Glucagon-like peptide-1 (7–36) amide: a central regulator of satiety and interoceptive stress

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Summary Glucagon-like peptide-1 (7–36) amide (GLP-1) is processed from proglucagon in the distal ileum as well as in the CNS. In the periphery, GLP-1 acts as an incretin factor and profoundly inhibits upper gastrointestinal motility ('ileal brake'), the latter presumably involving the CNS. Within the CNS, GLP-1 has a satiating effect, since administration of GLP-1 into the third cerebral ventricle reduces short-term food intake (and meal size), while administration of GLP-1 antagonists have the opposite effect. In addition, activation of GLP-1 receptors in certain brain regions elicits strong taste aversions. Similarities between toxin- and GLP-1-induced neuronal activity in the CNS (brain stem) suggest a role for central GLP-1 receptors in relaying interoceptive stress. Thus, regionally distinct GLP-1 receptor populations in the CNS may be involved in satiety or malaise. It is argued that the satiating and aversive aspects of GLP-1 serve homeostatic and nonhomeostatic functions with respect to maintenance of nutrient balance. © 1999 Harcourt Publishers Ltd

INTRODUCTION

Ingestion of food is a necessary and pleasant occupation that allows humans and other species to maintain caloric homeostasis and a certain level of body weight. Ironically, in doing so, one's 'milieu interieur' is put at risk because meal-induced fuel excursions can have deleterious effects on metabolic (e.g. glycosylation causing loss of enzymatic efficacy) and cardiovascular (e.g. triglyceride accumulation, increased blood pressure, etc.) processes.[1,2] To reduce these perturbations to a minimum, evolution has provided many species (including humans and rodents) with a fine-tuned system enabling ingested nutrients to be anticipated, efficiently digested, and stored.[3] One of these mechanisms includes passage of nutrients through the digestive tract, triggering the release of a number of peptides from endocrine cells located in the wall of various parts of the gastrointestinal tract. These peptides serve important functions in facilitating the process of nutrient digestion/storage. Among these, the truncated (i.e.

7–36) amidated form of glucagon-like peptide-1 (GLP-1) has attracted considerable attention over the last several years. Firstly, because of its remarkable peripheral insulinotropic effects that could be useful for clinical purposes. Secondly, because more recent data suggest an important role of this peptide in the central nervous system (CNS) control of ingestive behavior. Although the present paper mainly focusses on the latter issue, a short review of peripheral GLP mechanisms is necessary for a better understanding of the processes that relate GLP-1 to food intake.

GLP-1 FROM THE GASTROINTESTINAL TRACT

GLP-1 is processed from proglucagon in mucosal L cells of the distal portion of the ileum and in the A cells of the pancreas. Ingested food, particularly when rich in carbohydrates, causes the level of circulating GLP-1 (mainly of ileal origin) to increase, and in turn, GLP-1 potently stimulates the secretion of insulin from pancreatic B cells via receptor-mediated processes (for reviews, see refs 4 and 5). In contrast, it reduces the secretion of glucagon, at least under ad libitum feeding conditions.[6] While GLP-1 may have some direct stimulatory effects on glucose clearance in peripheral tissue[78] (presumably via activation of specific GLP-1 receptors in liver, muscle, kidney

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and adipose tissue), GLP-1's stimulatory effect on insulin secretion probably constitutes a major portion of its 'incretin' effect, i.e. dampening the post-ingestive rises in absorbed glucose.[9] Important evidence for the involvement of GLP-1 in maintaining normoglycemia are the data of Scriocci et al., showing that a targetted null mutation in the gene encoding for the GLP-1 receptor in mice results in a mild fasting hyperglycemia and glucose intolerance associated with a reduced glucose-stimulated insulin secretion after an oral glucose load.[10] Since this phenotype closely resembles that observed with type-II diabetes mellitus, GLP-1 treatment, or treatment with an inhibitor of the GLP-1 conversion enzyme, dipeptidyl-peptidase IV, could provide therapy for ameliorating glucose intolerance in the diabetic patients. A number of studies (e.g. ref. 11) indeed suggest that this strategy might be fruitful.

