Incretins and Amylin: Neuroendocrine Communication Between the Gut, Pancreas, and Brain in Control of Food Intake and Blood Glucose

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Abstract

Arguably the most fundamental physiological systems for all eukaryotic life are those governing energy balance. Without sufficient energy, an individual is unable to survive and reproduce. Thus, an ever-growing appreciation is that mammalian physiology developed a redundant set of neuroendocrine signals that regulate energy intake and expenditure, which maintains sufficient circulating energy, predominantly in the form of glucose, to ensure that energy needs are met throughout the body. This orchestrated control requires cross talk between the gastrointestinal tract, which senses the incoming meal; the pancreas, which produces glycemic counterregulatory hormones; and the brain, which controls autonomic and behavioral processes regulating energy balance. Therefore, this review highlights the physiological, pharmacological, and pathophysiological effects of the incretin hormones glucagon-like peptide-1 and gastric inhibitory polypeptide, as well as the pancreatic hormone amylin, on energy balance and glycemic control.

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INTRODUCTION

As type II diabetes mellitus (T2DM) and obesity rates continue to reach epidemic proportions (28, 51, 176), driving health and economic costs higher (49, 50), the need to find safe, effective, and economically achievable therapies for the treatment of these diseases is ever increasing. At the most fundamental level, T2DM is a disease characterized by a derangement in insulin receptor signaling and the resulting metabolic consequences of chronic hyperglycemia, whereas obesity represents the long-term physiological consequence of chronic overconsumption of energy in comparison to energy expended. Despite our ever-growing understanding of the environmental, anatomical, physiological, molecular, neuronal, and behavioral mechanisms that contribute to the etiology and pathophysiology of obesity/T2DM, it is clear that we have limited therapeutic options for either disease, and the management of T2DM requires lifelong treatment with several classes of pharmaceuticals (44, 162). Thus, more progress is required to identify novel physiologically relevant targets to (*a*) alleviate the derangements in insulin receptor signaling for the treatment of T2DM and (*b*) reduce energy intake and/or increase energy expenditure for the treatment of obesity. For these reasons, attention has been devoted to the investigation of incretin hormones such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), as well as noninsulin pancreatic β-cell-derived hormones such as amylin for the treatment of T2DM and obesity, as pharmacological manipulation of these neuroendocrine systems offers promising

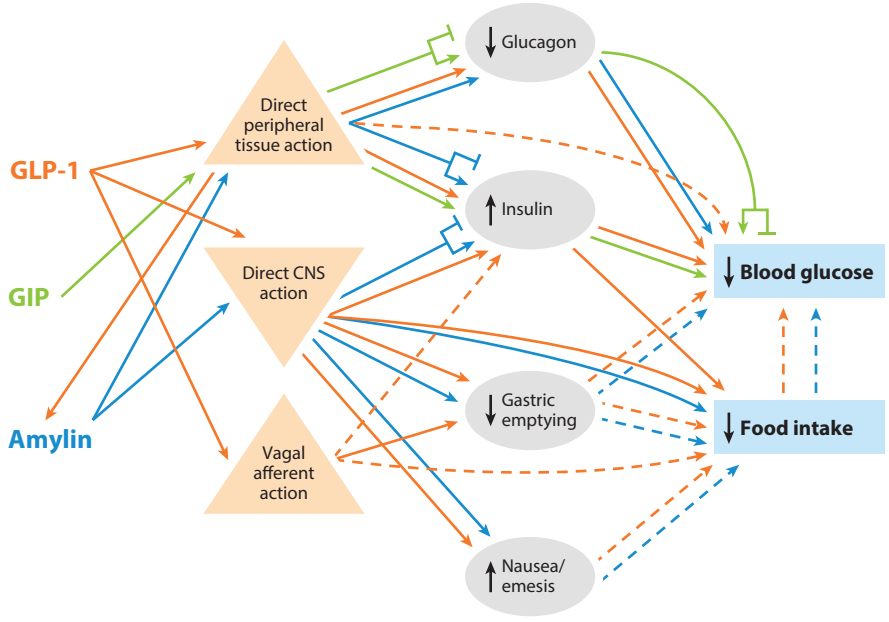

Figure 1

The mechanisms by which glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), and amylin regulate food intake and blood glucose involve complex, overlapping, and redundant endocrine and neuronal pathways. Solid lines indicate a direct mode of action, whereas dashed lines indicate control through an indirect mechanism. Lines with dual inhibition and arrow signs indicate evidence for both directions of effects. (Supporting literature for the pathways illustrated here that is not highlighted elsewhere in this review can be found here: 1, 4, 5, 13, 42, 52, 56, 160, 198, 199.)

therapeutic potential for both diseases. This review therefore focuses on the physiological and pathophysiological neuroendocrine mechanisms mediating the glycemic- and food intake–suppressive effects of amylin, GLP-1, and GIP (see **Figure 1** for an illustrative summary). Importantly, this review also highlights gaps in knowledge that may offer potential advances for improved therapeutics targeting each of these systems for the treatment of T2DM and obesity.

INCRETIN- AND AMYLIN-MEDIATED SIGNALING IN BLOOD GLUCOSE REGULATION

An incretin factor is a hormone that is secreted from the intestine (also termed insulinotropic gut peptide) in response to nutrient ingestion and elicits the secretion of insulin from the pancreatic β-cells to lower blood glucose levels postprandially (for reviews, see 8, 73). Accordingly, oral glucose administration will lead to a greater increase in plasma insulin levels when compared with the same amount of glucose given intravenously (47, 113). Thus, the incretin effect refers to the increase in the amount of insulin secreted from pancreatic β-cells following oral versus intravenous glucose administration, and it is estimated to account for approximately 50% of the total insulin secreted after oral glucose administration. The incretin effect is largely mediated by the neuroendocrine actions of two insulinotropic gut peptides, GLP-1 and GIP, that are secreted from enteroendocrine "L" and "K" cells, respectively, of the intestine following nutrient entry into the gastrointestinal (GI) tract (for reviews, see 66, 73). Interestingly, the physiological and

pharmacological effects mediated by GIP and GLP-1 ligands are not restricted to glycemic regulation, nor are they entirely due to direct activation of receptors expressed on pancreatic β-cells. Instead, the relevant GLP-1 receptor (GLP-1R) and GIP receptor (GIPR) populations mediating the physiological responses of these hormones are still being heavily explored. In the case of GLP-1, the biological processes regulated by this neuroendocrine system are abundant and include blood glucose regulation, regulation of gastric emptying, visceral stress, and cardiovascular and thermogenic effects. Importantly, GLP-1 also plays a critical role in the control of food intake and energy balance. Sections within this review provide a brief overview of GIP and GLP-1 physiology with special attention devoted to the endocrine, neuroanatomical, and behavioral mechanisms mediating the physiological effects of these incretin factors.

