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GLP-1 and weight loss: unraveling the diverse neural circuitry

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Kanoski SE, Hayes MR, Skibicka KP. GLP-1 and weight loss: unraveling the diverse neural circuitry. *Am J Physiol Regul Integr Comp Physiol* 310: R885–R895, 2016. First published March 30, 2016; doi:10.1152/ajpregu.00520.2015.—Glucagon-like peptide-1 (GLP-1) is currently one of the most promising biological systems for the development of effective obesity pharmacotherapies. Long-acting GLP-1 analogs potently reduce food intake and body weight, and recent discoveries reveal that peripheral administration of these drugs reduces food intake largely through humoral pathways involving direct action on brain GLP-1 receptors (GLP-1R). Thus, it is of critical importance to understand the neural systems through which GLP-1 and long-acting GLP-1 analogs reduce food intake and body weight. In this review, we discuss several neural, physiological, cellular and molecular, as well as behavioral mechanisms through which peripheral and central GLP-1R signaling reduces feeding. Particular attention is devoted to discussion regarding the numerous neural substrates through which GLP-1 and GLP-1 analogs act to reduce food intake and body weight, including various hypothalamic nuclei (arcuate nucleus of the hypothalamus, periventricular hypothalamus, lateral hypothalamic area), hindbrain nuclei (parabrachial nucleus, medial nucleus tractus solitarius), hippocampus (ventral subregion; vHP), and nuclei embedded within the mesolimbic reward circuitry [ventral tegmental area (VTA) and nucleus accumbens (NAc)]. In some of these nuclei [VTA, NAc, and vHP], GLP-1R activation reduces food intake and body weight without concomitant nausea responses, suggesting that targeting these specific pathways may be of particular interest for future obesity pharmacotherapy. The widely distributed neural systems through which GLP-1 and GLP-1 analogs act to reduce body weight highlight the complexity of the neural systems regulating energy balance, as well as the challenges for developing effective obesity pharmacotherapies that reduce feeding without producing parallel negative side effects.

glucagon-like peptide-1; obesity; exendin-4; food reward; liraglutide; Saxenda; Byetta; dipeptidyl peptidase-4

OBESITY PREVALENCE IN THE United States has increased by 75% since 1980, with more than one-third of adults categorized as obese and another one-third characterized as overweight (35, 111). With an estimated 80 million U.S. adults believed to have obesity (18), the overall cost of obesity-related illnesses per year has skyrocketed to $450–550 billion (17). Over the time period during which this exponential increase in obesity prevalence occurred, the average daily food intake for adults in the United States is estimated to have risen by ~300–500 kcal per day (28, 37), indicating that excessive eating is indeed a causal factor. Basic science pursuit into the neurobiology underlying excessive food intake is urgently needed as existing pharmacological and behavioral therapies offer limited success and gastrointestinal bariatric surgery, while effective at reducing energy intake, has serious adverse and irreversible consequences (69).

Glucagon-like peptide-1 (GLP-1) is a peptide secreted from L cells in the small and large intestine and from neurons in the nucleus tractus solitarius (NTS) of the caudal brain stem. On the basis of GLP-1's potent incretin effects, long-acting GLP-1 analogs are presently used as pharmacological therapies for Type 2 diabetes mellitus. These compounds also reduce food intake and body weight in both human clinical trials and in experimental animal models. In December 2014, the GLP-1 analog, liraglutide (trade name Saxenda), was approved by the Food and Drug Administration for weight loss treatment in obese individuals. Although this was an extremely encouraging development with regard to pharmaceuticals targeting the GLP-1 system for obesity, weight loss achievements in patients taking liraglutide are modest (typically 5–10% weight loss), and ~30–40% of patients taking liraglutide report frequent incidents of nausea, which can lead to discontinuation in ~10% of patients (38, 90, 110). Thus, basic science investigation into the neurobiology of GLP-1-mediated food intake and body weight reductions is needed to help guide the development of future GLP-1-based obesity pharmacotherapies

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(mono or combination therapies) that, compared with existing GLP-1 analogs, achieve a higher degree of weight loss, coupled with a lower prevalence of nausea and other concomitant negative side effects. Herein, we review current knowledge on the neurobiology underlying GLP-1R-mediated hypophagia and weight loss. In particular, we highlight emerging publications from our labs and others indicating in animal models that GLP-1R signaling reduces food intake and body weight through actions at multiple brain regions throughout the neuraxis. These findings highlight a growing appreciation in the field that basic science research on the neural controls of feeding behavior and obesity must extend analyses beyond the dogmatic view that energy balance is primarily controlled by traditional hypothalamic "feeding centers".