In addition to the effects of GLP-1 on pancreatic hormone secretion and fuel fluxes, GLP-1 has remarkable inhibitory actions on upper gastrointestinal motor and digestive functions (e.g. gastric emptying, gastric acid secretion, and pancreatic exocrine activity) in response to nutrients placed into the ileal lumen. These effects argue for a role of this peptide as an 'ileal brake'.[5] These effects of GLP-1 on gastric emptying were also observed in humans,[12,13] and appear to outweigh its insulinotropic effects. Thus, in addition to enhancing deposition of nutrients in storage tissue, meal-associated increases in circulating GLP-1 could also prevent abundant ingested nutrients from being dumped into the lower intestines. Because GLP-1's inhibitory effects on gastric acid secretion and pancreatic functioning relies on the integrity of the vagus nerve,[14,15] and because GLP-1's effect on gastrointestinal motility is modulated via adrenergic receptors,[16] it is very likely that some actions of GLP-1 involve the CNS. In addition, the fact that peripheral GLP-1 administration in normal, obese and diabetic humans produces remarkable reductions in short-term energy intake and promotes satiety also points to a possible involvement of the CNS in GLP-1 actions.[17–19]

CENTRAL GLP-1 PATHWAYS

In the mid-1980s, proglucagon mRNA was found in the dorsovagal complex,[20] and later, GLP-1 was detected by immunohistochemistry in several areas of the CNS, including the thalamus, hypothalamus, pituitary and hindbrain.[21,22] In vitro work of Kreymann et al. demonstrated that hypothalamic GLP-1 meets the important criteria of a neurotransmitter, since (1) GLP-1 was found in the synaptosome fraction of hypothalamic neural tissue, and (2) GLP-1 was released by calcium-dependent, potassium-induced depolarisation.[23] In addition, GLP-1 binds with high affinity to pituitary, thalamic–hypothalamic, and hindbrain regions (e.g. nucleus of the solitary tract, area postrema),[24] and immunohistochemistry[25] and in situ hybridization[26] revealed the presence of abundant GLP-1 receptors in these areas. The high affinity of receptors for GLP-1 in these areas was confirmed by demonstration that application of nanomolar concentrations of GLP-1 markedly stimulates cAMP formation.[25]

The stimulus (or stimuli) for neuronal GLP-1 transmission in the CNS remains a matter of debate. One possibility is that GLP-1-containing neurons or receptors are implicated in other neuropeptide-containing CNS circuitry or down-stream from classic neurotransmitter systems such as those containing noradrenalin, serotonin, or dopamine. Another possibility is that peripheral GLP-1 released by ileal stimulation acts on vagal (or visceral) afferent fibers,[27] where it could influence GLP-1 neuronal transmission in the CNS, analogous to that which has been proposed for another gut peptide, cholecystokinin (CCK).[28] This idea might fit with the location of GLP-1-containing neuronal cell bodies in the caudal aspect of the nucleus of the solitary tract (NTS) which project to thalamic and hypothalamic (i.e. the paraventricular and dorsomedial nucleus) forebrain regions.[22] One implication of a mechanism in which peripheral GLP-1 activates an ascending neuronal pathway to stimulate central GLP-1 pathways is that, at least, some of the effects of peripheral GLP-1 administration are expected to occur upon central administration of GLP-1. Consistent with a possible linkage of peripheral and central GLP-1 mechanisms is our unpublished observation that GLP-1 administration in a dose of 1 µg directly into the third cerebral ventricle (i3vt) causes a dramatic inhibition of gastric motility. Since this occurred without altering the level of blood glucose, this might rule out an effect by leakage from the CNS to the periphery. Finally, it is possible that GLP-1 from peripheral origin is able to reach the CNS through the general circulation, where it then could influence CNS pathways. Hence, GLP-1 receptors in blood–brain-barrier free areas, such as the subfornical organ and area postrema, are accessible to labelled GLP-1 administered into the general circulation.[29]