The pancreatic β-cells also produce amylin [a.k.a. islet amyloid polypeptide (IAPP)], a 37-amino-acid peptide that is cosecreted with insulin and also plays a role in the regulation of blood glucose and other physiological functions (103, 136, 156). Amylin's secretion is also modulated in part by the presence of nutrients in the GI tract; however, unlike incretin hormones, amylin's ability to modulate glycemic control is not thought to be a result of potentiated insulin release. Rather, the prevailing view is that amylin receptor activation reduces blood glucose by delaying gastric emptying, suppressing food intake, and inhibiting meal-related glucagon secretion (for reviews, see 104, 154, 155). Like the incretin hormones, these effects by amylin require distributed sites of action that necessitate activation of amylin receptors in the central nervous system (CNS). Recent advances in amylin physiology in relation to food intake and energy balance are discussed in sections below.

SYSTEMIC GLUCAGON-LIKE PEPTIDE-1 REGULATION OF BLOOD GLUCOSE AND ENERGY INTAKE

Vagal-Dependent Mediation of Glycemic Responses by Systemic GLP-1

Within the periphery, there are three distinct populations of GLP-1Rs relevant to glycemic control; these populations include GLP-1R expressed on (*a*) pancreatic β-cells, (*b*) vagal afferent fibers innervating the GI tract, and (*c*) vagal afferent fibers innervating the hepatoportal bed (for reviews, see 66, 73). The amount of endogenous postprandial GLP-1 released from intestinal L-cells in humans is correlated with the size of the meal. This is an important concept when considering the relevant GLP-1R population(s) within the periphery that may respond to secreted GLP-1 to control for blood glucose utilization under normal physiological conditions as well as during pathophysiological conditions resulting from gastric bypass and/or treatment with GLP-1-based pharmaceuticals for management of T2DM. Overwhelming evidence has shown that the vast majority of endogenously secreted GLP-1 is rapidly degraded by endopeptidases, such as the dipeptidyl peptidase IV (DPP-IV) enzyme, resulting in transient circulating levels of GLP-1 (for a review, see 73). Thus, under normal physiological conditions, paracrine-like signaling by GLP-1 plays a primary role in mediating intestinally derived GLP-1 effects (66, 67, 73). In other words, evidence supports that GLP-1 secreted from intestinal L-cells acts locally on adjacent GLP-1R expressed on the peripheral terminals of vagal afferent fibers innervating the intestine to promote for insulin secretion and subsequent glycemic control via a vago-vagal reflex (153) that stimulates the β-cells to secrete insulin (for a review, see 66).

Direct evidence for the GLP-1 paracrine mode of action comes from rodent studies performing selective surgical ablation of the common hepatic branch (CHB) of the vagus nerve, the principal hepatoportal-innervating branch of the vagus (194). Rats with ablated CHB afferents continue to retain similar glycemic- and food intake–suppressive responses to endogenously produced or

exogenously administered GLP-1, respectively, whereas rats with complete subdiaphragmatic vagal deafferentation (eliminating all vagal afferents) fail to show a GLP-1R-mediated incretin response and had a blunted suppression in glucose intake following exogenous systemic GLP-1 administration (194). Further support for an entero-vagal site of action by GLP-1 comes from the finding that inhibition of DPP-IV, specifically within the intestine and not in the general circulation, results in elevation of intestinal GLP-1 that can drive vagal afferent excitation and insulin secretion (191). Thus, the conservative conclusion drawn from these findings is that vagal afferent communication is needed to mediate the glycemic- and food-intake-inhibitory effects of systemic GLP-1 and is not dependent on the CHB but rather on neuronal signaling by the celiac and/or gastric vagal branches that innervate the GI tract.

Direct Activation of GLP-1R Expressed on Pancreatic β-Cells

The notion that paracrine-like signaling by intestinally derived GLP-1 is the primary physiological mode of action does not discount the potential secondary role of an endocrine-mediated mechanism that involves GLP-1 entering into circulation and having action on GLP-1R expressed either in the hepatoportal bed (97, 133, 134, 190) or directly on β-cells (100). Here, we discuss evidence for glycemic responses mediated by direct activation of GLP-1R expressed on pancreatic β-cells, as this effect undoubtedly occurs with pharmacological treatments targeting the GLP-1 system and/or with various gastric bypass surgeries (both discussed in further detail below).

Activation of GLP-1R expressed on pancreatic β-cells can result in coupling to $G\alpha_s$, $G\alpha_q$, $G\alpha_i$, and $G\alpha_o$ (8, 63, 125), stimulation of adenylate cyclase, elevated cyclic adenosine monophosphate (cAMP), and subsequent activation of protein kinase A (PKA) and C (PKC) as well as phospatidylinositol-3 kinase (PI3K) (57, 138). Interestingly, whereas the increase in adenylate cyclase and cAMP following β-cell GLP-1R activation is required for insulin secretion, activation of PKA does not appear to be a required component for this effect, although when activated, PKA signaling can potentiate insulin secretion (for a review, see 174). The GLP-1-induced increase in cAMP augments glucose-stimulated insulin secretion by increasing the immediate fusion of insulin granules in the β-cell to the plasma membrane and ensuing insulin exocytosis. This process is mediated by a PKA-dependent, but also a PKA-independent, pathway that involves Epac (exchange protein activated by cAMP) (85, 174). In addition to promoting insulin exocytosis from the β-cell, intracellular signaling cascades following GLP-1R activation stimulate insulin gene transcription and protein synthesis (43, 48, 53), putatively providing for a longer temporal control of postprandial insulin signaling. Finally, exciting complementary in vivo and in vitro evidence has pointed to a functional role for GLP-1R signaling in promoting β-cell proliferation and neogenesis (8, 118). Thus, continued exploration of the direct action of GLP-1 on β-cells is highly warranted as we continue to develop improved GLP-1-based pharmacotherapies for T2DM.