Getting to the Brain: Gut to Brain Pathways

During a meal, gastrically and intestinally derived food intake inhibitory signals accumulate and eventually counteract the positive meal-promoting gustatory and gastrointestinal (GI) signals, a process leading to satiation (i.e., meal termination). While several of these within-meal GI-derived gut peptides and neurotransmitters can communicate to the brain via humoral (i.e., endocrine) mechanisms, a large number of these GI-derived satiation signals are relayed to the brain via activation of specialized ionotropic and G protein-coupled receptors expressed on the dendritic terminals of the vagus nerve that innervate the organs of the alimentary canal. Receptors for several gut peptides are expressed in close cellular proximity to the specialized endocrine cells that are responsible for the synthesis and secretion of the particular hormone. Thus, the prevailing hypothesis is that many of the GI-derived satiation signals primarily act through a paracrine vagal mode of action. Support for vagal afferent mediation of many GI-derived satiation signals comes from basic science studies showing that chemical or surgical ablation of the vagal afferents attenuates the food intake-inhibitory response to various GI satiation signals (see Refs. 47 and 125 for review).

Endogenous GLP-1, secreted by the enteroendocrine "L" cells of the small intestine and large intestine, is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) to inactive metabolites, and, therefore, has a short circulating half-life of less than 10 min (60). Thus, endogenous GLP-1 is thought to primarily act in a paracrine fashion to stimulate GLP-1Rs expressed on the dendritic terminals of the celiac and gastric branches of the vagal afferents innervating the intestine. This GLP-1-mediated vagal activation reduces food intake via vagal-to-NTS glutamatergic signaling, and putatively also via vago-vagal reflex-mediated insulin release (see Ref. 52 for review). Additional evidence suggests that GLP-1Rs expressed within the hepatoportal region may also be responsible for endogenous GLP-1's glycemic effects (87, 107, 108, 149). Importantly, however, the common hepatic branch of the vagus is not required for the food intake inhibitory effects of pharmacological levels of GLP-1 (53). Thus, a conservative view of vagal GLP-1 physiology is that while GLP-1R expressed within the hepatoportal region can mediate GLP-1-induced incretin signaling, GLP-1Rs expressed on the common hepatic branch of the vagus are not required for endogenous GLP-1-mediated glycemic control or pharmacological GLP-1-mediated food intake suppression. Rather, much of the existing evidence supports a paracrine-mode of action for endogenous GLP-1 signaling on GLP-1R expressed on gastric or celiac branches of the vagus nerve that innervate the GI tract.

In addition to the paracrine vagal pathways discussed above, both endogenous GLP-1 and long-acting GLP-1 analogs readily cross the blood-brain barrier (BBB) (82, 83) and, thereby, have the capacity to act in the brain via humoral pathways involving putative BBB transport and subsequent direct action on GLP-1Rs in the brain through either BBB transport or by access to GLP-1Rs expressed on circumventricular regions in the brain (e.g., area postrema). Current thinking is that the rapid DPP-4-mediated degradation of peripherally secreted endogenous GLP-1 precludes it from entering the brain in meaningful concentrations (e.g., 60, 139). Thus, the source of endogenous GLP-1 acting on GLP-1Rs expressed in the brain may be primarily derived from hindbrain GLP-1-expressing neurons. Consistent with this interpretation, Langhans and colleagues (139) demonstrated that intraperitoneal injections of GLP-1 did not reduce the size of the first meal in rats with subdiaphragmatic vagal deafferentation (SDA), suggesting that a paracrine vagal pathway primarily mediates intake reduction by GLP-1. It is possible, however, that despite its short half-life in circulation, peripherally secreted GLP-1 acts in the brain under physiological conditions. Indeed, GLP-1Rs are expressed in peripheral organs that are distal to intestinal L cells [e.g., pancreas (64)], suggesting the existence of GLP-1 endocrine pathways. In the brain, endogenous GLP-1R signaling in the hippocampus is physiologically relevant to food intake control (discussed in more depth below) (65) and memory function (29), yet hindbrain GLP-1 neurons do not innervate the hippocampus (49, 65, 104). These findings mean that *1*) peripherally secreted GLP-1 acts in the brain (e.g., hippocampus) under physiological conditions, and/or *2*) hindbrain-derived GLP-1 communicates through both synaptic and nonsynaptic (e.g., humoral) mechanisms. With regard to the latter possibility, ~30% of GLP-1-producing neurons in the medial nucleus tractus solitarius (mNTS) were back-labeled by a retrograde neural tracer (cholera toxin subunit b) injected into the brain ventricular system, suggesting that axon terminals (or boutons en passant) of hindbrain GLP-1 neurons have access to the cerebroventricular system and potentially release GLP-1 into the cerebrospinal fluid (CSF). Consistent with this hypothesis, GLP-1-immunoreactive axons are present within the ependymal cell layer lining and the lateral and third cerebroventricles, and active GLP-1 peptide levels are present in both the CSF and in the hippocampal parenchyma under physiological conditions (i.e., in untreated rats) (65). Whether GLP-1 present in the CSF and acting on hippocampal and other neurons is of peripheral or central origin is unclear. Moreover, while DPP-4 expression is present in the brain and CSF (39, 140), the functional activity of DPP-4 centrally has not been systematically investigated (63, 85, 91). Thus, it is possible that the GLP-1 half-life may differ in the CNS vs. peripheral circulation based on differential expression of DPP-4 and other GLP-1-degrading enzymes. Another possibility is that GLP-1 reaches hippocampal GLP-1Rs via local microglial GLP-1 secretion (81); however, the extent that GLP-1 is released from CNS microglia cells is not well established and requires careful systematic validation.