GLP-1 REDUCES SHORT-TERM FOOD INTAKE

Based on the secretion pattern of GLP during and after meals, and because GLP-1 receptors and GLP-1-containing neuronal projections were abundantly found in CNS areas involved in food intake, it was predicted that stimulation of peripheral and central GLP-1 receptors would induce satiety. Hence, the prototypical satiety peptide, CCK, is also secreted in response to meals, and when administered intraperitoneally, or directly into the CNS, CCK causes a potent reduction in the size of subsequent

meals.[28] The finding that peripheral administration of GLP-1 reduces water intake,[30] but not food intake,[30,31] largely rules out the possibility that circulating GLP-1, at least in rats, alters food intake through a direct action on GLP-1 receptors in blood–brain-barrier-free areas. Two issues can be raised regarding this point. (1) Since peripheral administration of GLP-1 in humans,[17–19] but not in rats, reduces energy intake and promote satiety, this may suggest species differences with respect to the mechanisms by which GLP-1 can affect food intake. (2) It is possible that intraperitoneal (ip) or intravenous (iv) administration of GLP-1 in rats would simply not reach high enough levels of GLP-1 in the neighbourhood of putative GLP-1 receptors located on vagal or visceral afferents, relative to the situation in which GLP-1 is released endogenously. Thus, only GLP-1 secreted in response to nutrients in the ileum could be sufficient to alter afferent nerve traffic from gut to brain areas involved in regulation of food intake via the aforementioned ascending pathway. While these possibilities are somewhat speculative, the finding that nutrient infusion in the distal part of the ileum is a particularly potent stimulus to reduce food intake in humans[32] and in rats (Dr J. H. Strubbe, personal communication) is consistent with these arguments.

The idea that central GLP-1 receptors are involved in the regulation of food intake was originally supported by Turton et al., who found that third cerebroventricular (i3vt) administration of GLP-1 dose-dependently reduced food intake in rats, and that it stimulated neuronal activity (assessed by c-Fos-immunohistochemistry) in the paraventricular nucleus of the hypothalamus.[31] Later, GLP-1's inhibitory effect on food intake was confirmed by many groups including ours. Briefly, we delivered 0.3, 1, 3 and 10 μg of GLP-1 i3vt in rats prior to their dark phase and found that 3 μg was the lowest dose to reduce feeding over the ensuing 2-h period in the dark phase. Since neonatal treatment with monosodium glutamate leading to destruction of the arcuate nucleus of the hypothalamus yields animals insensitive to i3vt GLP-1's anorexigenic action, GLP-1 receptors within, or neuronal pathways arising from this hypothalamic area appear to mediate GLP-1's inhibition of feeding.[33]

We found that, besides elevating c-Fos-like immunoreactivity (c-FLI) in the PVN (31), i3vt GLP-1 also increased c-FLI in a number of other CNS regions, including the central nucleus of the amygdala, and areas in the brain stem such as the NTS, area postrema, and the parabrachial nucleus,[34] and this was later confirmed by others.[35,36] In general, these areas appear to overlap with those that are found to be c-fos-positive upon i3vt administration of CCK-8 in a dose that produces comparable reductions in short-term food intake to GLP-1.[37,38] In addition, CCK receptor antagonists, when adminis-

tered alone, produce reliable increases of meal size[28] and Turton et al. have evidence that this is also true for a GLP-1 antagonist.[31] Thus, the actions of GLP-1 to reduce feeding are seemingly analogous to those of CCK.

One implication of the similarities of CCK and GLP-1 would be that GLP-1 is expected to be a short-term regulator of food intake, without changing food intake and body weight on the long term. Hence, when CCK is administered at the onset of each spontaneous meal in non-deprived and freely feeding rats, it reliably reduces the size of each meal compared to the meal size of control animals, but daily caloric intake and body weight are not dramatically altered.[39] If the effects of GLP-1 are short-lived as well, animals would eat more in subsequent meals in order to compensate for the lost calories from the reduced first meals in order to maintain daily caloric intake and body weight. Consistent with this idea are our findings that, relative to controls, i3vt GLP-1 treatment over several days, either by osmotic minipump (delivering 30 μg GLP-1/day), or i3vt injections (15 μg twice per day, each prior to a 2-h window in which animals were allowed to feed) reduced food intake only during the first treatment day, but never affected body weight.[40] Thus, like CCK, i3vt administration of GLP-1 potently reduces the size of the subsequent meal, but the total daily food intake is not different from that of controls. Thus, if GLP-1 in the CNS does have a role as a control of food intake, it would appear to be as a short-term satiety signal and not a long-term regulator of caloric intake and body weight. Although there are some conditions in which chronic GLP-1 treatment appears to reduce long-term food intake and body weight,[41,42] our data are consistent with that of Scriocci et al., demonstrating that mice with deficient GLP-1 receptors have normal body weights.[10]

