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Novel neural pathways targeted by GLP-1R agonists and bariatric surgery

Mohammed K. Hankir^{1,2} · Thomas A. Lutz¹

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Abstract

The glucagon-like peptide 1 receptor (GLP-1R) agonist semaglutide has revolutionized the treatment of obesity, with other gut hormone-based drugs lined up that show even greater weight-lowering ability in obese patients. Nevertheless, bariatric surgery remains the mainstay treatment for severe obesity and achieves unparalleled weight loss that generally stands the test of time. While their underlying mechanisms of action remain incompletely understood, it is clear that the common denominator between GLP-1R agonists and bariatric surgery is that they suppress food intake by targeting the brain. In this Review, we highlight recent preclinical studies using contemporary neuroscientific techniques that provide novel concepts in the neural control of food intake and body weight with reference to endogenous GLP-1, GLP-1R agonists, and bariatric surgery. We start in the periphery with vagal, intestinofugal, and spinal sensory nerves and then progress through the brainstem up to the hypothalamus and finish at non-canonical brain feeding centers such as the zona incerta and lateral septum. Further defining the commonalities and differences between GLP-1R agonists and bariatric surgery in terms of how they target the brain may not only help bridge the gap between pharmacological and surgical interventions for weight loss but also provide a neural basis for their combined use when each individually fails.

Keywords Obesity · GLP-1 · Physiology · Pharmacology · Bariatric surgery · RYGB · VSG

Introduction

Deciding on when, where, and what to eat can preoccupy us a great deal. The modern-day environment is laden with sensory cues on our screens, radios, and billboards that frequently encourage us to consume energy-dense, highly processed foods which, over time, can lead to overeating and weight gain [1]. For decades, this trend seemed to be insurmountable contributing to an obesity pandemic that places an enormous burden on our collective health due to obesity's association with various conditions including type 2 diabetes, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and certain

types of cancer to name just a few [2]. Fortunately, the tide seems to have finally turned, and we are now witnessing an obesity drug revolution with the glucagon-like peptide 1 receptor (GLP-1R) agonist semaglutide spearheading the way [3]. Other gut hormone-based drugs have recently been introduced to the clinic or are still under clinical development and promise to be even more effective than semaglutide, such as the dual GLP-1R and glucose-dependent insulinotropic peptide receptor (GIPR) agonist tirzepatide [4] and the triple GLP-1R, GIPR, and glucagon receptor (GR) agonist retatrutide [5]. While the underlying mechanisms for how these gut hormone-based drugs cause such pronounced weight loss remains an area of intensive investigation, it is clear that they all ultimately target the brain to suppress food intake [6]. This was first suggested for the GLP-1R agonists exendin-4 and liraglutide when it was shown that the suppression of food intake that they cause upon systemic administration is prevented or attenuated when the GLP-1R antagonist exendin-9 is centrally administered in rats [7] and when central GLP-1Rs are deleted in mice [8]. In this Review, we discuss similar preclinical studies that present novel concepts in the neural control of food intake and body

✉ Thomas A. Lutz
thomas.lutz@uzh.ch

Mohammed K. Hankir
hankirm@tcd.ie

¹ Institute of Veterinary Physiology, University of Zurich, Zurich, Switzerland

² School of Biochemistry and Immunology, Trinity College Dublin, Dublin, Ireland

weight, with reference to endogenous GLP-1, GLP-1R agonists, and bariatric surgeries like Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG), which remain the most effective treatments for severe obesity [9]. Notably, because RYGB and VSG enhance the release of endogenous GLP-1 from enteroendocrine cells due to accelerated nutrient passage through the gut along with enhanced luminal bile acid signaling [10–13], this gut hormone was originally widely thought to contribute to their effects on food intake and body weight [14]. Studies using rodent models cast doubt on the single role of GLP-1 [15–19], although this does not preclude the possibility of common neural mechanisms of action of bariatric surgery with GLP-1R agonists, which we will show target distinct neural pathways to endogenous GLP-1. Indeed, endogenous GLP-1 and GLP-1R agonists appear to have differential access to the brain due to factors such as stability, transportability, and diffusivity [20]. Accordingly, unlike exendin-4 and liraglutide, the suppression of food intake caused by peripheral GLP-1 is attenuated by peripheral but not central administration of exendin-9 [21]. We will take a bottom-up approach starting with the peripheral nervous system and then progress up the brainstem through to the hypothalamus and finish at non-canonical brain feeding centers such as the zona incerta (ZI) and lateral septum.

The vagus nerve

The vagus nerve of the parasympathetic nervous system richly innervates the gastrointestinal tract where it controls various digestive processes ranging from gastric acid secretion to peristalsis [22]. Based mainly on receptor transcript expression in the nodose ganglia, where the cell bodies of vagal afferents reside, and nerve transection studies, endogenous gut hormones including ghrelin [23], cholecystokinin (CCK) [24, 25], GLP-1 [26], and peptide YY 3–36 (PYY_{3–36}) [27] are thought to control food intake via their interaction with vagal afferents in a paracrine manner. This has received support in more recent studies with GLP-1R agonists [7, 28] and PYY_{3–36} [29], provided that they were administered at lower (more physiological) doses. However, with the development of sophisticated techniques that track and manipulate the activity as well as characterize the connectivity of genetically defined vagal afferents, we now have a more nuanced view of how this sensory cell type detects and controls the intake of food [30]. For example, GLP-1R-expressing vagal afferents have been shown to form intraganglionic laminar endings (IGLEs) mainly in the wall of the stomach/upper duodenum in mice [31, 32], such that they are selectively activated by gastric/duodenal stretch and CCK, but unexpectedly, not by exendin-4 [32]. Accordingly, the acute appetite-suppressing effects of

liraglutide and the latest GLP-1R agonist iteration semaglutide (but not CCK) are preserved when GLP-1R-expressing vagal afferents are inhibited or selectively ablated [33, 34]. In line with these findings, deletion of GLP-1Rs in paired-like homeobox 2b (PHOX2B)-expressing neurons, which mark all vagal sensory afferents, minimally affects the acute appetite suppressing effects of exendin-4 and only partially prevents the weight loss caused by chronic treatment with the GLP-1R agonist dulaglutide [35]. On the other hand, GPR65-expressing vagal afferents form mucosal endings in duodenal villi, such that they are selectively activated by duodenal infusion of nutrients [32]. Notably, activating GLP-1R-expressing vagal afferents robustly suppresses food intake, while activating GPR65-expressing vagal afferents has a modest effect [31]. Taken together, these findings suggest that gastrointestinal distension as opposed to intestinal nutrient sensing also plays an important role in promoting satiation [31]. In line with this idea, activating oxytocin receptor (OXR)-expressing vagal afferents, which also form IGLEs in the muscular wall of the small intestine in mice, robustly suppresses food intake [31]. Thus, ways of artificially causing or mimicking gastrointestinal distension could potentially promote a negative energy balance in the long term. Indeed, RYGB, which causes marked gastrointestinal distension due to how it forces food passage through the reconfigured gastrointestinal tract, leads to the same central pattern of neuronal activation as activating GLP-1R-expressing and OXR-expressing vagal afferents in mice [31, 36, 37], while vagotomy partially prevents the appetite suppression and weight loss caused by RYGB in rats [38].