Unlike endogenous GLP-1, there is little debate regarding whether peripherally administered long-acting GLP-1 analogs

have direct action on brain GLP-1Rs. This was first demonstrated at the functional/behavioral level by Kanoski et al. (75), who revealed that intraperitoneal liraglutide and exendin-4 (Ex4) administration produced robust food intake and body weight suppression in both SDA rats and controls. Moreover, the hypophagic effects of intraperitoneal liraglutide and Ex4 were severely blunted when the GLP-1R antagonist, exendin-(9–39), was coinjected into the brain ventricular system. These complementary findings, which were recently replicated and expanded upon by other groups (131, 137), reveal that the clinically relevant food intake and body weight reductions associated with GLP-1 analog therapy involve, at least in part, BBB penetration and direct action on CNS GLP-1Rs. Thus, it is of critical importance to understand the mechanisms and sites of action through which central GLP-1R signaling reduces food intake. Moreover, the nausea effects associated with peripheral GLP-1 analog treatment also involve direct action on brain GLP-1Rs (80). Thus, one area of important future research with regard to developing more effective GLP-1-based weight loss therapies is to dissociate (if and where possible) the neural circuits mediating GLP-1R-associated anorectic effects from nausea and malaise.

Neural Pathways of GLP-1-Mediated Intake Suppression

Research on the neural mechanisms through which circulating endocrine or neuropetidergic signals influence energy balance has focused predominantly on nuclei in the ventromedial hypothalamus (e.g., arcuate nucleus), and to a lesser extent, on neurons in other hypothalamic nuclei and the caudomedial medulla. Recent studies have expanded focus beyond these common targets and include investigations into the parabrachial nucleus (PBN) (156), ventral tegmental area (VTA) (1, 62), medial prefrontal cortex (92, 133), amygdala and extended amygdala (72), nucleus accumbens (NAc) (20, 105, 126), and hippocampus (22, 76, 77). In this section, we highlight several recent papers revealing that, in additional to traditional hypothalamic feeding centers, GLP-1R signaling in several brain nuclei is physiologically and pharmacologically relevant to food intake and body weight control.

Hindbrain substrates. GLP-1R expressed within the caudal brain stem are sufficient to mediate the acute food-intake suppressive effects of systemically delivered GLP-1R agonists (56). Within the hindbrain, nuclei of the dorsal vagal complex (DVC; comprising the NTS, area postrema, and DMV) stand out as critical substrates in the control of energy balance, autonomic function, and metabolism (see Ref. 47 for review). While all three nuclei of the DVC express the GLP-1R (42), it is the NTS GLP-1R-expressing cells, in particular, that are both pharmacologically (54) and physiologically (51) relevant to the control of food intake. It is not yet established whether NTS preproglucagon (PPG) neurons express GLP-1R, although it was reported in mice that PPG neurons do not respond to GLP-1R ligands (59). The behavioral, cellular, molecular, and physiological mechanisms through which NTS GLP-1R activation leads to a suppression in feeding behavior is still under intense investigation. From a behavioral perspective, complementary reports suggest that NTS GLP-1R activation suppresses food intake, in part, by reducing the motivation to feed (5, 117). Previous research has shown that NTS GLP-1R activation also elicits a pica response (80), supporting the notion that NTS GLP-1R-mediated suppression of feeding may involve, at least in part, illness-like behaviors. Gastric stasis may contribute to the pica response following NTS GLP-1R activation, as DVC GLP-1R activation potently suppresses gastric emptying (56), an effect that may be exacerbated to the point of producing nausea under conditions of supraphysiological/pharmacological NTS GLP-1R activation (56). Under physiological conditions, however, it is likely that the suppression of gastric emptying following NTS GLP-1R activation serves to amplify within-meal satiation signaling, and thereby reduce motivated behaviors to work for and seek out food.

The PBN, a hindbrain nucleus serving as an important relay and integrator of neural inputs from both the brain stem and the forebrain, is another recently revealed target of GLP-1R-mediated hypophagia (4, 119, 143). The PBN has been implicated in the regulation of gustatory and hedonic aspects of feeding, as well as visceral satiety and illness. Central NTS GLP-1-producing neurons project to both the lateral and medial PBN in rodents and primates (4, 119, 121, 151), and GLP-1Rs are expressed in the lateral PBN (lPBN) (104). Activation of local GLP-1Rs in the lPBN [by intra-lPBN microinjections of the GLP-1 analog, Ex4] leads to a reduction of food intake and body weight. Moreover, ingestion of palatable food (e.g., chocolate, high-fat) and motivation to work for palatable food are reduced by intra-lPBN Ex4 injection (4, 119), thereby implicating lPBN GLP-1R in the regulation of hedonic aspects of feeding. That lPBN is crucial for both endogenous (4, 119) and exogenous (143) GLP-1R-mediated effects is suggested by data showing that direct infusions of GLP-1R antagonist, exendin(9–39), into the PBN increase food intake and lesions of this nucleus reduce the ability of peripherally injected Ex4 to exert its food intake-reducing effects. Moreover, robust lPBN neuronal excitation recorded with loose cell patch clamp and c-Fos induction after central Ex4 treatment suggests an excitatory role of GLP-1R in this nucleus (119). Little, however, is known about the neurochemical identity of PBN neurons that are targeted by GLP-1 fibers (or by GLP-1 or GLP-1 analogs in circulation). CGRP-producing neurons in the lPBN may be one potential target, since NTS GLP-1 neurons were shown to innervate this neuronal population in the PBN and centrally applied Ex4 increases CGRP gene expression (119). It is possible that this putative GLP-1-CGRP PBN pathway mediates both the food intake reduction and the nausea associated with GLP-1 ligands, as optogenetic activation of CGRP neurons reduces feeding (16) but also induces conditioned flavor avoidance (CFA) (15). However, Alhadeff et al. (4) observed that lPBN administration of low doses of Ex4 did not produce a pica response within 24 h after injections (4).

