor antagonist (GLP-1 RA), exendin 9–39, was associated with hyperphagia and increased fat accumulation after high fat feeding in rats.

The relationship between the peripheral and the central GLP-1 system is also unclear. Williams reported that while central blockade of the GLP-1 system with ICV administration of exendin 9–39 blocked the actions of central but not peripheral GLP-1, peripheral (intraperitoneal) exendin 9–39 blocked the appetite-suppressing actions of peripheral, but not central GLP-1, indicating that the two systems do not depend on each other for activity. However, other studies did report blocking effect of central exendin 9–39 on the effects of peripheral GLP-1 RAs. At any rate, the GLP-1 neurons do not express GLP-1 receptors (but may be depolarized by leptin), but it is of interest that other neurons in the dorsal motor nucleus of the vagus with efferent projections to the stomach do increase their firing rates in response to GLP-1.

GLP-1 secreted from the gut is also likely to be a physiological regulator of appetite and food intake. The first experiments demonstrating effects of peripheral GLP-1 in humans were published by Flint et al. in 1998. These investigators used visual analog scores for appetite registration and also studied the effect on ad libitum food intake. The doses used were highly physiological. Subsequent studies defined the dose–response relationships and demonstrated that an effect was also apparent in obese subjects and in obese patients with type 2 diabetes (T2DM). In a meta-analysis of available data, Verdich et al. demonstrated that the effect on food intake was linearly related to the dose of GLP-1 infused. Subsequent studies with stable GLP-1 RAs leave no doubt about the effectiveness with respect to inhibition of food intake, see below.

The question then arises whether peripheral GLP-1 is a physiological regulator of food intake. Again, the antagonist exendin 9–39 has helped answer the question. Thus, when given intraperitoneally, the antagonist significantly augmented food intake in rats in the light period and the late dark period (periods of limited food intake); conversely, little effect was noted at the onset of the dark period, where food intake is maximal, suggesting that during this period the inhibitory systems are shut down and therefore there is nothing to antagonize. In another study, a new, long-acting GLP-1 RA (an acylated GLP-1/exendin 9–39 hybrid) not only inhibited food intake but also lowered body weight. Similar studies have not yet been carried out in humans, but studies of weight loss after gastric bypass operations showed a correlation with GLP-1 responses. These observations also support the hypothesis that peripheral GLP-1 is a physiological regulator of appetite/food intake.

IS GLP-1 INVOLVED IN THE PATHOGENESIS OF OBESITY?

In accordance with the proposed actions for GLP-1, levels of this peptide increase in response to nutrient intake and the magnitude of the secretory response depends on the amount of nutrient consumed. However, it has been clearly shown that circulating levels of GLP-1 are reduced in obese patients. Results from a study carried out more than 25 years ago indicated that the normal enteroglucagon (= glicentin + oxyntomodulin, co-secreted with GLP-1 from the L cells) responses to meals were decreased by about 75% in obese subjects. Similar findings were made in more recent studies. By contrast, GIP responses are often increased rather than decreased. The reason for the differential effects of meal ingestion on GLP-1 and GIP levels is not known. GLP-1 responses to oral stimulation have been negatively correlated to body mass index (BMI), and weight loss was associated with increasing GLP-1 responses to meal ingestion.
It has been suggested that the decrease may be related to the insulin resistance that accompanies weight gain and/or reduced L-cell responsiveness to carbohydrates secondary to increased levels of circulating fatty acids.\textsuperscript{6,56} The major rise in plasma GLP-1 is often observed following completion of a meal, later than the presumed effect on eating occurs,\textsuperscript{57} which is in agreement with the notion that entry of digested nutrients into the L cells provide the stimulus for secretion.\textsuperscript{58} However, GLP-1 levels do show an early increase (10 min) after meal ingestion in humans,\textsuperscript{47,59} presumably because of secretion from L cells situated in the upper jejunum.\textsuperscript{6}

Interestingly, a recent study showed that both moderate and intense exercise increased GLP-1 levels and decreased hunger and food intake post-exercise.\textsuperscript{60} Overall, individuals who have lost weight as a function of changes in diet or exercise have increases in GLP-1,\textsuperscript{6} which may contribute to the weight reductions/maintenance observed with these interventions.

