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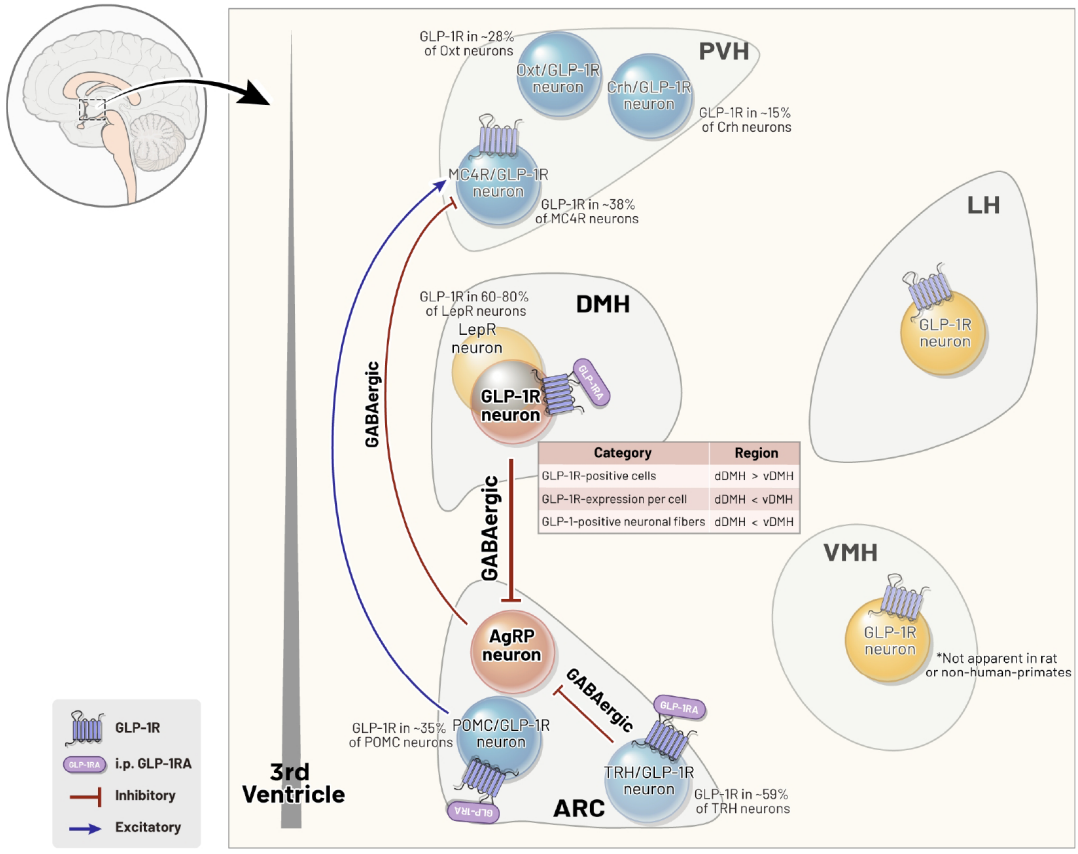

Highlights

- **GLP-1RAs act centrally to induce satiation and satiety, and influence cognition.**
- **DMH GLP-1R neurons drive pre-ingestive, cognitive satiation via feed-forward control.**
- **Hypothalamic GLP-1R neurons in ARC, DMH, PVH, LH, and VMH shape distinct feeding traits.**
- **Hindbrain and septal GLP-1R neurons modulate aversion and satiety.**
- **Novel GLP-1RAs improve efficacy and show promise beyond obesity such as addiction.**

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Glucagon-Like Peptide-1 and Hypothalamic Regulation of Satiation: Cognitive and Neural Insights from Human and Animal Studies

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Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as blockbuster drugs for treating metabolic diseases. Glucagon-like peptide-1 (GLP-1) plays a pivotal role in glucose homeostasis by enhancing insulin secretion, suppressing glucagon release, delaying gastric emptying, and acting on the central nervous system to regulate satiation and satiety. This review summarizes the discovery of GLP-1 and the development of GLP-1RAs, with a particular focus on their central mechanisms of action. Human neuroimaging studies demonstrate that GLP-1RAs influence brain activity during food cognition, supporting a role in pre-ingestive satiation. Animal studies on hypothalamic feed-forward regulation of hunger suggest that cognitive hypothalamic mechanisms may also contribute to satiation control. We highlight the brain mechanisms of GLP-1RA-induced satiation and satiety, including cognitive impacts, with an emphasis on animal studies of hypothalamic glucagon-like peptide-1 receptor (GLP-1R) and GLP-1R-expressing neurons. Actions in non-hypothalamic regions are also discussed. Additionally, we review emerging combination drugs and oral GLP-1RA formulations aimed at improving efficacy and patient adherence. In conclusion, the dorsomedial hypothalamus (DMH)—a key GLP-1RA target—mediates pre-ingestive cognitive satiation, while other hypothalamic GLP-1R neurons regulate diverse aspects of feeding behavior, offering potential therapeutic targets for obesity treatment.