Hypothalamic substrates. Most hypothalamic subnuclei express GLP-1R (104, 120, 136) and NTS GLP-1 neurons may provide endogenous ligand to these subnuclei (84, 93, 94, 96, 121, 147). Central injection of GLP-1 results in a clear neuronal activation in the hypothalamus (148), and various hypothalamic GLP-1R populations are implicated in nearly all aspects of GLP-1 impact on metabolism.

Electrophysiological data indicate that neurons in the paraventricular hypothalamic nucleus (PVH) are excited by Ex4 (2), and several studies support a role for PVH GLP-1R signaling in food intake regulation. Intra-PVH administration of GLP-1 suppresses palatable liquid diet intake over a 1-h

testing period (102) and reduces 30-min chow intake, effects that were not accompanied by CFA or locomotor changes (103). In addition, selective blockade of PVH GLP-1R results in hyperphagia and weight gain (84). GLP-1-containing terminals establish synaptic connections with PVH corticotropin-releasing hormone (CRH) and oxytocin, but not vassopresin, neurons and GLP-1 (and/or GLP-1 analogs) primarily activate CRH and nesfatin-1 neurons (and to a lesser extent oxytocin neurons) in the PVH (84, 129, 144, 145). Collectively, these data suggest that GLP-1-producing neurons are in an optimal position to regulate the hypothalmo-pituitary axis (HPA) axis, an idea further supported by data showing that central GLP-1 injections increase plasma corticosterone and ACTH (41, 86, 93). Moreover, acute restraint stress robustly activates GLP-1 neurons, an effect that is reversed with a single overnight fast (99). Thus, ascending GLP-1 projections from the NTS presumably transmit information on interoceptive stress from the hindbrain to the PVH, resulting in HPA activation (123). Commensurate with a role in stress regulation, GLP-1R signaling is critical in mediating a variety of interoceptive stressors (86, 122, 123). However, as indicated above, doses of GLP-1 infusions in the PVH can reduce food intake without producing CFA (103), suggesting that the hypophagic effects of PVH GLP-1R signaling may involve nausea-independent pathways. More research is needed, however, to reconcile whether PVH GLP-1R signaling reduces food intake and body weight via parallel and/or common anorectic and visceral stress-mediated pathways.

Liraglutide administration to the arcuate nucleus of the hypothalamus (ARH) in rats results in body weight loss and food intake reduction 24 h after injection (11). Another study did not find changes in food intake 2 h after ARH-targeted GLP-1 injections but did find a reduction in peripheral blood glucose levels (127), suggesting that ARH GLP-1R impacts peripheral glucose metabolism. A more recent paper revealed that peripherally injected fluorescently labeled liraglutide reaches neurons in the ARH and the PVH 6 h after injections in mice. However, only ARH, but not PVH, neurons were found to be critical for the body weight loss induced by peripheral liraglutide in that study, as liraglutide-induced body weight loss was diminished by ARH, but not PVH, infusion of exendin(9–39), or by PVH ablation in a separate study (131). Overall, the literature is somewhat inconsistent with regard to ARH vs. PVH contributions to GLP-1R-mediated food intake and body weight reductions and peripheral blood glucose metabolism.

In addition to the ARH and PVH, various other hypothalamic nuclei have been implicated in GLP-1's hypophagic effects. Electrophysiological studies suggest that GLP-1 may activate orexin, but not melanin-concentrating hormone neurons, in the lateral hypothalamic area (LHA) (2). GLP-1 injected locally into the LHA results in short latency and short-lasting (1–2 h) hypophagia (130), and liraglutide administration to the LHA in rats results in body weight loss and food intake reduction 24 h after injection (11). GLP-1 injected locally into either the ventromedial hypothalamic nucleus (VMH) or the dorsomedial hypothalamic nucleus (DMH) also results in short latency, short-lasting (1–2 h) hypophagia (130). However, neither VMH nor DMH injections of liraglutide produce changes in food intake 24 h after injections (11). The authors of this latter study suggested that GLP-1R in the VMH contribute, instead, to energy expenditure, since liraglutide injections into the VMH (but not other hypothalamic nuclei) activate brown adipose tissue thermogenesis, as well as white adipose tissue browning by reducing the activation of AMPK (11).