CENTRAL GLUCAGON-LIKE PEPTIDE-1 REGULATION OF BLOOD GLUCOSE AND ENERGY BALANCE

CNS GLP-1 in Control of Glycemia

The CNS GLP-1 system plays a critical role in regulating glucose utilization in peripheral tissues (12, 64, 97) and is a potent stimulator of insulin secretion (97). Glucose intolerance has been reported in rats with chronic forebrain intracerebroventricular (icv) administration of the GLP-1R antagonist exendin-(9-39) or with virally mediated knockdown of the GLP-1 precursor preproglucagon (PPG) in the nucleus tractus solitarius (NTS) (12). Moreover, acute forebrain icv

delivery of the GLP-1R antagonist exendin-(9-39) attenuates the utilization of glucose and increases glycogen synthesis in skeletal muscle (73). These findings indicate an endogenous role for the CNS GLP-1 system in glycemic control, yet the specific CNS GLP-1R-expressing nuclei and mechanisms mediating central GLP-1's effects on glycemic regulation remain poorly understood.

The CNS GLP-1R-mediated effects on blood glucose regulation presumably involve modulation of the hypothalamo-pituitary-adrenocortical (HPA) axis (117) and/or autonomic pathways from the brain to the skeletal muscle and pancreas. Examples of similar hypothalamic and brain stem glucose-sensing pathways that modulate pancreatic insulin secretion and peripheral glucose utilization have been reviewed extensively elsewhere (185, 186, 196). GLP-1R activation can have divergent behavioral and physiological effects depending on the site of activation. Within the hypothalamus, activation of GLP-1R in the arcuate nucleus (ARH) suppresses hepatic glucose production and increases β-cell insulin secretion; however, no discernible effects on food intake have been reported (164). Conversely, activation of GLP-1R localized within the paraventricular nucleus of the hypothalamus (PVH) significantly reduces food intake but does not alter glucose homeostasis (164). The glycemic effects of hypothalamic GLP-1 are not limited to the ARH, as GLP-1R activation in the ventral medial hypothalamic nucleus (VMH) also modulates blood glucose (8).

Beyond the collective body of research examining hypothalamic GLP-1R-mediated effects on glycemia, however, there has been little investigation of nonhypothalamic GLP-1R-expressing nuclei in control of blood glucose. This is surprising considering that neural processing by the brain stem is sufficient to mediate the suppressive effects of GLP-1 on food intake and gastric emptying as well as many of the energy expenditure parameters of GLP-1 (e.g., core temperature, heart rate) (69). Moreover, given the well-documented role of parasympathetic-mediated pathways that involves dorsal motor nucleus vagal (DMV) efferent signaling in control of glucose tolerance (185, 186, 196), that PPG-expressing neurons in the CNS are located almost exclusively in the NTS, and that GLP-1 signaling in the DMV excites pancreatic-projecting vagal motor neurons (192, 193), it stands to reason that hindbrain GLP-1R signaling may modulate blood glucose concentrations.

CNS GLP-1 in Control of Energy Balance

Current US Food and Drug Administration (FDA)-approved GLP-1-based pharmacotherapies for T2DM treatment are either orally taken (DPP-IV inhibitors) or systemically injected (GLP-1R agonists), and undoubtedly both classes of drugs result in increased activation of GLP-1R expressed on the terminals of vagal afferent fibers innervating the GI tract and supporting organs of the alimentary canal (for reviews, see 25, 66, 73). The role of vagal afferent signaling in mediating the food intake–suppressive effects of intestinally derived GLP-1 has also been extensively reviewed (59, 66, 73). Importantly, activation of central GLP-1Rs results in many of the same behavioral and physiological responses that are observed following peripheral GLP-1R ligand administration (e.g., inhibition of feeding, increased insulin secretion, reduced gastric emptying) (69, 96, 97, 166). When systemically administered, the GLP-1R agonists liraglutide and exendin-4 sufficiently penetrate the blood-brain barrier (BBB) and gain access to the brain in amounts sufficient to drive a physiological/behavioral response (80, 83), making it difficult to disentangle the effects originating in the periphery from those effects mediated by direct CNS activation. Instead, the best evidence supporting the relevance of the CNS GLP-1 system in energy balance regulation are reports showing an endogenous role for the CNS GLP-1 system by (*a*) chronic blockade of CNS GLP-1R by forebrain administration of the selective antagonist exendin-(9-39), which results in increased food intake and body weight (12, 116, 189), and (*b*) targeted viral knockdown of central GLP-1-producing PPG neurons, which results in hyperphagia and elevated weight gain (12).

The current challenge for the field is to characterize the autonomic, endocrine, and behavioral responses mediated by individual GLP-1R-expressing nuclei. Indeed, although many CNS nuclei relevant for energy balance express GLP-1R, to date only a select few have been demonstrated to be physiologically required for the normal control of feeding (2, 41, 65, 166). Therefore, we first highlight recent advances in our understanding of the brain stem, hypothalamic, and mesolimbic GLP-1R-mediated effects controlling for energy balance and subsequently focus on potential areas of new research, with an eye toward hippocampal cognitive processes that involve GLP-1 signaling.