A second category of peptides, including insulin and leptin, act in a fundamentally different fashion. When administered continuously into the CNS over days, both insulin[43] and leptin[44] produce persistent reductions in food intake and body weight at doses that have no effect when administered into the periphery, suggesting that the CNS is the likely target for this action. Since both insulin and leptin are secreted in proportion to body adiposity, signaling of each in the CNS has been considered a likely factor to close a feedback loop enabling body adiposity to be maintained at a certain level (for a review, see ref. 45). In this event, they probably interact with meal-generated satiety factors, such as CCK, and possibly GLP-1 as well. An effect of leptin signaling on GLP-1 neuronal activity seems tenable in light of the findings by Goldstone et al. that leptin receptor mRNA coexpresses with GLP-1 in NTS neuronal cell bodies. In addition, they found that leptin inhibition of food intake can be prevented by blockade of GLP-1 receptor
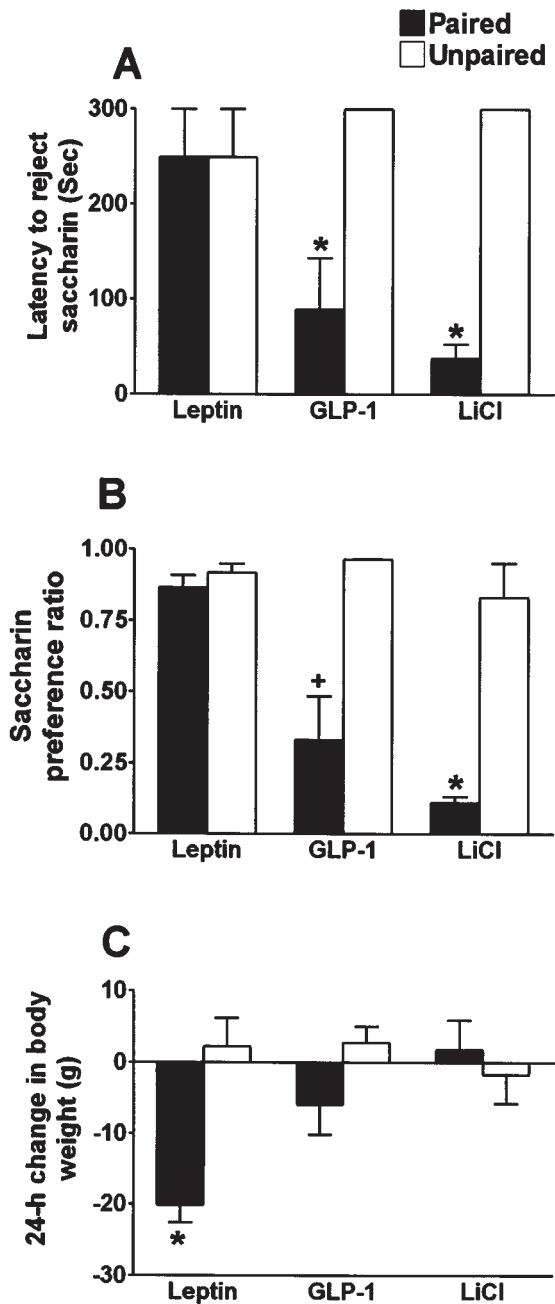
Fig. 1 Mean (±SE) latency to reject intraorally infused saccharin (A) and preference for saccharin in a consumption test (B) after conditioned taste aversion training. Preference was defined as consumption of saccharin divided by total fluid (saccharin + water) consumption. Filled bars represent paired subjects that received saccharin immediately followed by drug [leptin (3.5 µg), GLP-1 (10.0 µg), or LiCl (127 mg/kg)], and open bars represent unpaired subjects that received saccharin and drug on separate days. Panel C depicts 24-h changes in body weight of treated animals on first day of exposure to drugs (filled bars) and to control solution (synthetic cerebrospinal fluid). +Significant at $P < 0.05$ relative to unpaired; *$P < 0.001$ relative to unpaired. (From ref. 54.)