Mesolimbic substrates. The mesolimbic circuitry is well known for its vital role in mediating the reinforcing properties of drugs of abuse and natural rewards (155). Drugs of abuse, as well as food, activate VTA dopamine neurons and increase dopamine release in the striatum. This dopaminergic projection represents a common denominator for most reinforcing substances (155). Both key mesolimbic nuclei, the VTA, and the NAc, express GLP-1R (104) and receive projections from GLP-1-producing neurons in the NTS (7, 26, 121). Activation of GLP-1R in these nuclei reduces reward-motivated behavior for both palatable food and alcohol (23, 135), as well as cocaine (138). Intake of regular chow, high-fat diet, and body weight are reduced after intra-VTA or intra-NAc core or shell Ex4 injections (7, 23, 26). Importantly, activation of NAc or VTA GLP-1Rs does not produce pica or conditioned taste avoidance (7, 23, 26), suggesting that the mesolimbic GLP-1 circuitry may mediate food intake reduction without tapping into the nausea and visceral stress effects associated with peripherally administered GLP-1 ligands. The role of endogenously released GLP-1 in these areas is supported by data showing that intake of chow, liquid sucrose meal, high-fat diet, or alcohol is increased after local injection of a GLP-1R antagonist into mesolimbic nuclei (7, 25, 26, 135). Interestingly, the effect of endogenous GLP-1R activation on feeding behavior may differ in the core vs. the shell of the NAc, as blockade of GLP-1Rs in the core increases high-fat diet intake, whereas blockade of shell GLP-1Rs is without effect (7).

Dopamine neurons are an obvious target for GLP-1R activation, considering the well-established role of dopamine in the control of reward-motivated behaviors and the newly discovered role of GLP-1 in general reward reduction. However, the relationship between these two signals may be more complex than expected. A simple and logical mechanism would dictate that GLP-1R activation inhibits VTA dopamine neurons, dopamine production, and accumbal dopamine release. However, activation of central GLP-1R was actually shown to increase protein and gene expression of the rate-limiting enzyme responsible for dopamine synthesis, tyrosine hydroxylase (TH) (9, 106). The elevation in TH may be mediated by activation of presynaptic GLP-1Rs located on glutamatergic terminals in the VTA (106), which may contribute to increased somatodendritic release of dopamine in the VTA (3) associated with inhibition of NAc and cortex-projecting dopamine neurons. Another recent report revealed that activation of paired-like homeobox 2b (Phox2b)-positive neurons in the NTS, some but not all of which also express GLP-1, excites dopamine-producing neurons in the VTA that project to the NAc shell (152). However, the specific relevance of these findings to the GLP-1 system is limited by the fact that Phox2b is expressed by a diverse set of hindbrain autonomic neurons that do not express GLP-1 (73).

Alternatively, since VTA dopaminergic neurons also project to the amygdala, acute central Ex4 increases dopamine turnover in the amygdala and activation of dopamine receptors in the amygdala reduces food intake, it is likely that VTA-to-amygdala dopamine projections represent an important circuit

underlying the hypophagic effects of central GLP-1 (9). Data indicating that dopamine release is not altered in the NAc, as measured by fast-scan cyclic voltammetry in rats by bath application of Ex4 (105), further support a complex relationship between GLP-1R activation and mesolimbic dopamine signaling.

Peripheral injections of Ex4 have also been shown to reduce cocaine, nicotine, and alcohol-induced accumbal or striatal (but not basal) dopamine release measured by in vivo microdialysis in mice (30, 31, 138). Since peripheral application of GLP-1 analogs allows for drug access to various peripheral, as well as CNS GLP-1R populations, it remains unclear whether mesolimbic GLP-1Rs are directly involved in this effect. At least within the VTA, a previous report has shown that the 24-h intake suppressive effect of a systemic administration of Ex4 is attenuated by intraparenchymal administration of the VTA GLP-1R by the antagonist exendin-(9–39) (106). Providing even further complexity to the GLP-1R-mediated effects on motivated behaviors are recent reports showing that GLP-1R populations outside of the classic mesolimbic VTA-accumbens pathway are involved in the regulation of food reward behavior (PBN, NTS, or ventral hippocampus; discussed below) (4, 5, 65, 117, 119).