Spinal afferents

Sensory information emanating from the gastrointestinal tract also reaches the central nervous system by way of the dorsal horn of the spinal cord where primary sensory neurons of the splanchnic nerve terminate [33]. While vagal afferents have received the bulk of the attention in the peripheral neural control of food intake and body weight, an increasing number of studies suggest that spinal afferents play a similar role [33]. For example, akin to GLP-1R-expressing vagal afferents, wingless-related integration site 1 (WNT1)-expressing spinal afferents densely innervate the muscular wall of the ileum and large intestine [37]. Interestingly, inhibiting WNT1-expressing spinal afferents increases food intake [37], suggesting a physiological role for this sensory cell type in suppressing food intake. Notably, while deletion of GLP-1Rs in WNT1-expressing neurons does not affect basal food intake and body weight, the acute appetite-suppressing effects of exendin-4 and chronic weight-lowering effects of dulaglutide are diminished [35]. These findings suggest that spinal afferents also seem to play

a major role in mediating the effects of GLP-1R agonists on energy balance.

Another example of the control of food intake by spinal afferents comes from a comprehensive study on endogenously released GLP-1 [39]. Because enteroendocrine cells are electrically excitable and fire action potentials [40, 41], they can be artificially activated by chemogenetics or optogenetics like neurons [42, 43]. Activating GLP-1-expressing enteroendocrine cells in the ileum in this manner as well as ileal infusion of picomolar concentrations of GLP-1 (thereby mimicking endogenous release) causes marked gastric dilation and suppression of food intake in mice, which is prevented by ileal infusion of exendin-9 [39]. Interestingly, GLP-1Rs are expressed in intestinofugal neurons that innervate the stomach via the celiac ganglion [39]. Accordingly, ablating pre- and post-ganglionic sympathetic intestinofugal neurons prevents the effects of ileal GLP-1 on stomach dilation and food intake [39]. Conversely, activating pre- and post-ganglionic sympathetic intestinofugal neurons recapitulates the effects of ileal GLP-1 on stomach dilation and food

intake [39]. Further, ablating spinal afferents, but not vagal afferents, prevents the inhibitory effects of ileal GLP-1 and artificial stomach dilation on food intake [39]. These findings suggest that rather than only acting in a simple paracrine manner to suppress food intake, endogenously released GLP-1 causes stomach dilation via intestinofugal neurons, which in turn is sensed by spinal afferents innervating the stomach and then transmitted to higher centers via the spinal cord as part of a complex neural arc (Fig. 1). They also provide a salient example of how contemporary neuroscientific techniques have allowed for the mechanistic study of gut-brain communication at an unprecedented level of detail.

The medulla of the caudal hindbrain

The nucleus tractus solitarius (NTS) of the medulla in the caudal hindbrain is the site where vagal afferents terminate. In rodents, the NTS lies either side of and is heavily interconnected with the area postrema (AP) [44, 45]. Because AP

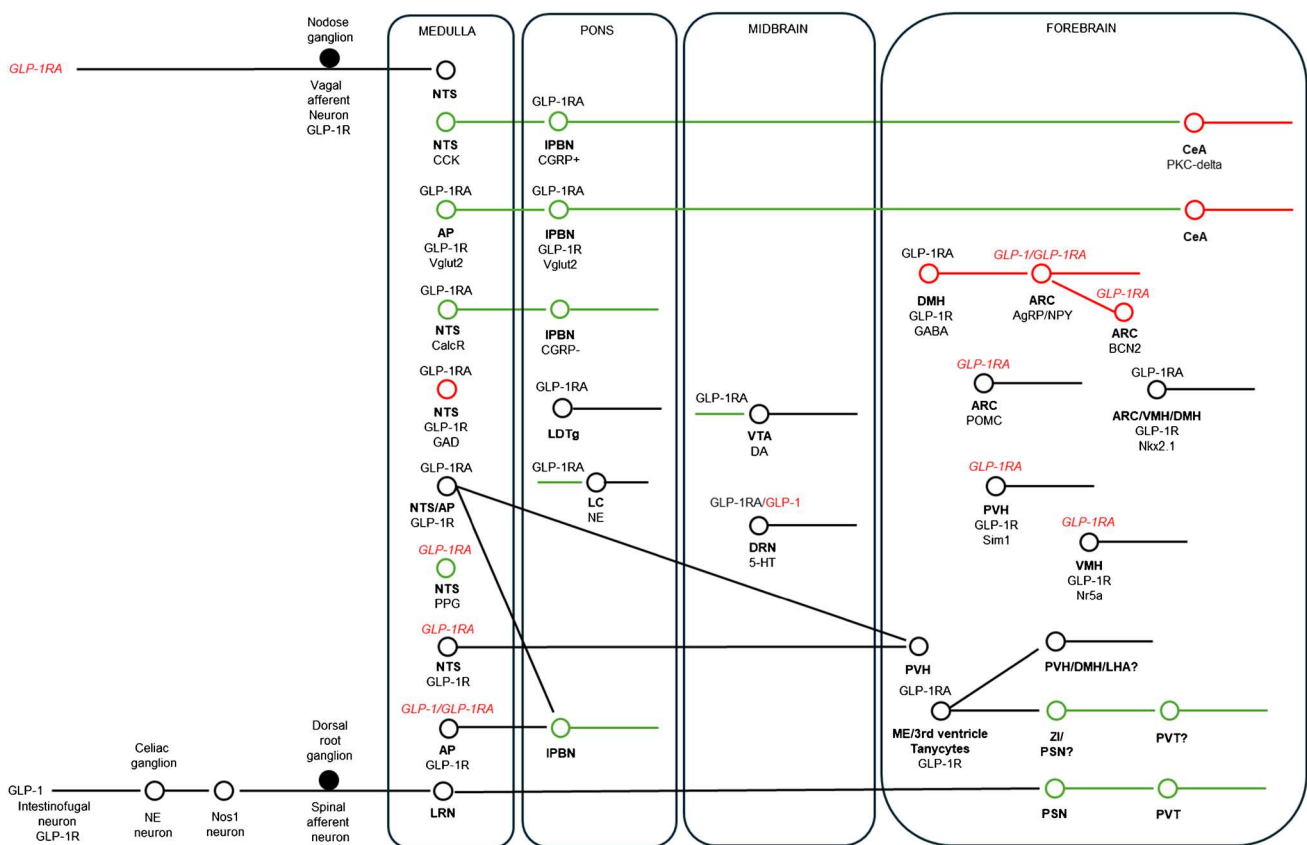


Fig. 1 Wiring diagram for GLP-1R agonist-mediated appetite suppression and weight loss. This schematic summarizes peripheral and central neural pathways directly or indirectly targeted by endogenous GLP-1 hormone and systemically administered GLP-1R agonists (GLP-1RA) exendin-4, liraglutide, and/or semaglutide. Text in red italics highlights regions where GLP-1 and GLP-1RAs do not exert