GLP-1 and hypothalamic/brain stem signaling. As briefly discussed above, examinations of hypothalamic GLP-1-mediated energy balance effects have been somewhat surprising. Despite the fact that GLP-1Rs are expressed on ARH proopiomelanocortin neurons, which are required for the regulation of energy balance (for a review, see 34), activation of ARH GLP-1R has no effect on food intake (164). Conversely, pharmacological activation of GLP-1R in the PVH, lateral nucleus of the hypothalamus (LH), dorsal medial nucleus of the hypothalamus (DMH), or VMH suppresses food intake (114, 115, 166). Among these hypothalamic structures, however, to date only the LH GLP-1R populations have been shown to be physiologically relevant for the control of food intake, as blockade of LH GLP-1R produces a short-term increase in food intake (166). Further studies are therefore needed to determine whether blockade of GLP-1R in the PVH, DMH, and VMH can lead to an increase in food intake in order to establish whether endogenous GLP-1 signaling in each of these sites is physiologically relevant for food intake regulation. Thus, although the hypothalamus is innervated abundantly by GLP-1 axonal projections from the NTS (101, 102, 151, 152), hypothalamic processing alone does not seem sufficient to mediate all of the feeding effects by the CNS GLP-1 system. Thus, a much broader exploration of GLP-1 neuroanatomy is needed with regard to energy balance control.

Despite the importance of forebrain GLP-1R signaling for food intake regulation (2, 38, 41, 96, 102, 115), hindbrain neural processing is sufficient to mediate the food intake–suppressive effects of peripherally or centrally administered GLP-1R agonists (69). Within the hindbrain, GLP-1R signaling in the medial NTS (mNTS) is physiologically relevant for the normal control of food intake (65). Furthermore, pharmacological activation of mNTS GLP-1R produces a robust suppression of food intake that can be sustained for over 24 hours (68, 200). Previous findings indicate that NTS GLP-1R-mediated suppression of food intake requires a cAMP/PKA-dependent activation of p44/42-mitogen-activated protein kinase and simultaneous suppression of adenosine monophosphate-activated protein kinase (AMPK) (68). Because the intake-suppressive effects of hindbrain GLP-1R activation are so robust and long lasting, additional cAMP/PKA-dependent intracellular signaling pathways are undoubtedly required to mediate the suppression of intake by GLP-1R activation. Indeed, hindbrain GLP-1R-mediated suppression of food intake also involves a PI3K-PIP3-dependent translocation of Akt to the plasma membrane and subsequent suppression of Akt phosphorylation (159). Together, these intracellular signaling pathways interact to control for the feeding effects produced by mNTS GLP-1R activation, as a disruption of any one of these signaling pathways is sufficient to attenuate the food intake–suppressive effects produced by hindbrain GLP-1R activation. It is highly likely that these intracellular signals act together with additional downstream intracellular targets to modify transcriptional control, theoretically making an NTS GLP-1R-expressing neuron more sensitive to other anorectic signals processed within the NTS (for a review, see 60).

GLP-1 and mesolimbic reward signaling. Drawing upon the appreciation that the excessive food intake that contributes to human obesity is not driven by metabolic need, a number of laboratories have made major advances in our understanding of the role that GLP-1 signaling in

the nuclei of the mesolimbic reward system (MRS) has in energy balance control (2, 38, 41). This growing body of literature builds on the field's collective understanding of gustatory signaling from the oral cavity (primarily taste) and its synaptic connections to the MRS (135). Indeed, gustatory projections to limbic structures are responsible for engaging the nucleus accumbens (NAc) to modulate dopamine signaling (135). Although these discoveries inform our thinking about feed-forward neural circuitry that promotes feeding, the contributions of antagonizing signals communicated to the MRS that accumulate as consumption of a meal progresses remain an extremely hot topic for investigation. The hypothesis that NTS GLP-1-producing PPG neurons function as a hub to connect within-meal GI-derived satiation signals with the hedonic/reward circuitry of the MRS provides a plausible mechanism to explain why the rewarding value of food is decreased in a sated state (6, 11, 26, 171, 172). To this end, recent complementary reports show that NTS PPG neurons project directly to the ventral tegmental area (VTA) (2) and NAc core and shell (2, 41). The connections to the VTA and NAc core were shown to be physiologically relevant for the control of palatable food intake, as GLP-1R blockade in either nucleus increased palatable high-fat diet intake (2). Given that dopaminergic projections from VTA to NAc are well established and dopamine signaling in the MRS modulates food intake (92, 130), it is plausible that the reduction in food intake via GLP-1R activation in the VTA and NAc involves modulation of dopamine signaling and/or synthesis via presynaptic and/or postsynaptic mechanisms. In addition to dopamine, it has been proposed that opioid, γ-aminobutyric acid, and glutamate signaling in the MRS are also involved in regulating feeding (7, 93, 108, 109, 121, 130). At least for the VTA, recent behavioral and electrophysiological evidence suggests that GLP-1Rs are expressed on presynaptic glutamatergic axon terminals whose cell bodies reside in other nuclei [e.g., NTS, prefrontal cortex, central nucleus of the amygdala (CeA)] (119). Activation of the VTA GLP-1R reduced the intake of palatable high-fat diet primarily by reducing meal size, with minimal and inconsistent effects on meal frequency (119). The anorectic effects of intra-VTA GLP-1R activation were shown to be mediated in part by glutamatergic AMPA/kainate, but not *N*-methyl-D-aspartate (NMDA), receptor signaling (119).

Beyond modulation of nutrient intake, emerging evidence suggests that satiation hormones, including GLP-1, may also regulate the reinforcing effects of alcohol intake and drugs of abuse (for a review, see 181). Thus, the GLP-1 system may serve as a novel target for drug discovery programs aimed at developing pharmacotherapies for drug addiction (91). Given that the reinforcing effects of natural rewards (like palatable food) and drugs of abuse are regulated, in part, by the MRS (39, 130, 143, 167), it is possible that CNS GLP-1 signaling may also regulate drug taking and seeking. Recent studies demonstrate that peripheral administration of a GLP-1R agonist attenuates psychostimulant-induced conditioned place preference (CPP) and that these effects are associated with reduced extracellular dopamine levels in the NAc (46, 58). Unfortunately, it is not clear from these studies whether the effects of a peripherally administered GLP-1R agonist on psychostimulant-induced behavioral responses are due to direct stimulation of GLP-1R in the brain or occur through an indirect vagally mediated mechanism that influences the MRS. Perhaps more importantly, because nausea and malaise-like symptoms are common adverse effects associated with high doses of peripherally administered GLP-1R agonists (83) (such as the high doses used in the aforementioned CPP studies), it is impossible to disentangle reduced expression of CPP from place avoidance. Thus, further research is desperately needed to determine whether direct GLP-1 action in the MRS can modulate drug taking and seeking and do so in the absence of nausea/malaise (discussed in further detail below).