activity.[46] However, this effect does not necessarily suggest GLP-1 receptor involvement in all down-stream

actions of leptin. GLP-1 receptor deficient mice have normal body weights,[10] while it is well known that leptin receptor-deficient rodents (db/db mice, fa/fa Zucker rats) become morbidly obese. Since animals with a deficiency in leptin signaling respond normally to both i3vt GLP or CCK to reduce short-term food intake, however, without changing daily caloric intake or body weight,[40,47] aberrant CCK or GLP-1 receptor functioning does not underlie the obese phenotype in leptin-receptor deficient rodents.

In contrast to the absence of GLP-1 involvement in control of body weight, however, aberrant CCK receptor functioning appears to promote hyperphagia and obesity.[48] This suggest that CCK and leptin could act synergistically to control body weight. Such an interaction between leptin and CCK in normal animals might function permitted that the levels of leptin are elevated, but not when those of CCK are elevated.[49]

GLP-1 CAUSES CONDITIONED TASTE AVERSIONS

Observed reductions in food intake or body weight associated with administration of peptides may be the result of an induced state of satiety. However, before a peptide can be considered a naturally occurring satiety factor, it must be determined that it does not induce other states that could account for reduced food intake.[43,50] While the ability of exogenous GLP-1 to modulate consummatory behavior is consistent with the suggestion that this peptide is an endogenous regulatory agent, it is possible that i3vt administration of GLP-1 produces nonspecific effects such as motor impairment, loss of memory, or aversive side-effects such as visceral illness. Such nonspecific effects would likely cause reductions in food intake and could explain the anorexia associated with central administration of GLP-1.

The conditioned taste aversion (CTA) paradigm is a useful and commonly used technique to determine if administration of compounds is associated with aversive side-effects. Briefly, under normal conditions, rats will avidly consume large amounts of palatable foods, such as solutions containing saccharin. However, if consumption of a saccharine solution is followed by an ip injection of an emetic agent, such as lithium chloride (LiCl), rats will avoid drinking the saccharine solution in the future, demonstrating a CTA.[51] These data suggest that LiCl has aversive properties, and that the rat has learned to associate these aversive properties with the saccharine solution. The CTA is a unique and robust form of learning which can be conditioned after only one taste–toxin pairing, even when the taste and the aversive agent are separated by several hours.[52] Thus, the CTA paradigm is a powerful tool for assessing potential aversive side-effects associated with administration of peptides.

To determine if GLP-1 is associated with aversive side-effects, we first exposed rats to a 0.15% saccharine solution via an intraoral (io) cannula and then immediately gave them i3vt infusion of GLP-1 (10.0 μg); additional animals received i3vt infusion of leptin (3.5 μg) in a dose that produced similar short-term (4 h) anorexia as that produced by GLP-1.[34,53] Several days later, when re-exposed to the saccharine solution, control rats that received the saccharin and GLP-1 on separate days continued to ingest the saccharine solution. However, rats that had received the saccharin paired with GLP-1 on the same day actively rejected the tastant on the test day. These data indicate that i3vt infusion of GLP-1 is associated with aversive side-effects. Interestingly, i3vt infusion of leptin, in a dose that caused long-term reductions in food intake as well as body weight, did not condition a CTA.[54]

We later showed that the lowest dose of i3vt GLP-1 (3 μg) to reduce food intake was also the lowest dose to produce a CTA (ref. 55; but see ref. 30). Importantly, i3vt CCK-8 in a dose (6 μg) to reduce short-term food intake to the same extent as 3 μg of GLP-1 did not cause a CTA,[37] and thus argues for a principal difference between the involvement of GLP-1 and CCK in the control of food intake.

We used several other procedures that have been suggested as measures of aversive side-effects.[56,57] Briefly, similar to ip administration of LiCl, i3vt administration of GLP-1 caused a significant reduction in NaCl appetite in rats that had been made sodium deplete with the drug furosimide (unpublished data). Furthermore, central infusion of GLP-1 caused Pica behavior, the eating of non-nutritive substances such as synthetic clay, a behavior also induced by ip injection of LiCl.[58] The parallel between the effects found with GLP-1 and the emetic agent LiCl at each of these measures strengthens the argument that GLP-1 produces aversive side-effects, and could be synonymous to the findings of Asarian et al.,[59] who showed that i3vt GLP-1 reduces sham-feeding, but, based on microstructural licking analysis, it did not seem to induce satiety. Instead, they argued that GLP-1 reduced orosensory reward.