their effects based on recording, deletion, inhibition, and/or ablation approaches. Neurons in red are GABAergic, and neurons in green are glutamatergic. In the LC and VTA, GLP-1RA agonists are thought to increase excitatory input onto postsynaptic neurons via presynaptic GLP-1Rs on glutamatergic neuronal terminals

neurons are not fully shielded by a blood–brain barrier [46], the AP/NTS is considered to be the first site of integration of hormonal and neural signals pertaining to acute energy status. Notably, while AP/NTS neurons express GLP-1Rs [3, 47], inhibiting GLP-1R-expressing AP neurons does not prevent the appetite-suppressing effects of endogenously released GLP-1 [39], likely because of low amounts of GLP-1 reaching these neurons due to rapid GLP-1 degradation by the enzyme dipeptidylpeptidase IV (DPP-IV) [48]. Nevertheless, AP/NTS neurons seem to be a major target of GLP-1R agonists which are more stable in the bloodstream [49, 50]. Indeed, systemically administered, fluorescently labeled liraglutide and semaglutide gain access to the AP/NTS [51, 52], and administration of exendin-4 into the NTS reduces food intake in rats [53]. Moreover, combined (but not individual) ablation of GLP-1R-expressing neurons in the AP and NTS prevents the appetite-suppressing effects of chronic systemic exendin-4 and semaglutide as well as the weight-lowering effects of chronic systemic semaglutide in mice [34]. On the other hand, inhibiting GLP-1R-expressing GABAergic neurons or deleting GLP-1Rs in the NTS alone is sufficient to partially prevent the appetite-suppressing and/or weight-lowering effects of chronic systemic liraglutide in rats [54]. While the latter findings are also at odds with work showing that GLP-1Rs in glutamatergic rather than GABAergic neurons mediate the effects of chronic systemic liraglutide on energy balance in mice [55], they provide important insight into the neurochemical and neuroanatomical identity of a neuronal network targeted by GLP-1R agonists (Fig. 1). A contribution of NTS astrocytes to the appetite suppression caused by acute GLP-1R agonists also seems possible from evidence showing (1) expression of GLP-1Rs in this cell type, (2) functional responses of astrocytes to exendin-4 and liraglutide, and (3) negation of appetite suppression from administration of exendin-4 into the NTS when astrocyte metabolism is selectively inhibited in this region [56].

A major issue with clinically approved GLP-1R agonists like liraglutide and semaglutide is that they cause nausea and vomiting, which hampers patient compliance [3, 57]. Thus, a burgeoning question in the obesity drug field is whether weight-lowering drugs target separate aversive or non-aversive pathways in the brain to suppress food intake. In this context, activating GLP-1R-expressing neurons in the AP induces aversion [34, 58], while in the NTS, this does not seem to be the case [34]. Moreover, GLP-1Rs in the AP are both necessary and sufficient for the aversion caused by systemic exendin-4 [58] and necessary for the aversion caused by systemic semaglutide [34]. Remarkably, while inhibiting GLP-1R-expressing neurons in the AP prevents the aversion caused by exendin-4 and semaglutide, the chronic inhibitory effects of the two GLP-1R agonists on food intake and body weight are preserved [34, 58]. Similarly, ablating the AP does not prevent the acute appetite suppression caused by

systemic exendin-4 [59] and liraglutide [54] in rats. These results suggest that GLP-1R agonists can theoretically be designed to achieve appetite suppression without causing nausea by bypassing GLP-1R-expressing neurons in the AP. Theoretically, one way this can be achieved is by conjugating GLP-1R agonists to a ligand that binds to a receptor exclusively expressed in the NTS. A similar approach has successfully been applied with the selective NMDA receptor antagonist MK-801, with striking effects on food intake and body weight in mice [60].

Within the caudal NTS are two important, non-overlapping subpopulations of neurons that form an integral part of a well-characterized hindbrain feeding circuit. These neurons either express the neurotransmitter norepinephrine (NE) or the neuropeptide CCK and are monosynaptically connected to calcitonin gene-regulated peptide (CGRP)-expressing neurons in the lateral parabrachial nucleus (IPBN) of the pons [61], which are in turn monosynaptically connected to protein kinase C (PKC)-delta-expressing neurons in the central nucleus of the amygdala (CeA) in the forebrain [62, 63], thus forming a tripartite functional unit. Accordingly, refeeding after a fast activates NE-expressing/CCK-expressing NTS neurons [61], CGRP-expressing IPBN neurons [63], and PKC-delta-expressing CeA neurons [62]. Similarly, activating NE-expressing/CCK-expressing NTS neurons [61], CGRP-expressing IPBN neurons [63] or PKC-delta-expressing CeA neurons reduces meal size [62]. This hindbrain feeding circuit is often referred to as an aversive pathway since activating CCK-expressing NTS neurons [64] and CGRP-expressing IPBN neurons [63] causes aversion, with the latter being required for the aversive effects of systemic lithium chloride (LiCl) in mice [65]. In the context of GLP-1R agonists, systemic exendin-4 robustly activates CGRP-expressing IPBN neurons, and its chronic weight-lowering effects are attenuated by their silencing [63]. While not shown, this is most likely mediated by activation of GLP-1Rs in upstream CCK-expressing NTS neurons by exendin-4 since NE-expressing NTS neurons do not appreciably express GLP-1Rs [66]. Notably, both systemic liraglutide and semaglutide treatments robustly activate AP/NTS, IPBN, and CeA neurons [51, 55] through GLP-1Rs expressed in glutamatergic, but not in GABAergic, neurons [55], possibly contributing to their aversive effects. Indeed, GLP-1R-expressing AP neurons, but not GLP-1R-expressing NTS neurons, project to the CGRP-expressing IPBN neurons to cause aversion [34].