GLP-1 and hippocampal signaling. In addition to nuclei traditionally associated with homeostatic (e.g., ventromedial hypothalamus, caudal brain stem) and rewarding (e.g., nucleus

accumbens, ventral tegmental area) aspects of feeding behavior, GLP-1Rs are also expressed in the hippocampus, a telencephalic structure linked with learning and memory function (117). In a series of papers, Greig and colleagues demonstrated that GLP-1 has neuroprotective effects against excitotoxic damage in hippocampal neurons (139) as well as against amyloid-beta peptide-induced neuronal death (140). Shortly thereafter, a pivotal paper from During et al. (45) demonstrated the functional relevance of hippocampal GLP-1R in learning and memory function. Pharmacological activation of CNS GLP-1R (via icv GLP-1 infusion) improved learning performance in a spatial learning test that is sensitive to hippocampal damage. Further evidence that hippocampal GLP-1R signaling improves learning and memory was provided by During and colleagues' (45) results showing that GLP-1R-deficient mice were impaired in a hippocampal-dependent contextual learning problem and that viral vector–mediated upregulation of GLP-1R gene expression targeted to the hippocampus markedly enhanced spatial learning performance relative to controls.

Having established a role for GLP-1 signaling in hippocampal-dependent learning, the challenge for the field is to elucidate the neurophysiological mechanisms through which GLP-1 exerts its memory promoting and neurotrophic effects on hippocampal neurons. GLP-1 has been shown to improve impairments in hippocampal synaptic plasticity (NMDA-mediated long-term potentiation) induced by pharmacological (195) or genetic (107) rodent models of Alzheimer's disease, as well as synaptic plasticity deficits induced by streptozotocin-induced diabetes (75). Given that the FDA-approved long-acting GLP-1R analogs exendin-4 and liraglutide are able to sufficiently penetrate the BBB and act on CNS receptors (80, 86, 110), these neurotrophic properties may have clinical relevance for Alzheimer's and other dementias. In fact, chronic exendin-4 treatment in rodents restores learning and memory deficits induced by high-fat-diet feeding (55) or by intrahippocampal lipopolysaccharide administration (74). Similar findings by Holscher and colleagues have demonstrated that chronic liraglutide treatment prevented memory impairments induced by a transgenic mouse model of Alzheimer's (112) and by diet-induced obesity (111). Thus, these GLP-1 analogs may prove to be clinically useful for dementia and other types of cognitive dysfunction that target the integrity of the hippocampus.

Given the robust influence of learning and memory processing on feeding behavior (for reviews, see 33, 72, 79, 88, 187), it is likely that the memory-promoting effects of hippocampal GLP-1R signaling are directly linked with the anorectic CNS actions of GLP-1. Neural processing in the hippocampus links contextual information with previous experience to guide behavior appropriately (16, 78, 90). This can influence feeding behavior that is based on external contextual cues (e.g., optimal foraging locations, feeding inhibition in predator environment) as well as by integrating internal contextual cues with previous experience related to obtaining and/or consuming food. For example, rodents with selective hippocampal lesions cannot learn or retain a discrimination task in which different magnitudes of food deprivation serve as discriminative stimuli signaling the presence or absence of a palatable food reward (sucrose) (32). The internal context may be represented in the hippocampus via neuroendocrine signaling by GLP-1 and other peripherally derived hormonal signals whose circulating levels vary with short- and long-term energy status. Indeed, in addition to GLP-1R, the hippocampus is densely populated with receptors for insulin, leptin, cholecystokinin, and ghrelin (31, 71, 173, 202). A series of recent studies shows that neuronal processing in the ventral subregion of the hippocampus modulates appetitive behavior and food intake via signaling by both anorectic and orexigenic neuroendocrine ligands. The adipose tissue–derived hormone leptin acts on receptors in the ventral subregion of the hippocampus to suppress food intake and motivated responding for palatable food (runway performance for sucrose) (82). In contrast, ghrelin receptor signaling in this region potently increases food intake, operant responding for sucrose, and meal initiation in response to environmental cues associated

with food reward (81). Although this hypothesis has not been directly tested, it may be the case that hippocampal GLP-1R signaling influences food seeking and consumption by promoting memory processes that link the internal energy status with previous experience to influence feeding behavior.

GASTRIC INHIBITORY POLYPEPTIDE REGULATION OF BLOOD GLUCOSE AND ENERGY BALANCE

Like GLP-1, GIP stimulates glucose-dependent insulin secretion and insulin transcription/translation as well as β-cell growth and preservation of β-cell survival under normal physiological conditions (for a review, see 162). However, unlike GLP-1, few energy balance effects are produced by GIP treatment alone, and much of the beneficial glycemic effect of GIP signaling is impaired in states of chronic hyperglycemia (77). The latter fact has greatly precluded any significant pharmacological advancement for the GIP system as a primary treatment strategy for T2DM. It is also worth noting that there are many conflicting reports showing opposing metabolic benefits arising from activation or inhibition of GIP receptors. For example, GIP administration in hyperglycemic patients with T2DM promotes glucagon secretion and worsens glucose tolerance (29), an effect contrary to GIP-mediated effects in euglycemic nondiabetic conditions (162). Yet, in mouse models, genetic deletion of the GIP receptor improves glucose tolerance and insulin sensitivity (for a review, see 25). Thus, although emerging combination therapies involving GIP signaling are now being pursued as a potential treatment strategy for disruptions in glycemia and energy balance (162), the cautious view at this moment would be one that supports extensive further preclinical and clinical trials for GIP-based pharmacotherapy before considering any GIP-based compound as a viable treatment option for T2DM and/or obesity.