INVOLVEMENT OF GLP-1 SIGNALING IN LICL-INDUCED NEURONAL ACTIVATION

As mentioned above, i3vt GLP-1 causes activation of c-FLI in several brain regions.[34-37] We were struck by the similarity in the pattern of c-FLI produced by i3vt GLP-1 and ip injection of LiCl, particularly in brainstem regions that are thought to be involved with CTA learning, such as the NTS, area postrema (AP), and the lateral parabrachial nucleus (PBN).[60,61] Because GLP-1 is synthesized in brainstem neurons, we speculated that GLP-1
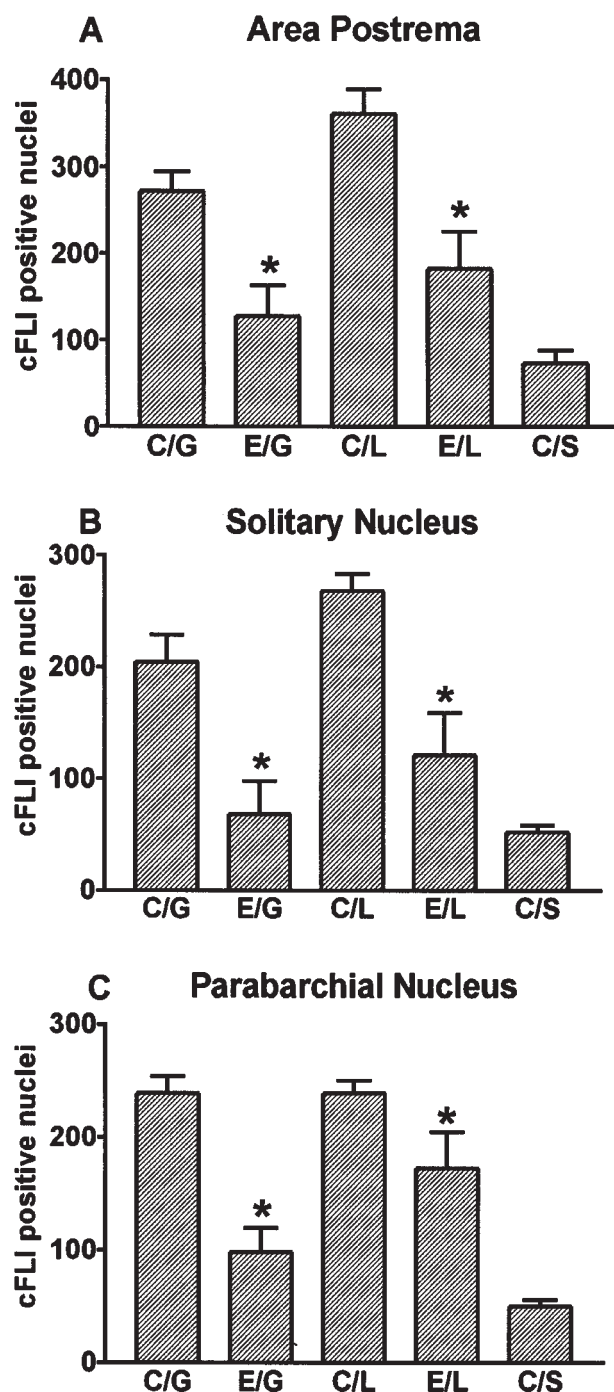

Fig. 2 Mean (±SE) number of nuclei positive for cFLI in the area postrema (A), the nucleus of the solitary tract (B), and the lateral parabrachial nucleus (C) following i3vt infusions. Group C/G was pretreated with infusion of synthetic cerebrospinal fluid followed by infusion of GLP-1; Group E/G was pretreated with infusion of dHGex-4 followed by infusion of GLP-1; Group C/L was pretreated with infusion of synthetic cerebrospinal fluid followed by ip injection of LiCl; Group E/L was pretreated with infusion of dHGex-4 followed by ip injection of LiCl; and Group C/S was pretreated with infusion of synthetic cerebrospinal fluid followed by ip injection of isotonic saline. *$P < 0.05$ relative to synthetic cerebrospinal fluid pretreated groups. (From ref. 62.)

may be involved with neuronal signaling in the brainstem following injection of LiCl.[62] A hint of such a mechanism has been provided by Rinaman,[63] who observed that peripheral administration of toxins, including LiCl, stimulated c-FLI in neuronal cell bodies in the NTS that contain GLP-1. Combined tracer injections indicated that a portion of these project to the PVN.