As for CCK, GLP-1 is also expressed as a neuropeptide in glutamatergic NTS neurons [67] that inhibit food intake when activated [68]. These neurons send widespread projections to brain regions that highly express GLP-1Rs [66, 69], where administration of GLP-1R agonists reduces food intake and GLP-1R antagonists increase food intake such as the bed nucleus of the stria terminalis (BNST) as a notable

example [70] (Fig. 1). The latter suggests a physiological role for GLP-1-expressing NTS neurons in promoting a negative energy balance; however, both their inhibition and ablation fail to have a major effect on baseline food intake and body weight in mice suggesting otherwise [71, 72]. Indeed, GLP-1R knockout mice do not develop obesity [73] although postembryonic deletion of GLP-1Rs in the paraventricular nucleus of the hypothalamus (PVH) leads to weight gain due to increased food intake [72]. Despite not being absolutely necessary for the control of energy balance, GLP-1-expressing NTS neurons do seem to mediate stress-induced hypophagia and satiation associated with inordinately large meals [71]. Interestingly, ablating GLP-1-expressing NTS neurons fails to prevent the appetite-suppressing effects of systemic liraglutide and semaglutide in mice [74], which is consistent with the lack of GLP-1R expression in these cells [75, 76]. Considering that systemic GLP-1R agonists and central GLP-1 appear to target different central nervous system pathways, these treatments would be expected to additively reduce food intake, which proved to be the case [74].

Based on single-cell RNA sequencing data, a separate subset of NTS neurons, beyond those expressing NE, CCK, and GLP-1, has consistently been identified as glutamatergic calcitonin receptor (CalcR)-expressing neurons in the AP/NTS [67, 77]. These neurons overlap with NE-expressing, but not CCK-expressing, NTS neurons [78], and their activation suppresses food intake without causing aversion [78]. Consistently, CalcR-expressing NTS neurons project to non-CGRP-expressing IPBN neurons [78]. Moreover, inhibiting CalcR-expressing NTS neurons increases food intake and partially prevents the appetite-suppressing effects of exendin-4, while their silencing leads to weight gain on a high-fat diet [61, 63]. These latter findings established CalcR-expressing NTS neurons (and their downstream targets) as physiological controls of energy balance. This concept was corroborated in a study on prolactin-releasing hormone (PRLH)-expressing NTS neurons, which represent a subset of CalcR-expressing NTS neurons [79]. Considering that the amylin receptor agonist cagrilintide [80] is in clinical development for the treatment of obesity [81], CalcR-expressing NTS neurons may thus be possible targets.

Given that genetically defined neurons in the NTS like those that express CCK and the CalcR suppress food intake via separate pathways, it is possible that their combined activation has an additive effect, which proved to be the case [82]. In the context of bariatric surgery, these neuronal populations are more highly activated after VSG compared to sham surgery in mice; however, their silencing has no impact on the reduced food intake or weight loss caused by the procedure [82]. These findings suggest that VSG does not only recruit CCK-expressing/CalcR-expressing NTS neurons to exert its inhibitory effects on energy balance. Additionally,

these findings provide a salient example of how activation of specific populations of neurons by an intervention does not necessarily imply that these neurons drive changes in behavior associated with that intervention. Considering that RYGB leads to increased meal-induced activation of NE-expressing NTS neurons in mice [36], it would be interesting to determine the impact of their silencing or ablation on food intake and body weight, with preliminary data suggesting a modest and temporary effect [83].

The pons

The pons lies in the middle of the brainstem sandwiched in between the medulla oblongata and midbrain and sits just anterior to the cerebellum. Because of its anatomical location, the pons is involved in various functions ranging from sensory processing to motor control. As mentioned above, the IPBN of the pons is heavily implicated in the aversive and non-aversive control of feeding via CGRP-expressing and non-CGRP-expressing neurons, respectively. Indeed, GLP-1-expressing NTS neurons project to the IPBN [84, 85], and administration of exendin-4 into this brain region, where it has direct excitatory effects [85], robustly reduces food intake [84–86] and increases the expression of CGRP [85]. Conversely, the administration of exendin-9 into the IPBN increases food intake [84, 85]. Given that the dorsal pons has only recently been sequenced at the single-cell level of resolution [87], this will allow the future functional characterization of other cell types in this brain region that control food intake and body weight. Considering that the pons transcriptome in humans [88] is similar to that of mice, especially in the PBN [87], this is likely to be of clinical relevance.

Locus coeruleus (LC) neurons of the pons are the major NE system of the brain and are traditionally implicated in arousal. Dating as far back as the 1930s, this system has been implicated in appetite suppression and weight loss due to its targeting by amphetamines [89], which has been confirmed by contemporary neuroscience techniques. For example, activating LC-NE neurons robustly suppresses food intake and causes weight loss in mice [90]. Curiously, activating LC-NE neurons causes hungry mice to drop their food, suggesting that these neurons serve to distract from feeding [90]. In the context of GLP-1R agonists, GLP-1-expressing NTS neurons project to the LC [69], and administration of exendin-4 into this brain region robustly suppresses food intake and causes an aversive response in rats [91]. In electrophysiology experiments, exendin-4 increases glutamatergic input onto LC-NE neurons [91]. Importantly, systemic semaglutide activates LC-NE neurons, and its acute appetite-suppressing effects are blunted when GLP-1Rs in the LC are blocked with local infusion of exendin-9 [91]. While it

remains to be established if specifically inhibiting LC-NE neurons has a similar effect, these findings suggest that systemic GLP-1R agonists activate presynaptic GLP-1Rs on glutamatergic terminals synapsing onto LC-NE neurons, leading to their activation and suppression of food intake. When considering the findings of Sciolino et al. [90], the dependance of systemic semaglutide on LC GLP-1R activation in suppressing food intake might explain anecdotal evidence that people taking semaglutide often report no longer being preoccupied with thoughts about food.

The lateral dorsal tegmental nucleus (LDTg) of the pons receives dense axonal projections from the hindbrain. Systemically administered, fluorescently labelled exendin-4 accesses the LDTg, and administration of exendin-4 into this brain region suppresses food intake without causing aversion [92], unlike in the LC [91]. Conversely, administration of exendin-9 into the LDTg increases food intake [92]. Importantly, like the LC, the acute inhibitory effect of systemic exendin-4 on food intake is prevented when GLP-1Rs are blocked by exendin-9 in the LDTg [92]. Together, these findings suggest that systemic GLP-1R agonists suppress food intake via aversive and non-aversive pathways in the pons via GLP-1R-expressing LC and LDTg neurons, respectively.

The midbrain

The midbrain lies in the uppermost part of the brainstem and is traditionally implicated in visual, auditory, and pain processing. Evidence suggests that the midbrain is also involved in the control of food intake. The midbrain dopaminergic system in particular has been heavily implicated in the rewarding or hedonic aspects of eating, especially the projection from the ventral tegmental area (VTA) to the ventral striatum (the mesolimbic pathway) [93]. For example, activating dopaminergic VTA neurons increases operant responses for a food reward [94], while inhibiting these neurons by activating GABAergic VTA interneurons has the opposite effect [95]. Further, sucrose infusion into the gut activates dopaminergic VTA neurons in a vagal afferent-dependent manner to reinforce its intake [96]. Conversely, activating GLP-1-expressing NTS neurons reduces high-fat diet intake by inhibiting dopaminergic VTA neurons through both reduced glutamatergic and enhanced GABAergic input [97].