**GLP-1 in bariatric surgery**

Conversely, results from several studies have indicated that elevation of GLP-1 may be involved in the weight loss observed in patients who undergo bariatric surgery.\textsuperscript{61,64} GLP-1 levels increase dramatically in response to meal ingestion\textsuperscript{65} and, as mentioned above, levels correlate with decreases in weight and appetite.\textsuperscript{62} The mechanisms underlying the increase in GLP-1 levels associated with bypass surgery are not fully understood. Results from one recent study indicated that patients who have undergone bypass surgery have an 11.6% decrease in dipeptidyl peptidase-4 (DPP-4) activity,\textsuperscript{66} and as that enzyme inactivates GLP-1, this change could contribute to increased peptide levels. It has also been shown that insulin resistance reduces GLP-1 secretion in response to an oral glucose challenge,\textsuperscript{67} and it has been shown that bypass surgery significantly decreases insulin resistance,\textsuperscript{68} but again these mechanisms would only be expected to explain a very small part of the increase. Rather, it is the surgical rerouting of ingested nutrients to the distal small intestine with a high density of L cells that increases GLP-1 secretion (the hindgut hypothesis).\textsuperscript{69,70} This was demonstrated clearly in a case report where a meal was given to a patient on two consecutive days 5 weeks after gastric bypass, one via the oral route (by-passing the stomach and upper small intestine) and the other via a gastrostomy catheter.\textsuperscript{71} The oral meal resulted in the expected exaggerated post-bypass GLP-1 response, whereas the response to the gastric meal resembled preoperative responses. The exaggerated GLP-1 response after bypass in patients with T2DM has been demonstrated to be responsible for at least part of the improved beta-cell function and therefore resolution of diabetes using the receptor antagonists,\textsuperscript{72} but so far similar studies regarding appetite/food intake have not been reported.

**MECHANISMS OF GLP-1 INHIBITION OF SATIETY/FOOD INTAKE**

How does peripheral GLP-1 interfere with the regulation of satiety and food intake? As mentioned, plasma concentrations rise after meal intake, but it turns out that newly released GLP-1 is degraded and inactivated (at least with regard to its insulin-releasing effects) almost instantaneously after its release. Newly released GLP-1 diffuses across the basal lamina and into the lamina propria, enters capillaries where the enzyme, DPP-4, is located in the luminal membranes of the endothelial cells and degrades the peptide, so that only 1/3 to 1/4 of the intact peptide is left once the products reach the portal vein.\textsuperscript{73} In the liver, more DPP-4 degrades 50% of what is left,\textsuperscript{74} leaving very little intact GLP-1 for circulation;\textsuperscript{73} a soluble DPP-4 may degrade what is left.\textsuperscript{73} The plasma concentration of intact GLP-1 does rise, but the rise represents only a small percentage of what was originally secreted.\textsuperscript{76} In view of the dose–response relationship,\textsuperscript{39} it seems impossible that these minor increases could be responsible for any inhibition of food intake. A similar elevation in the concentration of intact GLP-1 may be obtained by inhibitors of DPP-4,\textsuperscript{77} however, inhibitor treatment has no effect on body weight.\textsuperscript{78}

Instead, GLP-1 released by L cells in the gut may reduce food intake through an effect on peripheral GLP-1 receptors located on vagal sensory afferents in the gut or perhaps in the hepatoportal region of the liver.\textsuperscript{73,79–81} These nerve fibers have their cell bodies in the nodose ganglion where abundant GLP-1 receptor mRNA has been demonstrated.\textsuperscript{82,83} The neurons subsequently project to the NTS. Indeed, neurons of the NTS have been shown to be activated (c-fos expression) in response to peripheral GLP-1 administration.\textsuperscript{84} In turn, the activated NTS neurons may not only directly influence the vagal motor nuclei in the dorsal part of the brain stem\textsuperscript{85} but also project to hypothalamic nuclei, including the arcuate (presumably mainly involved in glucose regulation\textsuperscript{86}), the paraventricular nucleus (PVN) of the hypothalamus and the amygdala.\textsuperscript{16,84} Note that the NTS neurons are probably not the GLP-1–expressing neurons. Efferent pathways reaching and regulating the function of gastrointestinal organs and pancreas may emerge from the hypothalamus and the dorsal motor nuclei.\textsuperscript{37}

This concept is supported by results from further studies in animals showing that either total subdiaphragmatic vagotomy\textsuperscript{88} or selective vagal deafferentation\textsuperscript{89,90} significantly decreased the food intake reduction and weight loss associated with peripheral administration of GLP-1. A similar neural pathway was also demonstrated to apply to GLP-1–induced inhibition of gastric emptying, antral motility and gastric-end pancreatic secretion.\textsuperscript{91,92} Thus, in humans, gastric acid secretion, stimulated by a purely vagal stimulus, namely shame feeding, is completely abolished by high physiological doses of GLP-1,\textsuperscript{93} and the inhibitory effect is lost after truncal vagotomy.\textsuperscript{94}