Hippocampus and beyond. The hippocampus is a brain structure that is historically linked with learning and memory function. More recently, this brain region has been associated with the higher-order control of feeding behavior (see Refs. 13, 74, 77, 112 for reviews). GLP-1Rs are robustly expressed in the glutamatergic pyramidal neurons in the hippocampus (particularly, the ventral/caudal subregion in the rodent) (104), and as discussed above, the lack of axonal GLP-1 innervation in the hippocampus suggests that endogenous GLP-1 reaches hippocampal neurons via a humoral route (either from peripheral GLP-1 in circulation, hindbrain-derived GLP-1 released into the CSF, or both) (65). Several papers have reported neuroprotective and synaptic plasticity-promoting effects of hippocampal GLP-1R signaling (40, 66, 71, 98, 100, 101, 114, 115, 153), and a pivotal paper from During et al. (29) demonstrated the functional and endogenous relevance of hippocampal GLP-1R in learning and memory function. Intracerebroventricular GLP-1 infusion improved learning performance in a hippocampal-dependent spatial learning test and GLP-1R-deficient mice were impaired in a hippocampal-dependent contextual learning problem. Importantly, viral vector-mediated upregulation of GLP-1R gene expression targeted to the hippocampus in GLP-1R-deficient mice markedly rescued spatial learning deficits relative to controls (29), indicating an endogenous role for hippocampal GLP-1R in spatial memory function.

Whereas the "dorsal" hippocampal subregion (analogous to the posterior hippocampus in primates) is primarily associated with spatial memory function, neural processing in the ventral subregion of the hippocampus (vHP; analogous to the anterior hippocampus in primates) modulates appetitive behavior and food intake via signaling by both anorectic and orexigenic endocrine signals (77). The adipose tissue-derived hormone leptin acts on vHP neurons to reduce food intake and motivated responding for palatable food (78). On the other hand, vHP ghrelin receptor signaling potently increases food intake and food reward-motivated behaviors via downstream communication to the LHA (76). A recent paper by Hsu et al. (65) revealed that GLP-1R signaling in the vHP robustly reduces food intake, particularly for high-fat palatable food, whereas physiological relevance was established by results showing that vHP GLP-1R antagonist injections increased feeding (65). These hypophagic effects appear to require nutrient consumption as vHP GLP-1R activation by Ex4 reduced meal size and motivated lever press responding for palatable food when food was periodically available during testing; however, no effect was observed on meal frequency or appetitive responding when food was not available (conditioned place preference paradigm). Importantly, vHP infusions of Ex4 at doses that reduced food intake did not produce a CFA, indicating that in addition to the mesolimbic circuitry, the vHP is another target for GLP-1 to affect feeding behavior and body weight regulation without concomitant nausea/malaise.

In addition to the hippocampus and the various hindbrain, hypothalamic, and mesolimbic neural substrates described above, abstracts from recent conference proceedings indicate that the lateral dorsal tegmental area (116) and the lateral septum (146) are also sites of relevance to GLP-1R-mediated hypophagia, suggesting that we are only beginning to understand the complete neural circuitry through which GLP-1 and GLP-1 analogs reduce food intake and body weight and mediate visceral stress. What is clear, however, is that the anorectic effects of endogenous GLP-1 and pharmacological GLP-1 analogs involve a complex and widely distributed neural network that extends well beyond traditional hypothalamic feeding centers.

Species and sex differences. The GLP-1 system is largely homologous across mammalian species; however, some species differences have been reported. For example, Lachey et al. (89) reported that while the toxin lithium chloride (LiCl) activates hindbrain PPG neurons in both rats and mice, CNS GLP-1R blockade in the rat attenuates LiCl-mediated CFA in rats, but not in mice. Moreover, ~100% of PPG neurons in mice are responsive to leptin-mediated activation of intracellular JAK-STAT pathway (an indicator of leptin receptor responsivity), whereas ~0% of PPG neurons respond to leptin in the rat (67) (see below for further discussion on GLP-1-leptin interactions). The distribution of GLP-1 (PPG) neuronal innervation throughout the brain is similar across species, including the rodent (rat and mouse), nonhuman primate, and human (49, 151, 159). In contrast, some differences in GLP-1R expression across species have recently been reported. For example, while GLP-1Rs are robustly expressed in the rodent (rat and mouse) (21, 104) and human hippocampus (8), a recent report using a GLP-1R antibody reported relatively low GLP-1R expression in the nonhuman primate hippocampus (58). Another clear difference in GLP-1R expression can be found between mice and rats in the nucleus accumbens (7, 23, 26, 58). For the most part, however, the GLP-1 system appears to be largely conserved across species.

In addition to species differences, there may also be sex differences in the effects of GLP-1R stimulation. Sex is a major biological variable with regard to the neural regulation of feeding behavior (10). Nearly all studies probing the neural substrates of GLP-1-induced hypophagia have been done in male animals, and thus, the relevance of these findings to both sexes is unclear. Ex4 was recently shown to reduce operant responding for food reward in females more potently than in males (118). Interestingly, blockade of CNS estrogen signaling

attenuates Ex4-induced reduction of operant responding equally in both sexes (118), suggesting that the interaction of GLP-1R signaling with estrogen receptor signaling is independent of sex. This idea is further strengthened by data showing that coactivation of GLP-1R and estrogen receptors selectively in GLP-1R-expressing tissues with conjugated GLP-1-estradiol synergistically reduces food intake and body weight independently of sex (34).