In the context of GLP-1R agonists, GLP-1-expressing NTS neurons project to the VTA [98], and administration of exendin-4 into this brain region reduces food intake [98–100] and the motivation to obtain a food reward [99, 100] without causing aversion [98–100]. Moreover, the acute appetite-suppressing effects of systemic exendin-4 are diminished by the administration of a GLP-1R or AMPA receptor antagonist into the VTA [99]. In

electrophysiological experiments, exendin-4 increases glutamatergic input onto dopaminergic VTA neurons via activation of presynaptic GLP-1Rs on glutamatergic afferents [99], analogous to the mechanism in the LC described above [91]. Additionally, co-administration of nicotine with liraglutide has additive inhibitory effects on food intake and body weight associated with increased activity of dopaminergic VTA neurons [101], while the GLP-1-MK-801 conjugate similarly has additive effects on food intake and body weight associated with increased activity of VTA neurons [60]. Clearly, future studies need to be performed to clarify the role of dopaminergic VTA neurons in controlling food intake and body weight. Interestingly, while GLP-1-expressing NTS neurons also project to the ventral striatum [102] and administration of exendin-4 into this brain region reduces food intake and the motivation to obtain a food reward [100, 102], this treatment does not affect ventral striatal dopamine release [103]. Instead, electrophysiological and behavioral experiments suggest that exendin-4 increases the activity of ventral striatal neurons and reduces food intake, respectively, via presynaptic GLP-1 receptors in glutamatergic neurons and subsequent postsynaptic AMPA receptor activation [103], analogous to the aforementioned mechanism in the VTA [99].

Another important dopaminergic population of neurons in the midbrain arises from the substantia nigra and projects to the dorsal striatum (the nigrostriatal pathway). While these neurons were traditionally implicated in controlling motor function, accumulating evidence suggests that they are also involved in food reward receipt, particularly in the form of fat as part of a gut-brain pathway. For example, dorsal striatal dopamine release from intragastric fat infusion is blunted in obesity associated with reduced levels of the fat-derived signaling molecule oleoylethanolamide (OEA) in the small intestine in mice [104]. Accordingly, supplementing OEA to obese mice reverses this state of dorsal striatal dopamine deficit in a vagal-afferent-dependent manner [104]. Moreover, the suppression of fat intake from systemic OEA is prevented when a mixed dopamine 1 receptor (D1R) and dopamine 2 receptor (D2R) antagonist is infused into the dorsal striatum [104]. In the context of bariatric surgery, RYGB increases small intestinal OEA synthesis associated with increases in dorsal striatal dopamine release and D1R availability in rats [105]. Moreover, the suppressed fat intake after RYGB is prevented by blocking intestinal OEA signaling, vagotomy, or blocking dorsal striatal D1R signaling [105]. This pathway was recently defined more precisely, indicating that right vagal afferents that innervate the duodenum form part of an elaborate polysynaptic circuit involving neurons in the right ventromedial NTS, non-CGRP-expressing neurons in the dorsal IPBN and dopaminergic neurons in the substantia nigra [106]. Further,

the appetite-suppressing effects of CCK are blocked with ablation of right vagal afferents, neurons in the IPBN and substantia nigra, and antagonism of D1R/D2Rs in the dorsal striatum [106], suggesting overlapping central mechanisms of CCK with RYGB.

The midbrain is also home to serotonergic neurons of the dorsal raphe nucleus (DRN), which sends widespread ascending and descending projections throughout the brain. These neurons were traditionally implicated in regulating affect and are the target of selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, which are clinically approved antidepressants. These drugs are also appetite suppressants and were prescribed for obesity until they were withdrawn owing to negative side effects [107]. Serotonin-expressing neurons of the DRN are also glutamatergic and are activated by feeding and PYY_{3–36}, and their activation suppresses food intake [108]. Interestingly, an adjacent population of GABAergic neurons is activated by fasting but inhibited by the proopiomelanocortin (POMC) cleavage product alpha-melanocyte stimulating hormone (alpha-MSH), and their activation increases food intake [108]. In the context of GLP-1R agonists, GLP-1-expressing NTS neurons send projections to serotonergic DRN neurons, and chemical depletion of serotonin as well as blockade of central 5-HT_{2A} receptors, but not 5-HT_{2C} receptors, prevents the inhibitory effects of chronic central exendin-4 on food intake and body weight in rats [109]. Moreover, the inhibitory effects of chronic systemic liraglutide on food intake and body weight are blunted with blockade of central 5-HT_{2A} receptors [109]. These findings were unexpected as the 5-HT_{2C} receptor agonist lorcaserin was a previously used treatment for obesity prior to being recalled from increasing the risk of cancer development and as the appetite-suppressing effects of acute peripheral GLP-1 are diminished in 5-HT_{2C} receptor KO mice [110, 111]. However, the effects of acute peripheral liraglutide are preserved in 5-HT_{2C} receptor KO mice [111], again suggesting different central pathways are targeted by endogenous GLP-1 and GLP-1R agonists. Interestingly, RYGB controls 5-HT_{2A} receptor availability in the ventral striatum in rats [112], suggesting that GLP-1R agonists and bariatric surgery may both target the midbrain serotonergic system to exert their inhibitory effects on energy balance.

Neurons in the midbrain periaqueductal grey (PAG) surrounding the cerebral aqueduct have long been implicated in the modulation of pain as well as in the learning and action of defensive and aversive behaviors [113]. Accumulating evidence suggests that PAG neurons also control energy balance. For example, activation of GABAergic neurons in the ventrolateral (vlPAG) suppresses food intake, while their inhibition increases food intake [114]. Further, chronic activation of GABAergic vlPAG neurons causes marked weight loss in diet-induced obese mice due to both a suppression of food intake and an increase in energy expenditure [115].

These neurons reduce their activity before meal initiation, suggesting that they normally serve as a break to feeding [115]. Remarkably, this inhibitory effect is potentiated after chronic consumption of a high-fat diet due to a marked increase in GABAergic input and reduced expression of the calcium channel subunit *Cacna2d1* [115]. Accordingly, viral-mediated restoration of *Cacna2d1* in vlPAG GABAergic neurons normalizes GABAergic input in these neurons and markedly reduces body weight due to reductions in food intake and increases in energy expenditure [115]. These findings suggest that a high-fat diet impacts inhibitory plasticity in the midbrain, which can be corrected by restoring normal neuronal function. Notably, GLP-1-expressing NTS neurons project to the PAG [69] where GLP-1Rs are highly expressed [66], although it remains unclear what effects GLP-1R agonists have on energy balance in this brain region.