Keywords: Central nervous system; Diabetes mellitus, type 2; Glucagon-like peptide 1; Glucagon-like peptide-1 receptor; Glucagon-like peptide-1 receptor agonists; Hypothalamus; Incretins; Obesity; Satiation

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have garnered significant attention in the global pharmaceutical market. Glucagon-like peptide-1 (GLP-1) is an incretin hormone derived from the transcription product of the proglucagon gene, primarily secreted by intestinal L-cells in response to nutrient intake [1]. It plays a critical role in glucose homeostasis, enhancing insulin secretion, suppressing glucagon release, and delaying gastric emptying.

In addition to its metabolic effects, GLP-1 acts centrally to maintain energy balance by activating glucagon-like peptide-1 receptors (GLP-1Rs) located in key regions of the brain. These include regions in the hypothalamus, brainstem, and mesolimbic reward pathways, which collectively regulate eating behavior such as food intake, satiation, and satiety. Additionally, the effects of GLP-1RAs on cognitive processes are currently being explored, broadening our understanding of their therapeutic mechanism in controlling metabolism.

This review will briefly cover the history of GLP-1 discovery and development of incretin-based drugs. Next, we will discuss human studies about the effects of GLP-1 on the central

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nervous system (CNS) and cognitive behavior, and animal studies that imply cognitive actions regulated by the hypothalamus. We will then go through the mechanism of GLP-1 acting on neural circuits within the CNS that regulate satiation and satiety, particularly focusing on regulation by the hypothalamus.

DISCOVERY OF GLP-1 AND DEVELOPMENT OF INCRETIN-BASED DRUGS

The discovery of secretin in 1902 was the hallmark for the initiation of gastrointestinal endocrinology [2]. In 1964, the development of insulin radioimmunoassay methods led to the discovery of the incretin effect, which demonstrated that oral glucose intake induces higher insulin secretion compared to intravenous (i.v.) glucose [3,4]. In 1973, Dupre et al. [5] proved that GIP, originally named 'gastric inhibitory polypeptide,' could explain this incretin effect by inducing glucose-stimulated insulin secretion, and renamed the peptide as 'glucose-dependent insulinotropic polypeptide.' Following the identification of GIP, the search for insulinotropic incretins persevered.

Meanwhile in 1982, Joel Habener's group performed a cDNA study on anglerfish, a rich source of pancreatic islet hormone mRNAs. They revealed that the glucagon precursor gene encoded additional peptides beyond glucagon [6,7]. Subsequently, a study by Bell et al. [8] conducted cDNA analysis of preproglucagon in hamsters, which revealed that mammalian genes differ from those of anglerfish and identified two novel peptides, terming them glucagon-related peptides 1 and 2 (GLP-1, GLP-2).

GLP-1's role as an insulinotropic incretin remained undetermined until GLP-1 (7-37), a truncated form of GLP-1, was identified by Mojsov et al. [9] as capable of stimulating insulin release in the rat pancreas, in contrast to GLP-1 (1-37), which did not alter insulin secretion. Holst et al. [10] further demonstrated that GLP-1 (7-37) extracted from pig intestine could stimulate insulin secretion in pig pancreas. In 1987, Kreymann et al. [11] performed studies in humans and confirmed GLP-1 (7-36) to be insulinotropic, suggesting its incretin nature. Indeed, i.v. infusion of GLP-1 (7-37) in subjects with and without diabetes elevated peak insulin levels by 10- and 3-fold respectively, and attenuated glucose levels [12]. These results suggested the possibility of GLP-1 as a treatment for diabetes, but limitations for therapeutic utility existed as endogenous GLP-1 had a short half-life in plasma of 1 to 2 minutes, degraded by the dipeptidyl-peptidase 4 (DPP-4) enzyme [13].

In 1992, Eng et al. [14] successfully isolated exendin-4 from the venom of the Gila monster (*Heloderma suspectum*), a lizard known for its infrequent but large meals weighing up to as much as one third of its body mass—suggesting the presence of adaptive metabolic mechanisms in the species [14,15]. Exendin-4, which shows 53% structural homology with GLP-1 (7-36), is as potent as endogenous GLP-1 in its insulinotropic effects via the mammalian GLP-1R. Strikingly, exendin-4 was stable against DPP-4 [16,17].