AMYLIN REGULATION OF BLOOD GLUCOSE AND ENERGY INTAKE

The blood glucose–lowering actions of amylin receptor agonists (i.e., pramlintide, salmon calcitonin) are among the most widely studied of amylin's multiple physiological functions (for reviews, see 103, 106, 155, 156). Indeed, the amylin analog, pramlintide, is FDA-approved for the treatment of both T1DM and T2DM. In addition to the blood glucose regulatory effects, amylin signaling also suppresses food intake and body weight. Accordingly, the amylin system is a potentially attractive target for the pharmacological treatment of obesity because of its anorectic actions. The intake-inhibitory effects of amylin receptor agonists are mediated by direct action in the brain following stimulation of amylin receptors (103, 106, 155, 156). Amylin receptors are fairly unique in that they contain one of two splice variants of the calcitonin receptor (CTa/CTb; a G-protein coupled receptor) heterodimerized with one of the receptor activity-modifying proteins (RAMP1, RAMP2, or RAMP3) (for reviews, see 147, 154). Despite the fact that amylin readily crosses the BBB and gains access to much if not all of the CNS (9, 10), where amylin receptors are widely distributed across the neuraxis (14, 15, 70, 175, 182), investigations of CNS nuclei and neuronal mechanisms mediating the anorectic effects of amylin signaling have been surprisingly restricted. A more comprehensive analysis of the mechanisms through which CNS amylin signaling reduces food intake is particularly warranted given recent interest in combining amylin with leptin receptor agonism, antagonists of the opioid system (e.g., naltrexone), and/or inhibitors of dopamine/norepinephrine reuptake (e.g., bupropion) for obesity treatment (27, 30, 103, 146, 157, 188).

The anorectic and body weight–suppressive effects of amylin receptor activation are mediated by a distributed network across the CNS that, to date, is known to involve processing by the area

postrema (AP) (105, 123, 149), hypothalamus (145, 157), and VTA (120). Amylin action in the AP and VTA is physiologically relevant for the control of feeding and is also potentially clinically relevant because amylin receptor blockade in either site attenuates the intake-suppressive effects of systemically injected amylin analogs (104, 120, 123, 150). From a therapeutic standpoint for future pharmacological treatment of obesity and potentially eating disorders (i.e., binge eating), the finding that blockade of amylin receptors in the VTA attenuates the intake-suppressive effects of a peripherally administered amylin analog suggests the potential for peripheral amylin analogs to affect VTA neural processing in humans. Given the critical role of the VTA in reward and motivational aspects of food intake control via dopaminergic inputs to the NAc (87, 130, 169), it is plausible that amylin action in the VTA controls for food intake by modulating the rewarding/motivational value of palatable food (120) as well as the ability of environmental food cues to trigger excessive food seeking and consumption. Such hypotheses require extensive further testing.

PATHOPHYSIOLOGICAL EFFECTS OF AMYLIN- AND GLUCAGON-LIKE PEPTIDE-1-BASED PHARMACOTHERAPIES

As highlighted above, tremendous opportunities exist for further pharmaceutical advancements in GLP-1- and amylin-based treatments for diabetes and obesity. Among the most notable goals of future GLP-1 and amylin pharmacotherapies should be the development of receptor ligands that exert enhanced suppression of blood glucose, food intake, and body weight gain but are able to achieve each of these effects with reduced incidence of adverse events. Although it is true that FDA-approved GLP-1R (e.g., liraglutide and exenatide) and amylin receptor (e.g., pramlintide) ligands present negligible risks of life-threatening adverse events (e.g., cardiac abnormalities, depression, suicide ideation, renal failure) (19, 24, 124, 144, 161), neither class of drug is completely devoid of side effects that negatively impact quality of life and produce treatment attrition. Most notably, ~20–50% of T2DM patients prescribed GLP-1 medication experience nausea and/or vomiting, leading to discontinuation of drug treatment in ~6–10% and reduced dose tolerance in an additional ~15% (17, 23, 37, 76, 89). Similarly, patients prescribed the amylin analog pramlintide are conservatively estimated to be 1.8 times more likely to experience nausea compared to those receiving placebo treatment (for a meta-review, see 179).

Although the adverse effects of nausea and emesis (i.e., retching and vomiting) are reported for both GLP-1- and amylin-based pharmacotherapies, it is surprising how uninvestigated these phenomena are, as such staggering statistics limit the widespread use, efficacy, and potential future FDA approval of GLP-1R and amylin receptor ligands for obesity treatment. Perhaps a concern of researchers and pharmaceutical companies is that a portion of the food intake reduction produced by amylin and GLP-1R ligands is secondary to the induction of nausea; this concept is worthy of consideration but is poorly understood. The lack of knowledge is partially attributable to the fact that unlike emesis, the subjective experience of nausea cannot be overtly measured in humans, which is underscored by the fact that available patient self-reporting tools for nausea have poor validity and reliability (21, 197). Another limitation related to the investigation of emesis/nausea/malaise by GLP-1R and amylin receptor ligands is that the vast majority of preclinical experimental investigations of these drugs have been conducted in rodents, which lack the anatomy and physiology to retch and vomit (for a review, see 3). Importantly though, the absence of emesis by rodents does not indicate an absence of nausea/malaise; a similar scenario is observed in humans who experience nausea but do not vomit. Any attempt to quantify malaise by GLP-1 and amylin pharmacology in the rodent must be done with the appreciation that the analyses are indirect semi-quantifiable measures of a subjective feeling and thus take advantage of alternative models: (*a*) taste reactivity (61, 62), the quantification of innate oral-motor facial responses

indicative of aversion or acceptance; (*b*) conditioned taste avoidance (CTA), which is the avoidance of flavors or foods paired with illness (54); and (*c*) pica, which is the consumption of nonnutritive substances (e.g., kaolin clay) in response to nausea-inducing agents (35, 36, 122), a behavior that may represent an innate adaptive response to reduce the adverse effects of toxins in the organism. Although they are time-consuming, analyses that involve multiple measures of malaise done in concert with complementary experimentation in alternative animal models that do vomit (e.g., shrew and ferret) will collectively deepen our understanding of the neurobiological mechanisms of emesis/nausea/malaise induced by GLP-1 and amylin pharmacology. Indeed, in the case of GLP-1, we (83) and others (94, 163) have suggested that the field as a whole must utilize a multi-model approach to disentangle physiological (e.g., regulation of food intake and blood glucose) and pathophysiological (e.g., nausea/vomiting) effects produced by GLP-1 pharmacology.