Neurochemical and Cellular Mechanisms

Intracellular and cellular signaling mechanisms. The GLP-1R-mediated intracellular signaling responses in pancreatic β-cells has guided investigations examining GLP-1-mediated effects in other tissues (e.g., neurons, heart, and kidney) (see Refs. 47 and 50 for review). Within the NTS, GLP-1R activation results in rapid PKA-induced suppression of AMPK (54) and Akt (68) activity, as well as simultaneous activation of p44/42 MAPK (also known as ERK1/2) signaling(54). While these PKA-, Akt-, MAPK-, and AMPK-signaling responses are required to mediate the suppression of food intake by NTS GLP-1R activation, it remains unclear from a mechanistic standpoint how these GLP-1R-mediated intracellular signaling events affect neuronal excitability, and ultimately feeding behaviors. Interestingly, NTS neural processing of additional intake inhibitory signals, such as leptin, melanocortin, and GI-derived vagally mediated glutamatergic signals, have also each been independently shown to involve some of the same intracellular signaling pathways (e.g., PKA, MAPK, and AMPK) (55, 57, 141, 142). Thus, further analysis of the cellular phenotypes mediating GLP-1's effects on these signaling cascades may reveal important insights for development of future antiobesity drugs by identifying key neural substrates to target in conjunction with GLP-1R agonists. To this end, a recent report (79) (discussed in more depth below) showed that combined administration of a GLP-1 analog and the adipocyte hormone, leptin, engage complementary intracellular signaling pathways (e.g., pSTAT3, PTP1B) to reduce food intake and body weight. These types of systematic evaluations of combinatorial intracellular signaling pathways in other CNS GLP-1R-expressing nuclei, and for anorectic systems other than leptin, have not been conducted.

Inflammation. Inflammatory and body weight control processes interact in the periphery and in the brain, and GLP-1 holds an intricate relationship with both processes. Both in vitro and in vivo evidence suggests that GLP-1 reduces inflammatory markers (19, 24, 70, 88, 113, 157); however, in certain situations involving interactions with biological targets that influence energy balance, GLP-1 appears to increase inflammatory signaling. The proinflammatory cytokines IL-6 and IL-1 appear to be crucial for the food intake and body weight-reducing effect of GLP-1 in rats and mice (134), as pharmacologic or genetic blockade of IL-1 or IL-6 signaling abolishes the intake and weight-reducing effects of Ex4. In vivo and in vitro evidence demonstrate Ex4-induced upregulation of IL-6 in several brain areas key to energy balance regulation, including the hypothalamus, the NTS/DVC, and the PBN (119, 134). That brain interleukins can exert hypophagic effects downstream of circulating endocrine signals is not unprecedented. Indeed, well-known metabolic regulators like insulin, leptin, and amylin were shown to increase brain interleukin signaling (36, 95). Thus, it is possible that IL-6 is a central integrator of a variety of peripheral metabolic signals. The CNS cell types producing IL-6 in response to these peripheral signals remain unresolved, and existing evidence points to neurons, astrocytes, and microglia as potential targets of GLP-1 interleukin interactions. For example, in one study Ex4-induced IL-6 gene expression in a neural cell line (134), whereas elevated production of IL-1 by astrocytes in response to LPS was reduced by GLP-1 (81). In the same study, 5-day amylin incubation in primary hypothalamic or cortical microglial cultures resulted in increased IL-6 mRNA and media secretion (81). Thus, while the effect of GLP-1 on microglial IL-6 is not yet known, it is possible that, similar to amylin, it directly targets the microglia.

Adding another level of complexity to these interactions are data indicating that inflammation-induced hypophagia may actually result from brain GLP-1R activation since the food intake-reducing effect of LPS can be blocked by pharmacological blockade of hindbrain GLP-1R (46), and LPS stimulates GLP-1 release from murine microglial cell cultures (81). Other data show IL-6 also drives the release of GLP-1 from the intestinal L cells or pancreatic α-cells during exercise (32).

A collective summation of the complex relationship of GLP-1 with inflammatory signals is to suggest a role for bidirectional and pathophysiological state, as well as tissue/cell type-dependent mechanisms being affected by GLP-1R signaling. Importantly, the intricate relationship of GLP-1 with inflammatory signals has not yet been evaluated in the context of obesity, a pathophysiological state of increased inflammation that is likely to alter how GLP-1 interacts with interleukins. Thus, it is an essential topic of future research endeavor in this area.

GLP-1-leptin interactions. GLP-1 is a clinically relevant system for weight loss, and heightened focus has recently been given to combining GLP-1-based signaling pathways with other biological anorectic targets to develop novel and more effective obesity pharmacotherapies (33). While many putative synergistic targets for GLP-1 have been identified (e.g., gastric inhibitory polypeptide, peptide YY), here, we focus on the most widely studied: the interaction between GLP-1 and the adipocyte hormone leptin. Leptin appears to be an important biological signal through which GLP-1 additively or synergistically interacts to reduce food intake and body weight. For example, combined peripheral treatment of leptin and Ex4 produces greater intake reduction and weight loss in rats than either treatment alone (14, 154). Furthermore, central GLP-1R blockade [intracerebroventricular exendin-(9–39)] attenuates food intake suppression by intracerebroventricularly administered leptin (43, 109). Hindbrain neurons are one critical site for leptin receptor (LepRb) and GLP-1R interaction, as Ex4 and leptin codelivery to the 4th ventricle (restricting ligand availability to hindbrain substrates) yields additive food intake and body weight reduction, and 4th intracerebroventricular exendin-(9–39) attenuates the intake reduction by hindbrain leptin delivery (158). The hypothalamus is also critical for LepRb and GLP-1R interaction as leptin increases GLP-1 peptide (44) and GLP-1R mRNA expression (128) in hypothalamic neurons.