The isolation of exendin-4 led to the development of exenatide as the first U.S. Food and Drug Administration (FDA)-approved diabetes drug in 2005 by John Eng, with collaboration from Amylin Pharmaceutical (San Diego, CA, USA). Meanwhile, a group led by Knudsen at Novo Nordisk (Bagsværd, Denmark) employed the approach of fatty acid acylation to facilitate albumin binding and attenuate degradation [18]. The final product, liraglutide (Victoza, Novo Nordisk), proved its effects in type 2 diabetes mellitus (T2DM) and was approved by the FDA in 2010 [19]. Liraglutide (Saxenda, Novo Nordisk) was further developed with a higher dosage than Victoza for chronic weight management, and was approved by the FDA in 2014, proving its weight loss effects in numerous clinical studies performed worldwide [20,21].

The success of clinical trials with exenatide and liraglutide sparked growing interest in therapies based on GLP-1. Semaglutide, developed to achieve a longer half-life than liraglutide, enables once-weekly administration and induced clinically significant weight loss in randomized controlled clinical trials [22]. Recent randomized controlled trial studies have also proven that weekly semaglutide was superior compared to placebo in reducing cardiovascular risks for obese patients [23].

Meanwhile, dual and triple agonists targeting receptors beyond GLP-1R are continuously developed in preclinical models. In 2009 the first form of dual agonists was discovered by Day et al. [24], targeting GLP-1R and the glucagon receptor (GCGR). In 2013, Day et al. [25] also discovered dual agonists targeting both GLP-1 and GIP receptors (GIPR). In 2015, triple agonists simultaneously targeting the GLP-1R, GCGR, and GIPR were also developed, whose weight loss in mice exceeded those of the dual agonists [26]. Clinical trials for these co-agonist incretin drugs are still continuously ongoing worldwide. Recently, the GIP/GLP-1R co-agonist tirzepatide has gone through several randomized controlled trials and was approved by the FDA for T2DM and obesity in 2022 and 2023,

respectively. Once-weekly administered tirzepatide proved to be both noninferior and superior in reducing glycosylated hemoglobin levels in T2DM patients and demonstrated robust weight loss in obese patients [27,28]. The emergence of clinically effective dual and triple agonists holds promise for enhanced metabolic outcomes, although the precise mechanisms of drug actions remain to be fully elucidated.

GLP-1 AND IMPLICATIONS IN COGNITIVE SATIATION: HUMAN STUDIES

GLP-1 has long been identified and validated as a biomarker peptide for satiation and satiety under physiological conditions [29,30]. Satiation refers to the process occurring 'during' a meal event that prompts eating termination and is associated with meal size, while satiety refers to the process occurring 'after' a meal event, inhibiting further eating until the next meal [30,31]. Satiation gradually rises during a meal event as hunger diminishes, peaking at meal termination. After the meal event, satiety gradually drops over time and hunger returns, starting a new cycle [32].

The satiety cascade, first proposed in the 1980s and modified throughout, indicates that satiation and satiety are governed by the interplay of metabolic, cognitive, and sensory factors, which are interconnected components [31,33,34]. Studies indicate that sensory and cognitive perceptions of food can indeed influence satiation by brain signaling, while the mechanism of this process is yet to be fully uncovered [35].

It is well known that peripheral injection of GLP-1R agonists interacts with the CNS [36,37]. Several human studies have proven that the actions of GLP-1R agonists in the brain are regulated by sensory and cognitive factors. We have previously investigated the acute effects of lixisenatide injection compared to saline in measurements of functional magnetic resonance imaging (fMRI) responses to visual food cues. In T2DM patients, lixisenatide reduced activation in brain areas including the hypothalamus, temporal lobar regions, lateral ventricle, and cortical areas in obese individuals in contrast to lean T2DM individuals, who showed increased activation in the areas [38].

fMRI studies on other GLP-1R agonists have also provided further evidence of their cognitive effects. In obese T2DM patients, exenatide reduced putamen activity to high-calorie food pictures, while enhancing putamen responses to low-calorie food pictures [39,40]. In a study conducted in obese male patients, all exenatide responders, defined as those who consumed lower food calories by exenatide administration compared to placebo, exhibited significantly higher hypothalamic connectivity measured by food cue-paired fMRI compared with placebo injection [41]. Furthermore, liraglutide treatment for 10 days in obese T2DM patients attenuated insula and putamen fMRI responses to food pictures in fasted and post-meal conditions, compared with insulin glargine injection [42].