If GLP-1 receptors mediate LiCl-induced neuronal activity, then blocking central GLP-1 receptors should block or attenuate LiCl-induced neuronal activation (i.e. c-FLI). We used a potent GLP-1 receptor antagonist, des-His1-Glu9 exendin-4 (DHEX-4). We found that this antagonist was more potent than the commonly used GLP-1 receptor antagonist, exendin-9-39, since DHEX-4 could block GLP-1 induced-anorexia when administered in a 1:1 ratio. Exendin-9-39 must be administered at a concentration 10 times greater than GLP-1 to block anorexia.[31] We first pretreated rats with DHEX-4 (10.0 µg), or vehicle. Rats were then either given i3vt GLP-1 (10.0 µg) or ip LiCl (76 mg/kg). As expected, pretreatment with the GLP-1 receptor antagonist attenuated GLP-1-induced c-FLI in the brainstem regions examined. More importantly, pretreatment with the GLP-1 receptor antagonist also attenuated LiCl-induced c-FLI in the AP, NTS, and PBN.[62]

We later found that the GLP-1 antagonist did not influence cholecystokinin octapeptide (CCK-8) induced c-FLI, indicating that the compound does not block c-FLI indiscriminately (unpublished data), nor did this antagonist block i3vt CCK-8's ability to produce a short-term reduction in food intake. These data indicate that central blockade of the GLP-1 receptor attenuates LiCl-induced cFLI, and suggest that neuronal activity in the brainstem caused by LiCl administration is mediated, at least in part, by GLP-1 signaling. Thus, GLP-1 is involved with the central actions of LiCl.

DISSOCIATION BETWEEN EFFECTS OF CENTRAL GLP-1 ON SATIETY AND VISCERAL ILLNESS

The similarities between the effects that are produced by central administration of GLP-1 and peripheral administration of the emetic agent LiCl, coupled with the observation that GLP-1 signaling is involved with the neuronal activation produced by LiCl administration, raises the possibility that those associated with satiety and aversion (i.e. visceral illness and malaise) are states on a unidimensional scale. Thus, it is possible that when central GLP-1 pathways are moderately stimulated, such as when a meal is ingested, one will observe behaviors that are consistent with satiety such as anorexia, grooming, and inactivity. On the other hand, when central GLP-1 pathways are highly stimulated, such as when an animal overconsumes food or eats a contaminated substance, one may observe behaviors consistent with visceral illness, such as inactivity, anorexia, and future rejection of the ingested substance (i.e. refs 51 and 64). According to this view, this is a unidimensional system in which the same GLP-1 pathway is involved with both satiety and visceral illness; the state that is produced in the organism will depend on the magnitude of stimulation of this pathway.

While this model may seem appealing from a simplistic point of view, accumulating data suggest that the unidimensional model is an inappropriate view of how GLP-1 is involved with satiety and aversion (i.e. visceral illness). First, while i3vt GLP-1 produces taste aversions at all doses that reduce food intake,[54,55] central infusion of GLP-1 directly into the paraventricular nucleus of the hypothalamus (PVN) has been shown to reduce short-term food intake at doses that do not support a CTA.[65] Thus, GLP-1 receptors in the PVN appear to be involved with regulating food intake, in the absence of producing aversive side-effects. Secondly, while LiCl can produce very robust CTAs over a wide range of doses, this drug does not easily produce anorexia except at high doses (e.g. ref. 66). If the unidimensional model of GLP-1 signaling were true, any dose of LiCl sufficient to support CTAs should also produce anorexia, yet low doses of LiCl can produce CTA in the absence of anorexia. Finally, recent unpublished data from our laboratory suggest that two independent GLP-1 pathways mediate the anorexia and the aversive side-effects that are produced by this peptide. Briefly, we found that bilateral lesion of the PVN prevented i3vt GLP-1 from reducing short-term food intake in rats. However, rats with PVN lesions still learned taste aversions when saccharin administration was immediately followed by i3vt GLP-1. The opposite results were obtained with rats that had received bilateral lesions of the central nucleus of the amygdala (CeA). Now, rats showed reductions in food intake following i3vt GLP-1, but they would not learn GLP-1-induced taste aversions. Thus, GLP-1-induced anorexia and taste aversions can be dissociated by lesioning procedures.