A recent paper by Kanoski et al. (79) examined the behavioral and intracellular mechanisms through which central LepRb and GLP-1R interact to reduce food intake. Liraglutide was administered subcutaneously to model human pharmaco-

logical treatment, whereas leptin was administered into the 3rd cerebral ventricle (i3vt) to target hypothalamic LepRbs. A relatively low dose of peripheral liraglutide (25 μg/kg) reduced food intake through a specific reduction in meal size when administered alone. However, when this dose of liraglutide was combined with a low dose of i3vt leptin (0.75 μg), an additive food intake reduction was observed that was mediated predominantly through a significant reduction in meal frequency that was not present with either drug alone. This LepRb-GLP-1R interaction may be mediated, in part, through a concert of common and complementary intracellular signaling pathways. Activation of pSTAT3 was elevated in hypothalamic tissue following liraglutide-leptin cotreatment, an effect greater than either treatment alone. In addition, SC liraglutide reduced expression of PTP1B (a negative regulator of leptin receptor signaling), revealing a potential mechanism for the enhanced pSTAT3 response following liraglutide-leptin coadministration. Collectively, these findings suggest that combined GLP-1-leptin-based drugs may be an important area for future pharmacotherapy development, particularly as heightened interest is focused on the potential for more effective combination-based pharmacotherapies for obesity (45, 150).

Summary and Conclusions

Following the discovery of GLP-1 in the early 1980s (12, 97), GLP-1-based diabetes and weight loss therapies (long-acting GLP-1 analogs, DPP-4 inhibitors) have been an area of intense investigation, particularly as obesity and diabetes rates have continued to increase at a dramatic rate since its discovery. While GLP-1-mediated food intake and body weight reductions are thought to be mediated by both peripheral (paracrine pathways) and central (neural and humoral pathways) GLP-1Rs, relatively recent discoveries are demonstrating that long-acting GLP-1 analogs are reducing food intake largely through direct action on brain GLP-1Rs (75, 80, 131, 137). These discoveries further incentivize researchers to unravel the neural circuitry of GLP-1R-mediated hypophagia. New insights into the neural systems underlying GLP-1-driven weight loss may guide the development of small-molecule or other innovative GLP-1-based pharmacological or viral therapies targeting unique phenotypes of GLP-1R-expressing brain nuclei.

In this review, we highlight several neural mechanisms through which GLP-1R activation reduces feeding, including specific intracellular signaling pathways, as well as interactions with inflammatory signaling pathways and the adipose-derived hormone leptin. GLP-1R agonists act in the brain to reduce feeding via action at various substrates distributed throughout the neuraxis, including the hippocampus (vHP), various hypothalamic nuclei (ARH, PVH, LHA), hindbrain nuclei (PBN, mNTS), and nuclei embedded within the mesolimbic dopamine reward circuitry (VTA, NAc). That GLP-1R signaling modulates feeding behavior in each of these nuclei implies a sense of redundancy inherent in this system, particularly given that the hypophagic (or hyperphagic) effects following pharmacological activation (or inactivation) of GLP-1R in individual nuclei are robust, an outcome seemingly inconsistent with an "additive system" in which these various nuclei work in concert to reduce energy intake. It may be the case, however, that the apparent redundancy in this system is an artifact of experimental pharmacology methods and that each separate GLP-1R population is modulated and influenced by the physiological or pathophysiological context. Within this framework, diverse physiological cues may be differentially accessible to and influential on individual GLP-1R-expressing loci. Future studies using site-directed chronic GLP-1R genetic manipulations in normally developed adult animals (e.g., via virally mediated RNA interference) may provide insight into the individual endogenous contributions of various GLP-1R-expressing nuclei to diverse feeding-relevant behaviors.

In some nuclei (e.g., VTA, NAc, vHP), GLP-1R activation reduces food intake and body weight without concomitant behavioral correlates of nausea/malaise, suggesting that targeting these specific pathways may be of particular interest for future next-generation GLP-1-based pharmacotherapies. The widely distributed neural systems through which GLP-1 and GLP-1 analogs act to reduce feeding, in some cases via diverse behavioral mechanisms, illuminates a growing appreciation in the field of ingestive behavior neuroscience to expand focus beyond traditional hypothalamic feeding centers.

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AUTHOR CONTRIBUTIONS

Author contributions: S.E.K., M.R.H., and K.P.S. drafted manuscript; S.E.K., M.R.H., and K.P.S. edited and revised manuscript; S.E.K., M.R.H., and K.P.S. approved final version of manuscript.

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