Interestingly, the effects of GLP-1R agonists have also been studied in non-obese patients without T2DM. In fasted healthy normal weight patients, GLP-1 (7-36) amide injection reduced fMRI activity induced by food images, in all brain areas studied (amygdala, insula, caudate, NAc, orbitofrontal cortex, and putamen), compared to saline injection [43].

Collectively, these results highlight the cognitive effects of GLP-1R agonists in response to food cues, implying that the effects of GLP-1R agonists on satiation and satiety extend to cognitive processes.

HYPOTHALAMIC FUNCTIONS IN COGNITIVE FEED-FORWARD REGULATION

The hypothalamus is a well-established area of the brain known to regulate feeding behavior and energy metabolism, where disruption can lead to obesity [44]. The actions of agouti-related peptide (AgRP) neurons and pro-opiomelanocortin (POMC) neurons in the arcuate nucleus (ARC), the most renowned cell types of the hypothalamus governing homeostatic actions and inducing hunger, were previously understood to be mainly regulated by internal nutritional status or hormones such as leptin or ghrelin [45]. However, fiber photometry studies validated that ARC^{AgRP} neural activity is inhibited within seconds after visual sensory cognition or the taste of food, in the preingestive stage [46-48]. Strikingly, the amount of reduction in ARC^{AgRP} neural activity was modulated by food calories, and the learning of nutritional value in a single trial promptly suppressed ARC^{AgRP} neural activity [49]. These results demonstrate the feed-forward nature of ARC^{AgRP} neurons through a learned anticipation process. The sudden drop in signals at the moment of sensory detection or food cognition may reflect the abrupt recognition of an anticipated resolution of energy deficit, rather than being driven by ingestive or hormonal signals which typically act over minutes to hours [50]. Our previous research further corroborated this viewpoint by proving that ARC^{AgRP} neural activity accounts for computational modeling

of 'need,' defined as predicted deficiency, which is the sum of current deficiency and future predicted changes [51]. This definition of 'need' implies the preemptive update of deficiency prior to ingestion, which can indeed occur through sensory cognition and anticipation of the future and may be advantageous for survival [52].

In addition, the leptin-receptor-expressing (LepR) neural activity in the dorsomedial hypothalamus (DMH), which sends GABAergic inhibitory inputs to ARC^{AgRP} neurons, is also known to be rapidly increased by sensory detection, the taste of food, or food cues [48,53,54]. DMH^{LepR} neurons receive afferents from the lateral hypothalamus $(LH)^{Vglut2}$ neurons, which are known to be necessary for the rapid responses to food cues [54]. Overall, these animal studies demonstrate the cognitive feed-forward hunger regulation mechanism that occurs in the hypothalamic region.

The hypothalamus can also be hypothesized to regulate satiation or satiety in a feed-forward manner. Indeed, in physiological conditions, plasma GLP-1 has been suggested to increase not only after meals, but also in the pre-ingestive, cephalic phase, with its peak observed about an hour prior to meal initiation in rats [55]. The following part of the review will discuss the hypothalamic actions regarding GLP-1, including its effects on satiation in cognitive stages.

HYPOTHALAMIC CONTROL OF GLP-1 ACTIONS ON SATIATION AND SATIETY: ANIMAL STUDIES

Various studies have focused on the hypothalamus as a target of different types of GLP-1R agonists. A study using fluorescently labeled lipidated analogues of exendin-4 showed that they are distributed in the hypothalamus [56]. Fluorescently labeled liraglutide reaches hypothalamic regions such as the ARC, paraventricular nucleus (PVH), and supraoptic nucleus (SON) after peripheral administration, with GLP-1R undergoing internalization after binding to liraglutide [57]. GLP-1RA binding to GLP-1R is indeed mediated by internalization of GLP-1R and GLP-1RA, consistent with the fact that GLP-1R is classified as a class B G protein-coupled receptor (GPCR) [57,58]. Whole brain microscopy following the injection of fluorescently labeled semaglutide revealed that semaglutide is present in parts of the hypothalamus, including the DMH, ARC, PVH, medial mamillary nucleus, and SON [59].

The specific mechanism of how GLP-1RAs can cross the blood-brain barrier and reach the hypothalamus has been a matter of debate. Hypothalamic tanycytes are glial cells located along the walls and floor of the third ventricle, which are known to play neuroendocrine roles such as detecting and transporting nutrients and hormones like insulin and GLP-1, as well as regulating neuronal activity [60-62]. The role of hypothalamic tanycytes has been studied in different types of GLP-1RAs. These cells are actively involved in the transport of exendin-4 to the brain cerebrospinal fluid [63]. In addition, GLP-1R expressions are found in tanycytes, and it is known that tanycytic GLP-1R is required for liraglutide's anti-obesity actions via its transport to hypothalamic cells [64]. Semaglutide can also bind to and activate tanycyte GLP-1Rs [59]. Further elucidation is needed about the function of tanycytes and tanycytic GLP-1R-dependent transport of GLP-1RAs.