The hypothalamus

The hypothalamus situated at the base of forebrain has long been implicated in body weight control [116, 117]. Key regions of the hypothalamus in this regard include the ventromedial hypothalamus (VMH), dorsomedial hypothalamus (DMH), PVH, and the lateral hypothalamic area (LHA), which all receive projections from GLP-1-expressing NTS neurons, where deletion or blockade of GLP-1Rs increases food intake and body weight [72, 118–120]. The arcuate nucleus (ARC) at the floor of the third ventricle has received particular attention because it lies either side of the median eminence (ME) which, like the AP, is not fully shielded by the blood–brain barrier [121] and has fenestrated capillaries therefore permitting access to circulating factors that control energy balance [122]. In the case of the fat-derived hormone leptin, this is believed to be facilitated by tanycytes lining the floor of the third ventricle in a two-step process. First, leptin is taken up by tanycytic end feet adjacent to ME capillaries and is transported into the CSF of the third ventricle in a leptin receptor-dependent manner [123, 124]. Second, leptin is transported back into the brain via tanycytes that protrude to hypothalamic nuclei [123, 124].

A similar uptake mechanism has been proposed for liraglutide based on evidence showing that inhibiting ME tanycytic function prevents activation of neurons in the PVH, DMH, and LHA as well as food intake suppression and weight loss from chronic systemic liraglutide treatment [125]. Further, deleting GLP-1Rs in ME tanycytes has similar effects [125], suggesting that liraglutide first activates GLP-1Rs in ME tanycytes to then gain access to and activate GLP-1R-expressing hypothalamic neurons and exert its effects on energy balance. Indeed, systemically administered, fluorescently labeled liraglutide and semaglutide gain access to the median eminence and ARC and to a lesser

extent the PVH and DMH [51, 126], while administration of liraglutide into the ARC, PVH, and LHA (but not the DMH and VMH) robustly reduces food intake [120, 127]. Conversely, the combined deletion of GLP-1Rs in hypothalamic neurons (ARC, VMH, and DMH) partially prevents the weight-lowering effects of chronic systemic liraglutide treatment [128, 129]. On the other hand, ablating the PVH or deleting GLP-1Rs in this brain region does not prevent the inhibitory effects on food intake and body weight of chronic systemic liraglutide [126, 130] or exendin-4 [128, 131]. Similarly, deleting GLP-1Rs in the VMH does not prevent the inhibitory effects of chronic systemic exendin-4 and liraglutide on food intake and body weight [132]. Taken together, these data suggest that GLP-1R agonists need to engage multiple extrahypothalamic and hypothalamic populations simultaneously to exert their inhibitory effects on food intake and body weight, at least in the chronic setting.

Within the ARC, two functionally opposing populations of neurons exist which co-express agouti-related peptide (AgRP) and neuropeptide Y (NPY) or POMC [133]. Acute studies generally show that activating ARC AgRP/NPY neurons increases food intake, while activating ARC POMC neurons suppresses food intake with the opposite profile seen with their respective inhibition [134–138]. Indeed, liraglutide is thought to acutely suppress food intake by activating GABAergic GLP-1R-expressing DMH neurons which project to and inhibit ARC AgRP/NPY neurons as determined by patch-clamp electrophysiology experiments on hypothalamic slices [129]. However, chronic inhibition or ablation of ARC AgRP/NPY neurons or chronic activation of ARC POMC neurons fails to affect body weight in a stable manner [139–142]. These findings have implications for obesity drug development and suggest that strategies need to be developed that not only target ARC AgRP/NPY or POMC neurons. Notably, simultaneously activating ARC AgRP/NPY neurons and inhibiting POMC neurons additively increases food intake in the acute setting [143]. It would therefore be interesting to determine if the opposite approach, i.e., simultaneously inhibiting ARC AgRP/NPY neurons and activating ARC POMC neurons, additively reduces food intake and leads to weight loss in the chronic setting as this would be therapeutically relevant. Another consideration to make when using this approach is the potential aversive effects of manipulating ARC AgRP/NPY neuronal activity. While activating ARC AgRP/NPY neurons has been shown to be both aversive [136] and rewarding [144] depending on the duration of activation, the positive valence associated with inhibiting ARC AgRP/NPY neurons [136] lends itself well to targeting these neurons for obesity drug development.

Like the other neuronal types discussed in this Review, the function of ARC AgRP/NPY and ARC POMC neurons has been interrogated in real-time *in vivo* in response to

different treatments using fiber photometry. This revealed that ghrelin robustly activates ARC AgRP/NPY neurons as soon as 30 s after its systemic administration, while it robustly inhibits ARC POMC neurons after a 15-min delay suggesting an indirect effect [145]. These results are entirely consistent with the known orexigenic effects of this stomach-derived hormone [146, 147]. In contrast, intragastric infusion of lipids, glucose, and amino acids all robustly suppresses the activity of ARC AgRP/NPY neurons as does systemic administration of CCK and PYY_{3–36} [148, 149]. Further, the suppression of ARC AgRP/NPY neurons by intragastric lipids is blocked by a CCK receptor antagonist [148] and is mediated by vagal afferents, while that of glucose is mediated by spinal afferents [150]. Notably, fiber photometry also revealed that systemic administration of GLP-1 [149] and liraglutide [148] does not affect the activity of ARC AgRP/NPY neurons, emphasizing how findings from patch-clamp electrophysiology experiments on hypothalamic slices can differ from the situation *in vivo*. Taken together [150], these findings suggest that nutrients and gut hormones may exert direct and indirect effects on the activity of ARC AgRP/NPY neurons via separate ascending neural pathways.

Single-cell RNA sequencing has revealed many cell types in the ARC [151, 152]. This analysis specifically in ARC POMC neurons revealed that leptin receptor-expressing and GLP-1R-expressing neurons are non-overlapping [153], which was confirmed in an independent study using *in situ* hybridization and transgenic reporter mice [154]. Acutely activating GLP-1R-expressing ARC POMC neurons robustly suppresses food intake [154]. Accordingly, acute administration of exendin-4 (but not GLP-1) into the ARC potently reduces food intake [128], while liraglutide directly activates ARC POMC neurons [126, 155] and its weight-lowering effects upon chronic systemic administration are partially prevented when exendin-9 is co-administered into the ARC [126]. On the other hand, the appetite-suppressing effects of chronic systemic exendin-4 are preserved in mice lacking GLP-1Rs in ARC POMC neurons [128] or when ARC neurons are ablated [34]. Similarly, the appetite-suppressing and weight-lowering effects of chronic systemic liraglutide are preserved in mice lacking GLP-1Rs in ARC neurons [130]. Collectively, the genetic findings suggest that targeting ARC neurons is not necessary for the action of GLP-1R agonists. This is underscored by the finding that ablating GABAergic basonuclin 2 (BNC2)-expressing neurons in the ARC, which strongly inhibit ARC AgRP neurons to mediate the effects of leptin on energy balance, has no impact on the acute appetite suppressing effects of semaglutide [156]. In the context of bariatric surgery, rats lacking melanocortin 4 receptors (MC4Rs), which are activated by the POMC-cleavage product alpha-MSH [157], are still responsive to VSG [158]; on the other hand, mice lacking MC4Rs are less responsive

to RYGB [159], suggesting that ARC POMC neurons are targeted by this particular bariatric surgery. Since MC4R-mediated suppression of appetite is at the level of PVH neurons projecting to the non-CGRP-expressing neurons in the IPBN [160], these findings suggest that RYGB targets this pathway.