However, there is also evidence that GLP-1 may act directly in the brain as a satiation signal.\textsuperscript{95,96} As noted previously, GLP-1 may have direct effects in the CNS because it can reach the brainstem via the subfornical organ and AP, which lack a typical blood–brain barrier.\textsuperscript{97} A direct central effect of GLP-1 is supported by results from a study which showed that only the effect of intraperitoneal, but not intravenous (intraportal), GLP-1 on eating required vagal afferent signaling.\textsuperscript{89,90} Thus, although supporting the assumption that the effects of endogenous GLP-1 released by the intestinal L cells may involve transmission via vagal afferents (which were supposed to be activated in the gut wall by intraperitoneal GLP-1 diffusing across the gut wall from the peritoneal cavity to engage the vagal receptors), additional pathways, engaged by IV GLP-1, must also exist and may include interaction with the brain sites accessible from the bloodstream.\textsuperscript{89} Indeed, in a recent study involving intraportal administration of GLP-1 (which inhibited food intake), neurons were activated (c-fos expression) in both the nucleus of the solitary tract, the AP and the central nucleus of the amygdala.\textsuperscript{98} Furthermore, it has recently been demonstrated that the hepatic branch of the vagus nerve is not essential for the regulation of food intake induced by intraperitoneal administration of GLP-1.\textsuperscript{99} On the other hand, the AP pathway does not appear to be solely responsible for the GLP-1–induced satiation as this was unaffected after deletion of the AP as well as the subfornical organ.\textsuperscript{95} In recent studies in humans, it was demonstrated that the acute inhibitory effect of peripheral GLP-1 on energy intake after a meal is lost in subjects with a truncal vagotomy.\textsuperscript{99}

Figure 2 illustrates a proposed pathway for GLP-1 signaling in relation to satiation and glucose metabolism.\textsuperscript{89,90,99} In response to the presence of nutrients in the gastrointestinal tract, intestinal L cells release GLP-1, which binds to receptors on vagal afferents innervating the gut. The resulting vagal activation sends a signal to neurons of the NTS. GLP-1 also reaches the pancreas via the circulation to act directly on β cells, although this contribution

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International Journal of Obesity (2013) 1161 – 1168
Incretin hormones and the satiation signal

JJ Holst

WEIGHT LOSS WITH GLP-1 RAs

Currently available GLP-1 RAs include liraglutide and exenatide. Liraglutide is a human GLP-1 RA analog with 97% homology to human GLP-1.106,107 Liraglutide has a 13-h half-life, which makes it suitable for once-daily administration.108 Exenatide is a full GLP-1 RA isolated from the saliva of a lizard, the Gila monster, with a 53% homology to native GLP-1 and a 2.5-h half-life after subcutaneous administration.106,109 This molecule is naturally resistant to DPP-4 and is now also available in an extended-release form allowing once-weekly administration.109 Results from multiple clinical trials have demonstrated that exenatide treatment results in weight loss in patients with T2DM. Clinical trial results have also shown that liraglutide results in weight loss whether used as monotherapy or as part of combination treatment in patients with T2DM.110,111 Meta-analysis of results for clinical trials with exenatide and liraglutide in patients with diabetes indicated that reductions in BMI versus placebo were −0.62 and −0.47 kg m−2, respectively.110 A separate systematic review of results for exenatide indicated weight losses of 3–6 kg over 52 weeks of treatment.111 Analysis of results of a subset of the LEAD-2 (Liraglutide Effect and Action in Diabetes) trial indicated weight loss of 0.9, 2.0 and 3.2 kg among patients treated with 0.6, 1.2 and 1.8 mg liraglutide over 26 weeks of treatment.112,113 Direct comparison of results for exenatide and liraglutide in the LEAD-6 trial indicated weight losses of 3.24 kg for liraglutide and 2.87 kg with exenatide over 26 weeks of treatment.116 Treatment with liraglutide (0.3–0.9 mg day−1) for 20 days significantly reduced waist circumference, waist/hip ratio and estimated visceral fat area in a small cohort of 20 Japanese patients with T2DM.117 The consistent weight reductions observed with liraglutide and exenatide in patients with T2DM have prompted evaluation of these agents in nondiabetic patients who require pharmacotherapy for weight loss (see below).118–120

Mechanisms underlying weight loss in patients receiving GLP-1 RAs for treatment of diabetes may include increased satiety signaling involving the pathways described previously. Studies in healthy volunteers have demonstrated that exenatide increases satiation and reduces caloric intake by 209.3 kcal versus placebo when administered 60 min before a standardized meal.121 Liraglutide has been shown to decrease energy intake in association with earlier satiation.122