The distribution of GLP-1R and the role of GLP-1R expressing neurons along with the effects of GLP-1RA in different areas of the hypothalamus have been thoroughly studied in various studies (Table 1, Fig. 1) [65-67].

Dorsomedial hypothalamus

GLP-1R are known to be expressed in the neurons of the DMH of mice and humans, and previous studies have emphasized its role in regulating metabolic responses by exendin-4 [68,69]. Direct injection of exendin-4 to the DMH reduced blood glucose levels, while liraglutide injection into the DMH did not alter 24-hour food intake or body weight [70,71]. Brain slice studies have shown that exendin-4 can increase the firing rates of DMH neurons, enhancing the neurons' sensitivity to a high-fat diet (HFD) compared to a control diet [72]. Long-term ablation of DMH GLP-1R resulted in hyperphagia and obesity, and blunted exendin-4-induced anorexigenic metabolic effects [68,73].

The DMH GLP-1R expressing cells are known to be predominantly GABAergic, while a smaller percentage of the population do express vesicular glutamate transporter 2 (VGLUT2) mRNA [68]. Activated by GLP-1, DMH GLP-1R neurons are known to be crucial for glucose regulation, mediated by a cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) dependent pathway. These glucose-sensitive actions operate through downstream connections to the dorsal motor nucleus of the vagus (DMV) to the pancreas [70,73].

To further investigate the function of DMH GLP-1R neurons, our group conducted a translational study to elucidate their behavioral role. Optogenetic activation of the neurons

Table 1. Animal studies of GLP-1R, GLP-1R neurons, GLP-1RA effects on hypothalamus

Brain region	Mice GLP-1R transgene [65][a]	Rat GLP-1R immunocyto-chemistry [66][a]	Monkey GLP-1R ISH [67][a]	Direct injection of GLP-1RA to brain region	Disruption of GLP-1R in the area	GLP-1RA i.p. injection +, Disruption of GLP-1R in the area	Calcium signal of brain region GLP-1R neurons	Neuromodulation of brain region GLP-1R neurons		GLP-1RA i.p. injection effects on brain region GLP-1R neurons
								Activation	Inhibition	
DMH	++	+++	++	(Exendin-4) Blood glucose level ↓ (Liraglutide) B.W. ~ Food intake ~	(DMH glp1r KD or ablation) B.W.↑ Food intake↑ Plasma TG↑ E.E. ↓ UCP1↓ Feed pattern disruption	(i.p. Exendin-4+glp1r KD) |Δ Food intake| ↓ |Δ B.W.| ↓ |Δ E.E.|↓ |Δ RER|↓	Neural activity ↑at pre-ingestive, or ingestive stages	Bout duration↓ Number of bout↓ Latency to ingestion termination ↓	Bout duration↑ Food intake↑	(Exendin-4) Potentiate DMH GLP-1R neurons' calcium signals
ARC	+++	++++	++++	(GLP-1, exendin-4, liraglutide) B.W. ↓ Food intake↓	(POMC glp1r KD) B.W. ~ HFD-induced weight gain ↑ Food intake ~ E.E. ~	(i.p. Exendin-4+POMC glp1r KD) |Δ Food intake| ~ (i.p. Liraglutide+ARC glp1r antagonist) |Δ Food intake| ↓		Food intake ↓		(Liraglutide, semaglutide) Increase excitatory tone to POMC neurons
PVH	+++	+++	+++	(GLP-1, exendin-4, liraglutide) B.W. ↓ Food intake↓	(Sim1 glp1r KD) B.W. ~ HFD-induced weight gain ~ Food intake ~ E.E. ↓ (Juvenile PVH glp1r KO) B.W.↑ Food intake↑ E.E. ~ (PVH glp1r antagonist) B.W.↑	(i.p. Exendin-4+Sim1 glp1r KD) |Δ Food intake| ~ (i.p. Liraglutide+PVH glp1r antagonist) |Δ Food intake| ~	Neural activity ↑at pre-ingestive, or ingestive stages	Food intake ↓	Food intake ↑	
LH	++	++	++	(Exendin-4) Lever-pressing ↓ (Liraglutide) B.W. ↓ Food intake↓	NAc GLP-1R expression ↑					
VMH	+++	-	-	(Exendin-4) B.W. ↓ Food intake↓ E.E. ↓ (Liraglutide) B.W. ↓ Food intake ~	(VMH glp1r KD) Food intake ~ B.W. ~ E.E. ~	(Exendin-4) |Δ Food intake| ~ (Liraglutide) |Δ B.W.| ~	-	-	-	-

GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; ISH, *in situ* hybridization; DMH, dorsomedial hypothalamus; B.W., body weight; KD, knockdown; TG, triglyceride; E.E., energy expenditure; UCP1, uncoupling protein 1; i.p., intraperitoneal; RER, resting energy requirement; ARC, arcuate nucleus; POMC, pro-opiomelanocortin; HFD, high-fat diet; PVH, paraventricular hypothalamic nucleus; KO, knockout; Sim1, single minded-1; LH, lateral hypothalamus; NAc, nucleus accumbens; VMH, ventromedial hypothalamus.

[a]GLP-1R expression detected by transgene expression in mice [65], density of GLP-1R-immunoreactive fibers in each brain region determined by rat immunocytochemistry [66], GLP-1R expression determined by ISH in non-human primates [67].

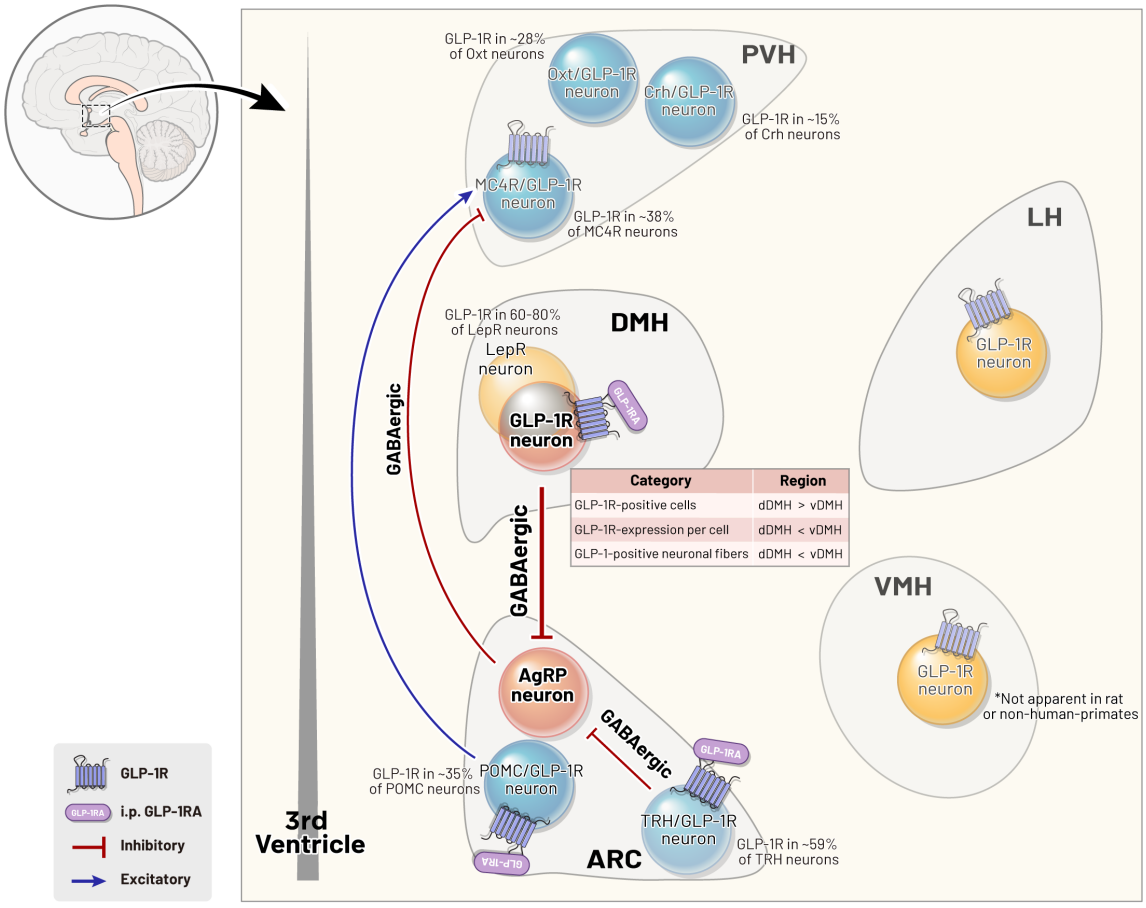

Fig. 1. Overview of hypothalamic glucagon-like peptide-1 receptor (GLP-1R) neurons. PVH, paraventricular hypothalamic nucleus; Oxt, oxytocin-expressing; Crh, corticotropin-releasing hormone-expressing; MC4R, melanocortin 4 receptor-expressing; DMH, dorsomedial hypothalamus; LepR, leptin-receptor-expressing; LH, lateral hypothalamus; dDMH, dorsal DMH; vDMH, ventral DMH; GLP-1, glucagon-like peptide-1; ARC, arcuate nucleus; AgRP, agouti-related peptide; POMC, pro-opiomelanocortin; TRH, thyrotropin-releasing hormone-expressing; VMH, ventromedial hypothalamus; i.p., intraperitoneal.