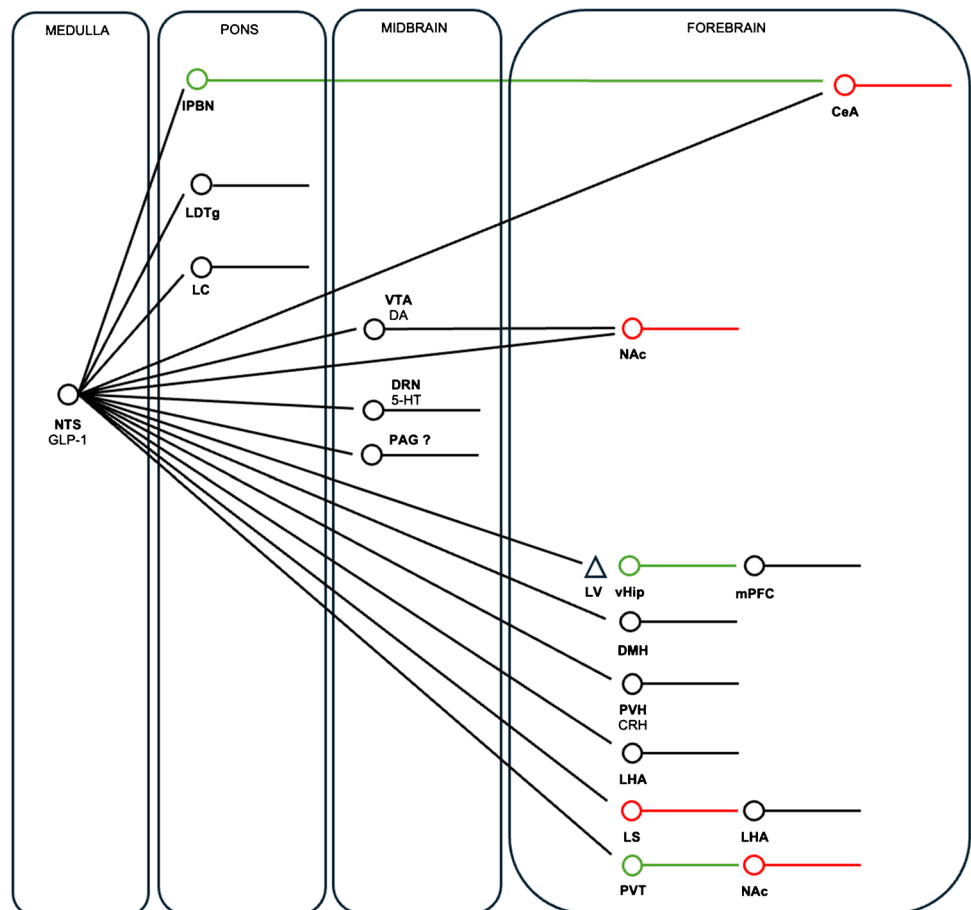
The zona incerta

The ZI is a horizontally elongated gray matter region situated in between the hypothalamus and thalamus and is implicated in a broad array of functions ranging from sleep to predator avoidance [161]. Accumulating evidence suggests that ZI neurons control energy balance [161]. For example, GABAergic neurons of the ZI are activated by ghrelin and their activation robustly increases the intake of high-fat food by inhibiting glutamatergic neurons of the PVT [162]. Notably, a glutamatergic projection from the paraventricular nucleus (PVN) activates the same glutamatergic PVT neurons to suppress food intake [162]. Considering that ileal GLP-1 activates glutamatergic PVN neurons to suppress food intake [39], glutamatergic PVT neurons might be the next

order neuron in this intricate pathway. Interestingly, semaglutide robustly activates PSN and PVT neurons, possibly by tancyte-mediated uptake [51], suggesting a convergence of endogenous GLP-1 and GLP-1R agonist action in the neural pathways that suppress food intake in the PVT. In line with this idea, inhibiting tancyte function prevents the activation of neurons in the ZI by liraglutide [125]. Since the GLP-1R is highly expressed in the upstream PSN and ZI [66], it would be interesting to determine their neurochemical phenotype and whether they are activated by peripheral GLP-1R agonists to suppress food intake. Along these lines, GLP-1-expressing NTS neurons project to the PVT, and administration of exendin-4 into this brain region reduces food intake and motivation for food reward, while exendin-9 has the opposite effect [163]. These PVT neurons in turn project to the ventral striatum and electrophysiological experiments revealed that GLP-1R activation in the PVT reduces excitatory drive in this region [163].

Dopaminergic neurons are also found in the ZI and have similar effects on feeding as GABAergic ZI neurons [164]. Remarkably, while dopaminergic VTA neurons have been extensively studied in the context of food reward and obesity, their ablation has little overall effect on food intake

Fig. 2 Wiring diagram for central GLP-1 projections and sites of appetite suppression and weight loss. This schematic summarizes the central projections of GLP-1-expressing NTS neurons and where local administration of GLP-1R agonists and antagonists control food intake or body weight. In the VTA and PVH, GLP-1 has presynaptic effects on glutamatergic and/or GABAergic neurons. Neurons in red are GABAergic, and neurons in green are glutamatergic