GLP-1 RAs also slow gastric emptying and decrease gut motility (whereas GIP does not possess such actions).123 The decreased gastric emptying observed with GLP-1 RAs may contribute to weight loss as it is known that gastric distension is associated with decreased food intake (and activation of GLP-1–producing neurons of the nucleus of the solitary tact).28 Exenatide slows gastric emptying of both solid and liquid meal components, and this is associated with decreased postprandial glucose levels.123 Clinical studies of liraglutide also indicate that it delays gastric emptying.124 although its effect during chronic treatment is much smaller.125 It has been suggested that delayed gastric emptying resulting from administration of a GLP-1 RA is due to inhibition of vagal afferent fibers.95,126 However, it is clear that GLP-1 and GLP-1 RAs inhibit appetite independently of their effects on gastric emptying as the effect is observed also in fasting individuals (with empty stomachs)27 and chronic treatment with liraglutide and exenatide brings about similar weight losses, although the effect of liraglutide on gastric emptying is very small compared with that contribute to weight loss. Ghrelin is an orexigenic peptide hormone. It is released into the systemic circulation mainly by the X/A-like cells in stomach mucosa.103 Results from recent studies have demonstrated that GLP-1 (both central, ICV and peripheral) inhibits ghrelin-stimulated neuronal activity in the hypothalamus as well as its effects on food intake.104,105 This may contribute to the effects of GLP-1 on meal consumption.

Figure 2. The neural pathway for the actions of GLP-1. GLP-1 secretion is stimulated by nutrients in (a) the gut lumen, and newly released GLP-1 diffuses across the basal lamina into the lamina propria. On its way to the capillary, however, it may bind to and activate (b) sensory afferent neurons originating in the (c) nodose ganglion, which may, in turn, activate neurons of the NTS (d). The same pathway may be activated by sensory neurons in (e) the hepatoporal region or in (f) the liver tissue. Ascending fibers from the NTS may generate reflexes in the hypothalamus, and descending impulses (from neurons in the PVN?) may activate (g) vagal motor neurons, that send (h) stimulatory or (i) inhibitory impulses to the pancreas and the gastrointestinal tract. Interactions between ascending sensory nerve fibers and vagal motor neurons may also take place at the level of the brain stem. Reprinted with permission from Holst, 2007.6

International Journal of Obesity (2013) 1161 – 1168
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may often be small because of the inactivation of GLP-1 caused by the enzyme DPP-4, which takes place in the gut before the hormone reaches the systemic circulation, but after it has had a chance to interact with the sensory afferents.30 Food intake also promotes the release of other gastrointestinal hormones (for example, cholecystokinin) that could increase the firing of GLP-1 neurons in the NTS.101 Afferent neural pathways are likely to participate as well. Stimulated GLP-1–expressing NTS neurons that signal satiation to brain areas may be involved in modulating food intake (mainly via the PVN) and glucose metabolism (mainly via the ARC) and thus may contribute to appetite suppression, although this is controversial.27 Regardless of the pathways involved, it is important to note that GLP-1 reduces appetite by affecting the function of regulating centers of the brain,102 rather than primarily affecting gastrointestinal motor activity (gastric emptying) or by causing nausea. Studies in humans also support the central effects of GLP-1. Thus, peak postprandial increases in plasma GLP-1 concentrations were found to correlate with increases in regional cerebral blood flow in the left dorsolateral prefrontal cortex (including the left middle and inferior frontal gyri). Both of these areas have been previously implicated to be involved in the regulation of food intake in animal and human studies.35 GLP-1 also has interactions with ghrelin that may
Pharmacological options for the treatment of obesity are limited, and most patients are unable to achieve sustained reductions in weight with diet and exercise alone. GLP-1 has multiple peripheral and CNS effects that contribute to satiation and decreased caloric intake. Indeed, part of the weight-loss-promoting effect of gastric bypass operations seems to involve exaggerated postprandial secretion of GLP-1. Furthermore, the GLP-1 RAs, exenatide and lixisenatide, have been consistently shown to decrease body weight when used for the treatment of hyperglycemia in patients with T2DM. Clinical trial results from obese patients without diabetes have shown that both exenatide and lixisenatide can produce significant reductions in body weight in such individuals. Thus, it is reasonable to suggest that these decreases may be due, at least in part, to increased satiation signaling associated with these GLP-1 RAs. This suggests that the GLP-1 RAs may be of use in the treatment of obesity, perhaps particularly with a view to prevent development of diabetes in obese subjects with impaired glucose tolerance.

CONFLICT OF INTEREST
JJH wrote the manuscript, with editorial assistance from the medical writer, reviewed and revised all outlines and drafts and approved the final version that was submitted. JJH has received payment as a consultant and speaker from Novo Nordisk Inc., for development of educational presentations from Forward Pharma and for travel, accommodations or meeting expenses from MSD.

ACKNOWLEDGEMENTS
I thank Robert W. Rhoades, PhD, of MedVal Scientific Information Services, LLC, for providing editorial assistance. This manuscript was prepared according to the International Society for Medical Publication Professionals’ Good Publication Practice for Communicating Company-Sponsored Medical Research: the GPP2 Guidelines. Funding to support the preparation of this manuscript was provided by Novo Nordisk Inc.

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