triggered immediate meal termination and reduced bout duration and frequency, while neural inhibition prolonged bout duration and increased food intake, showing that the neurons are necessary and sufficient for satiation. Furthermore, calcium signal recording of DMH GLP-1R neurons highlighted that learned anticipation of food induces a significant increase in neural activity even before contact with food. In addition, exendin-4 injection enhanced calcium signals in DMH GLP-1R neurons in the pre-ingestive stage, and exendin-4-induced pre-ingestive satiation was mitigated by optogenetic inhibition of DMH GLP-1R neurons. These findings confirm that DMH GLP-1R neurons mediate pre-ingestive, cognitive satiation elicited by GLP-1R agonists, a phenomenon that we also observed in a human study [69]. The role of DMH GLP-1R neurons can be likened to stepping on a vehicle's brake in response to a traffic signal—a learned anticipatory mechanism that prepares for meal termination independently of gut-derived feedback. This demonstrates a cognitive regulation of satiation, in which a feed-forward mechanism increases satiation before the initiation of a meal, eventually leading to meal termination (Fig. 2).

GLP-1R-LepR co-expressing neurons, localized primarily in the DMH in rodent and non-human primate models, mediate the suppression of food intake by liraglutide [74-76]. A recent study combining single-nucleus sequencing and spatial transcriptomics pinpointed the human hypothalamic GLP-1R-LepR co-expressing cluster, which strongly correlated with the mouse hypothalamic cluster that exhibits the second highest

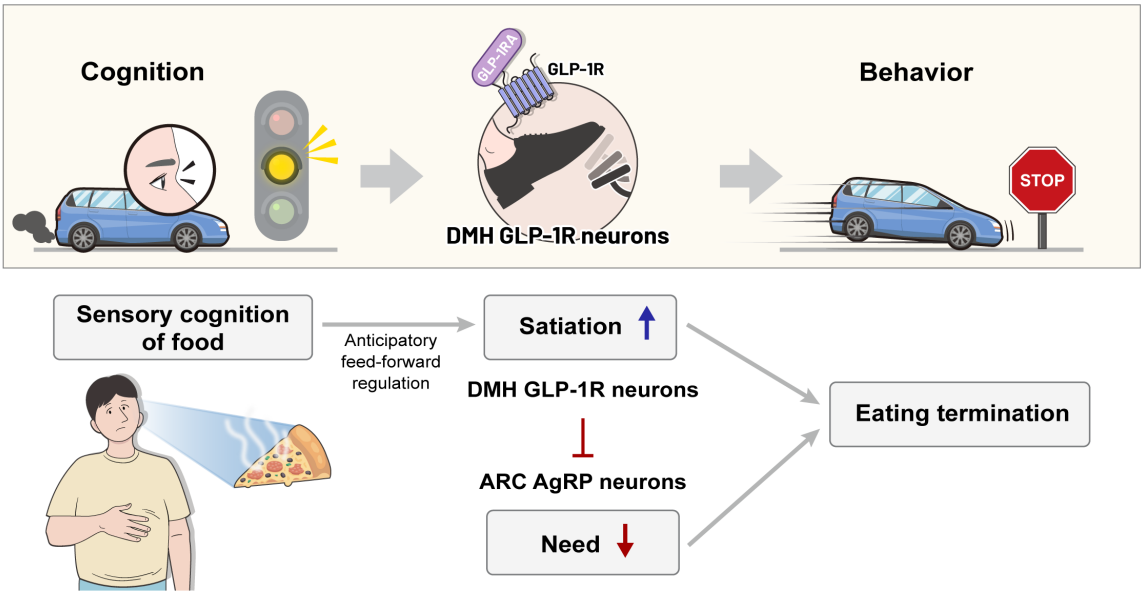

Fig. 2. Feed-forward cognitive control of satiation. The role of dorsomedial hypothalamus (DMH) glucagon-like peptide-1 receptor (GLP-1R) neurons regulating cognitive satiation can be likened to stepping on a vehicle's brake in response to traffic signals—a preemptive action taken before reaching the actual stop goal, reflecting a feed-forward control mechanism. These neurons project inhibitory signals to arcuate nucleus (ARC) agouti-related peptide (AgRP) neurons, ultimately contributing to meal termination. Notably, glucagon-like peptide-1 receptor agonists (GLP-1RAs) can potentiate the activity of DMH GLP-1R neurons.

expression of GLP-1R in the hypothalamus [76]. Notably, GLP-1R-LepR co-expressing cells proved to be crucial targets of newly synthesized GLP-1/leptin dual agonists, which create a negative energy balance and assist the action of leptin [75].