Although current amylin- and GLP-1-based pharmacotherapies are nonspecific with regard to the cell populations that they act on, future research must invent and explore highly site-targeted pharmacotherapies for these systems if we are to achieve desired effects (i.e., food intake and blood glucose reductions) without producing maladaptive responses (e.g., nausea/vomiting). For example, in GLP-1R$^{-/-}$ mice, re-expression of the GLP-1R exclusively on the pancreas is sufficient to restore much of the GLP-1 incretin effect (100). Thus, although vagal and CNS GLP-1R activation do participate in blood glucose regulation (for a review, see 64), it is intriguing to consider the potential beneficial glycemic effects of a second generation of GLP-1R ligands that would specifically act on pancreatic β-cell-expressing GLP-1R. Such a ligand would theoretically yield some glycemic improvements in T2DM patients with reduced incidence of adverse events. A similar strategy could also be applied to the GLP-1- and amylin-mediated mechanisms controlling for food intake and body weight. As discussed above, BBB penetrance is undoubtedly occurring for current amylin and GLP-1 ligands, and the physiological and behavioral effects produced by the activation of a given nucleus can be quite distinct from the responses yielded by receptor activation at another CNS structure. For example, selective VTA or NAc core GLP-1R activation reduces palatable food intake without producing any measured malaise in rodents (absence of CTA and pica) (2, 38, 41). Although it would be useful to confirm that VTA/NAc core GLP-1R activation does not produce emesis using a mammalian model capable of vomiting, the aforementioned complementary set of data identifies these GLP-1R-expressing mesolimbic nuclei as clinically attractive from the standpoint of creating a second-generation GLP-1 ligand to reduce food intake without producing nausea/malaise. Such a targeted ligand is greatly needed because current GLP-1R ligands are gaining access to the whole CNS, where GLP-1R activation in nuclei such as the NTS or CeA will produce a CTA and/or pica response along with varying degrees of food intake suppression (83, 96). As detailed in **Table 1**, many GLP-1R-expressing nuclei can modulate food intake when activated by GLP-1 or GLP-1R agonists. The task at hand for the field is to systematically evaluate the mechanisms by which food intake is suppressed by GLP-1R signaling in each of these nuclei and whether any adverse events (e.g., nausea) might be contributing to the feeding effects.

A ROLE FOR INCRETIN AND AMYLIN SIGNALING IN GASTRIC BYPASS–MEDIATED IMPROVEMENTS IN GLYCEMIA AND BODY WEIGHT

Bariatric surgery for the purposes of weight loss is currently among the top elective procedures across the United States. These procedures, which alter the GI tract to either limit nutrient exposure to absorptive sites within the proximal gut [e.g., Roux-en-Y gastric bypass (RYGB)] and/or limit the volume of food voluntarily ingested by the patient (e.g., gastric lap banding,

Table 1 Evidence for GLP-1-mediated feeding, glycemic, and malaise effects

Nucleus	Evidence for food intake control	Evidence for glycemic control	Nausea/malaise evidence
NTS	Physiological and pharmacological evidence	Unknown	Pica
AP	No direct pharmacological evidence	Unknown	Unknown
DMV	No pharmacological evidence	Unknown/possible	Unknown
PVH	Pharmacological evidence	No pharmacological evidence	No CTA
ARH	No pharmacological evidence	Pharmacological evidence	Unknown
LH	Physiological and pharmacological evidence	Unknown	Unknown
DMH	Pharmacological evidence	Unknown	Unknown
VMH	Pharmacological evidence	Unknown	Unknown
VTA	Physiological and pharmacological evidence	Unknown	No CTA or pica
NAcC	Physiological and pharmacological evidence	Unknown	No CTA or pica
NAcSh	Pharmacological evidence	Unknown	No CTA or pica
CeA	No pharmacological evidence	Unknown	CTA
HPF	Unknown/possible	Unknown	Unknown
Nodose (vagal afferent)	Physiological and pharmacological evidence	Physiological and pharmacological evidence	Not required for pica

Abbreviations: AP, area postrema; ARH, arcuate nucleus of the hypothalamus; CeA, central nucleus of the amygdala; CTA, conditioned taste avoidance; DMH, dorsal medial nucleus of the hypothalamus; DMV, dorsal motor nucleus of the vagus; HPF, hippocampal formation; LH, lateral nucleus of the hypothalamus; NAcC, nucleus accumbens core; NAcSh, nucleus accumbens shell; NTS, nucleus tractus solitarius; PVH, paraventricular nucleus of the hypothalamus; VMH, ventral medial nucleus of the hypothalamus; VTA, ventral tegmental area.

sleeve gastrectomy), have all been largely successful in promoting sustained weight loss in obese individuals and certainly serve as the standard in weight loss treatment strategies when compared to broadly disappointing results from most FDA-approved pharmacotherapies (131).

RYGB (especially laparoscopic RYGB) is still considered the gold standard for weight loss surgery, although these procedures are not without their limitations. Approximately 20–30% of RYGB patients fail to reach the typical postoperative weight loss and/or begin to regain large amounts of weight within the first year (84, 141, 165, 183). Despite this minority of the patient population, the vast majority of obese individuals undergoing bariatric surgeries achieve tremendous and unmatched metabolic and health outcome improvements. Perhaps the most remarkable positive health outcome from RYGB is that obese patients with T2DM see profound improvements in glycemic control, often within a matter of days (22, 141, 158, 180). Such strong metabolic improvements in RYGB patients have prompted considerable clinical and basic science research focused on elucidating the hormonal and metabolic mechanisms that may mediate these effects. Current thinking has shifted away from the original idea that metabolic improvements following RYGB were principally due to restricted absorption of nutrients, to new efforts aimed at unlocking what impact gastric bypass has on the neuroendocrine controls that govern food intake and glycemic regulation (158, 184, 201). Prevalent among this emerging research is the idea that GI-derived incretin hormones and amylin serve an integral role in enhancing satiation as well as regulating blood glucose in postoperative gastric bypass patients (98). Of similar interest are investigations that examine alterations in vagally mediated gut-to-brain communication following RYGB and what role, if any, these altered vagal communications play in weight loss and glycemic control (177).