Together these data indicate that GLP-1 can produce anorexia and aversive side-effects, but that different pathways are involved. These data are not consistent with the unidimensional model of satiety and visceral illness; rather, these data suggest that GLP-1 signaling is involved with multiple central pathways, each with a unique role in regulating different physiological states of the organism. These data also shed light on the interpretational problems that can arise when peptides are given centrally into the cerebroventricular system, rather than into specific brain regions known to express GLP-1 receptors. When given ventricularly, GLP-1 will act at receptors in many different brain regions, likely inducing multiple

physiological systems simultaneously. Thus, for example, GLP-1 receptors will be stimulated in the PVN, a region thought to regulate feeding, which may induce a state of satiety (and cause anorexia). At the same time, GLP-1 given into the cerebroventricular system will also stimulate GLP-1 receptors in brainstem regions such as in the NTS and the AP; stimulation of these regions may produce aversive effects such as visceral illness or malaise.[60,61] Because induction of these systems may produce similar behavioral outcomes (e.g. anorexia), it becomes difficult to interpret data when GLP-1 is given into the cerebral ventricles. Infusing peptides into discrete locations within the brain will produce data that can be more easily interpreted.

INTEGRATION OF PERIPHERAL AND CENTRAL GLP-1 PATHWAYS REGULATING NUTRIENT BALANCE

Mounting evidence suggests that GLP-1 is involved with the homeostatic regulation of nutrients in the organism. Peripherally, GLP-1 levels rise in response to consumption of food, and GLP-1 appears to be involved with glucose homeostasis as it augments insulin secretion and dampens the absorptive consequences associated with food intake, and prevents (via the 'ileal brake') rapid transit of bulk nutrients to lower intestines. These actions associated with the effect of central GLP-1 to cause reductions in food intake (in some areas without associated aversive side effects), might be considered a homeostatic regulation of the nutrient balance.

In addition to containing the necessary calories for maintenance of the energy balance, consumed food can be a vehicle for a variety of other substances (i.e. heavy metals, poison/venom, micro-organisms, etc.) that can cause distress to the gastrointestinal tract leading to malabsorption of nutrients (diarrhea). Malabsorption has been shown to augment the secretion of entero-glucagon.[67] Since GLP-1 and enteroglucagon (glicentin) are co-secreted, GLP-1 responses can be predicted to be pronounced under conditions of incomplete absorption of nutrients, such as in response to malassimilation caused by consumption of contaminated substances. In a recent debate by Nauck,[68] it was suggested that under such abnormal circumstances, a signal from the lower gut (e.g. GLP-1) that could (a) stop or retard gastric emptying and (b) slow digestive functions (gastric acid and pancreatic juice secretion) would be beneficial in order to limit nutritional losses. Thus, the ability of GLP-1 to inhibit gastric empting and slow digestive function may be an adaptive response to protect the organism from nutrient loss in circumstances of malassimilation (e.g. visceral illness).

While much work needs to be done on this problem, the exaggerated secretion of GLP-1 in response to erroneous nutrients in the ileum (e.g. during malabsorption) could tentatively be tied to the actions of GLP-1 in the CNS areas that may regulate nutrient balance via non-homeostatic mechanisms. Hence, using several measures, central infusion of GLP-1 appears to produce aversive side-effects, indicating that this peptide may induce a state of malaise or visceral illness. Thus, visceral illness caused by ingestion of toxic substances may be regulated by central GLP-1 pathways. Visceral illness is often associated with anorexia, and organisms tend to avoid future consumption of foods that have made them ill through associative processes.

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