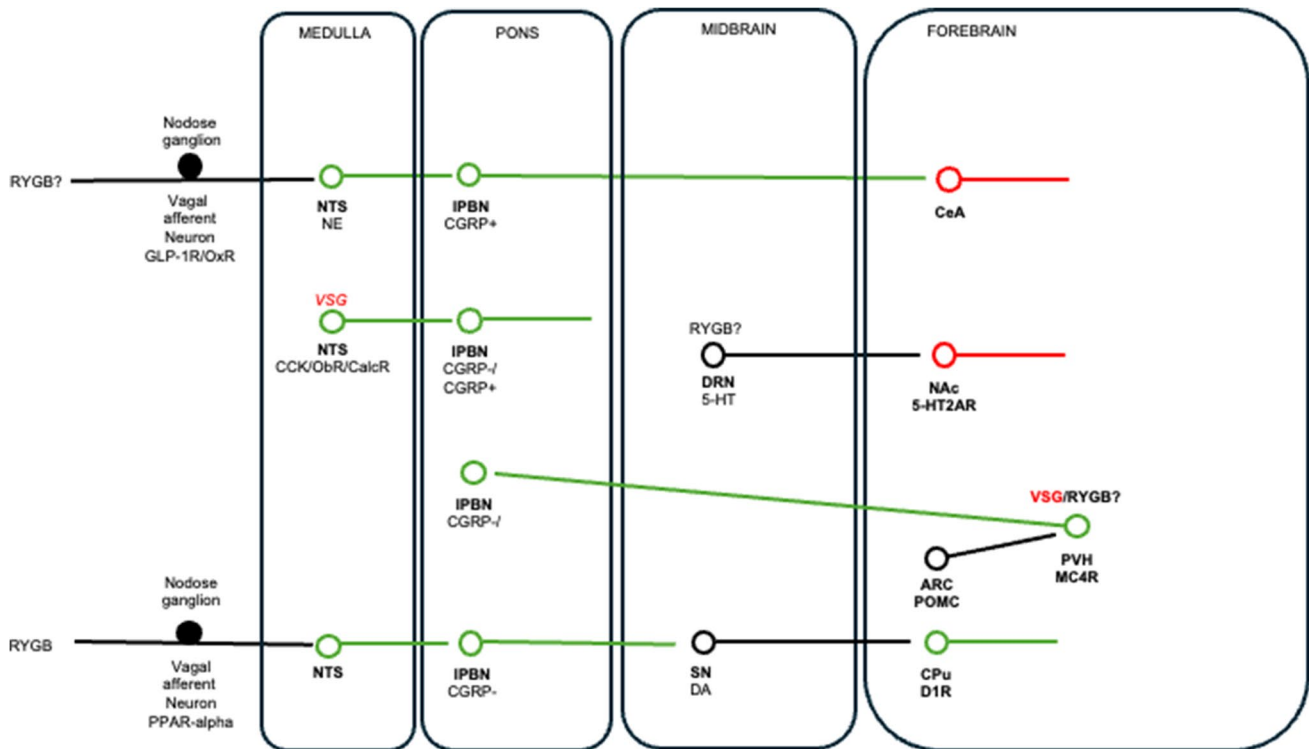


Fig. 3 Wiring diagram for bariatric surgery-mediated appetite suppression and weight loss. This schematic summarizes peripheral and central neural pathways targeted by RYGB and VSG. Text in red ital-

ics highlights regions where VSG does not exert its effects based on neuronal inhibition approaches. Neurons in red are GABAergic, and neurons in green are glutamatergic

and body weight [164]. In striking contrast, ablating dopaminergic ZI neurons reduces food intake and weight gain associated with reduced motivation to obtain a food reward [164], while activating dopaminergic ZI neurons robustly increases food intake and motivation to obtain a food reward [164]. Interestingly, chronic consumption of a high-fat high-sugar (HFHS) diet depolarizes resting membrane potential and increases excitatory input onto dopaminergic ZI neurons [164]. Similar to GABAergic ZI neurons, these dopaminergic ZI neurons project to and inhibit PVT neurons to robustly increase food intake [164]. These findings provide strong evidence that dopaminergic ZI neurons contribute to hedonic feeding and obesity, perhaps even more so than dopaminergic VTA neurons making them interesting candidates to study in the context of both bariatric surgery and GLP-1R agonists.

The septum

The septum is a subcortical forebrain area that controls various processes ranging from sleep to learning and memory. GLP-1-expressing NTS neurons project to the lateral

septum, and administration of exendin-4 into this brain region suppresses food intake [165]. Conversely, administration of exendin-9 into the lateral septum increases food intake, prevents the ability of nutrient load to suppress food intake [165], prevents stress-induced hypophagia [166], and increases the motivation to obtain a sucrose reward [167]. Accordingly, chronic activation of GLP-1R-expressing lateral septum neurons reduces food intake and body weight as well as causing aversion [130] while acutely inhibiting GLP-1R-expressing lateral septal neurons robustly increases food intake [168], and their silencing leads to weight gain on a high-fat diet [130]. At the circuit level, GLP-1R-expressing lateral septum neurons make GABAergic connections with the LHA where activation of their terminals decreases food intake [168]. Accordingly, exendin-4 in the lateral septum enhances GABA release onto LHA neurons [168]. Importantly, systemic liraglutide activates GLP-1R-expressing lateral septum neurons, while their silencing or deletion of GLP-1Rs partially attenuates the inhibitory effects of chronic systemic liraglutide on food intake and body weight in mice [130].

The hippocampus

The hippocampus is traditionally implicated in learning and memory. Accumulating evidence suggests that the ventral hippocampus contributes to the control of energy balance. For example, administration of leptin into the ventral hippocampus decreases food intake [169], while that of ghrelin increases food intake [170]. In the context of GLP-1R agonists, administration of exendin-4 into the ventral hippocampus reduces food intake without causing malaise, while exendin-9 increases food intake [171]. Further work showed that GLP-1R-expressing ventral hippocampal neurons are monosynaptically connected to the medial prefrontal cortex (mPFC), and the suppression of food intake and motivated behaviors by intra-ventral hippocampal administration of exendin-4 is lost with their inhibition or antagonism of NMDARs [172]. However, it remains unclear if this pathway is targeted by systemic GLP-1R agonist treatment (Fig. 2).

Summary

In this Review, we have summarized the peripheral and central neural pathways targeted by endogenous GLP-1 and GLP-1R agonists (Fig. 1). Owing to the development of sophisticated neuroscientific techniques for assessing neuronal activity and connectivity, tremendous progress has been made in defining these neural pathways at an unprecedented level of molecular, anatomical, functional, and behavioral detail. Overall, evidence suggests that GLP-1R agonists directly and indirectly target a distributed network of neurons to exert their effects on food intake and body weight (Fig. 1). Much less is known about the neural circuits targeted by bariatric surgery (Fig. 3), and there is a pressing need to apply the methodology used for GLP-1R agonists in the corresponding rodent models of RYGB and VSG in this context [173]. This is of potential clinical relevance, as further defining the commonalities and differences between GLP-1R agonists and bariatric surgery in terms of their central mechanism of action may not only help bridge the gap between the pharmacological and surgical treatments for obesity but may also provide a neural basis for their combined use when each individually fail [174, 175].

Author contribution MKH: conceptualization, writing, preparation of figures, revising TAL: conceptualization, writing, revising.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval N/A.

Competing interests TAL: consultant and scientific collaborator with Novo Nordisk; the collaboration has no direct or indirect influence on the statements made in this review.

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