The Vagus Nerve and RYGB

The role of vagal afferent innervation within the GI tract and subsequent transmission of sensory signals regulating food intake are well established (18, 170). Removing vagal input to the hindbrain via chemical or surgical ablation of selective branches can significantly diminish the satiating potency of numerous hormones and signaling molecules controlling energy balance. Similarly, diet-induced obesity may result in reduced sensitivity to satiation signals (see, e.g., 40) and increase expression of orexigenic vagal signaling (137), either of which could lead to or exacerbate hyperphagia and obesity. Despite such well-known involvement in energy balance, there exists a paucity of reports that address whether vago-vagal signaling alterations contribute to metabolic improvements following RYGB. During this procedure it is likely that a significant number of vagal fibers are resected, which may impact satiation signaling as well as hormonal release. Recent work by Peters and colleagues (142) suggests that the effects of vagotomy involve a considerable degree of plasticity within both vagal afferent and synaptic transmission of vagal fibers to the NTS. These experiments highlight a potential system of transient withdrawal and remodeling of the vagal network that may serve to explain some of the neuroendocrine effects of gastric bypass. Surgical resection of the CHB of the vagus, a primarily sensory branch with afferent innervation of the liver, proximal duodenum, and pancreas, has little effect on intake following RYGB in the rat (177). However, these results do not preclude involvement of more distal branches/sites of vagal innervation such as the celiac branch, which as a result of anatomical repositioning of the roux and common limbs, could receive more nutrient and/or vagal sensory activation than in normal physiology.

Incretin Hormones and Amylin Following RYGB: Why Is RYGB So Successful?

Although many hormones and gut peptides have alterations in their secretion, plasma concentrations, and postprandial responsiveness following RYGB, for the purposes of brevity we focus here on GLP-1, peptide YY (PYY)3-36, and amylin as major neuroendocrine signals accompanying both the weight loss and normalization of glycemia following RYGB. Numerous preclinical and clinical studies are in agreement that RYGB patients show a rapid and sustained increase in postprandial GLP-1 secretion that is greater in magnitude than that seen in either obese nonsurgical controls or obese controls undergoing other gastrointestinal surgery (i.e., gastric banding) (98, 132, 168). Similar results have been shown with PYY3-36 (129, 168). Collectively, these findings are consistent with the notion that the rapid and sustained postprandial GLP-1 and PYY3-36 secretion observed following RYGB could result from a greater concentration of nutrients being exposed to the L-cells in the jejunum and ileum because a large portion of the stomach and all of the duodenum have been bypassed. An additional, nonexclusive idea is that specific enteroendocrine cells, like the L-cells, adapt in response to the anatomical reorganization of RYGB, resulting in enhanced proliferation and expression of the cell type. Indeed, there are reports showing an upregulation of immunoreactivity for GLP-1- and PYY-producing cells in the intestine following RYGB (128, 131).

It would be useful to elucidate how enhanced secretion/satiating ability of GLP-1 and PYY3-36 could impact obesity treatment as a welcome alternative to radical bariatric procedures. Recent data from Reidelberger and colleagues (148) showed that when exendin-4 and PYY3-36 were coadministered to diet-induced obese rats using multiple dosing/administration strategies, including doses consistent with plasma observations in RYGB patients, the food intake– and body weight–suppressive effects became increasingly complex to interpret owing to the apparent tolerance of dosing, tachyphylaxis, and counteraction by competing orexigenic mechanisms, which together mitigate the suppressive effects of exendin-4 and PYY3-36. Thus it is clear that the simple boosting of the signal of distal gut satiation/incretin hormones via RYGB and the exact mechanisms

that account for this increase in postprandial GLP-1 and PYY secretion following RYGB warrant further investigation. The consequences are just beginning to be examined in both humans and animals (95, 99, 126, 127, 158, 184, 201).

Among the most emergent potential players in the peripheral signaling enhancement following RYGB is amylin. Postprandial increases in amylin have been reported following RYGB (178); however, over time (and unlike GLP-1 and PYY3-36) amylin levels tend to decrease or show little change (20). As highlighted above, it is also likely that amylin and GLP-1 act through distinctive and largely complementary mechanisms to produce ameliorative effects on weight loss and maintenance as well as restoration of glucose homeostasis following RYGB (for a review, see 155).

SUMMARY AND FUTURE DIRECTIONS FOR THERAPEUTIC ADVANCEMENT

The opportunity for advancement in pharmaceutical treatments of obesity and T2DM continues to expand with the new discoveries of the physiological and pathophysiological effects mediated by the amylin and GLP-1 systems. As detailed above, further exploration of the cellular/molecular signaling pathways of GLP-1R and amylin receptor activation will likely provide new opportunities for future pharmacotherapies targeting signaling pathways that interact with the GLP-1 and amylin systems. The development of second-generation receptor agonists for GLP-1R and the amylin receptor that can selectively target specific nuclei in the CNS may also provide an opportunity to treat diseases without producing undesirable adverse events (e.g., nausea). Recent discoveries of GLP-1 and amylin action in the mesolimbic reward system in control of energy balance are also exciting when one considers the possible implications for pharmacological targeting of these systems as a means to treat other diseases, such as drug addiction and depression, that are associated with a disrupted perception of reward and pleasure. Finally, given the redundancy of neuroendocrine systems involved in the regulation of energy balance as well as in the maintenance of blood glucose concentrations, it seems logical that a realistic and sustainable pharmacological approach to the treatment of either obesity or T2DM will require a cocktail of new, highly specific drugs that act in concert to produce an enhanced suppression of food intake and/or glycemic concentration. As discussed in this review, combination drug therapies would be well suited to include amylin- and/or GLP-1-based ligands.

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