As previously mentioned, DMH LepR neurons are known to be activated by sensory cue information and the taste of food [48,53,54]. Activation of DMH LepR neurons has been shown to be sufficient to inhibit food intake [53]. However, the authors concluded that DMH LepR neurons are not essential for satiation or satiety, as the study found no significant increase in food intake or body weight following inhibition or disruption of these neurons [54]. More recently, another study demonstrated that DMH LepR neurons respond to oro-sensory cues, acting as negative feedback signals to promote meal termination. Chemogenetic inhibition of DMH LepR neurons led to increased food intake by increasing the number of licking bouts without altering bout length, in contrast to the increased bout duration in DMH GLP-1R neurons, implying that DMH LepR neurons play a role in satiety [48]. Some of this discrepancy may result from differences in observed behavior (licking vs. eating), or from the complexities of semantic distinctions between terms such as satiation or satiety. Additionally, some discrepancies may be explained by our findings, which show that mRNA co-localization of LepR and GLP-1R varies depending on the anatomical location within the DMH, with a higher overlap percentage in the caudal part of the DMH than the rostral part [69]. Some studies have also found a higher density of GLP-1R-positive cells in the dorsal DMH (dDMH) than the ventral DMH (vDMH), and a higher density of GLP-1-positive neuronal fibers in the vDMH than the dDMH [72]. Moreover, the LepR neurons specifically within the dDMH were recently studied for their role in activating brown adipose tissue (BAT) thermogenesis, while not altering food intake [77]. Further research is needed to clarify regional differences within the DMH in the expression of GLP-1R and LepR, their upstream and downstream circuits, and how they can contribute to satiation or satiety in different feeding phases. Furthermore, the role of DMH GLP-1R neurons or LepR neurons in sensory-specific satiety, a phenomenon in which repeated exposure to a particular taste reduces food intake, is an area for further study.

Arcuate nucleus

The ARC of the hypothalamus is one of the sites with abundant GLP-1R distribution [78]. Direct injection of 1 nmol GLP-1, exendin-4, or liraglutide to the ARC significantly suppressed

food intake and body weight, with the effects observed over the 24 hours following injection [71,79,80].

It has been shown that GLP-1Rs are expressed in POMC neurons in the arcuate, while not in the neuropeptide Y (NPY)/AgRP neurons of the ARC [57,81]. Some studies have reported that knockdown of GLP-1R in ARC POMC neurons didn't alter body weight or composition, food intake, and energy expenditure, nor did it significantly alter the reduction of food intake by intraperitoneal (i.p.) exendin-4 [80]. However, other studies have indicated that POMC GLP-1R knockdown can increase HFD-induced weight gain, and ARC GLP-1R blockade by GLP-1R antagonists attenuated the anorexic effects of liraglutide [57]. This discrepancy may be due to the different drug types, or intervention of other pathways or compensatory mechanisms after disruption of GLP-1R. Further studies are needed for elucidation.

Exendin-4, liraglutide and semaglutide can directly or indirectly stimulate POMC neurons in the ARC, while indirectly inhibiting NPY/AgRP neurons via presynaptic GABAergic neurons [82-84]. While previous fiber photometry results showed that administration of GLP-1 or liraglutide did not significantly alter ARC AgRP/NPY neuron calcium signals post 30-minute injection, after 2 hours post-injection, the rapid suppression of AgRP calcium signals after cognition of food was indeed attenuated by liraglutide [49,82,85]. Our patch-clamp electrophysiology results corroborate these findings, demonstrating that GLP-1RAs directly activate DMH GLP-1R neurons, which in turn send inhibitory projections to ARC AgRP/NPY neurons [69].

Chemogenetic activation of GLP-1R neurons in the ARC, particularly neurons co-expressing POMC and GLP-1R in male mice, significantly suppressed feeding [86,87]. In addition to POMC, other markers in the ARC that potentially represent targets for GLP-1RAs are currently being studied. ARC GABAergic neurons that express thyrotropin-releasing hormone (TRH), approximately 60% of which expressed GLP-1R, were found to have GABAergic afferents directly targeting AgRP neurons. ARC TRH neurons were directly activated by liraglutide and were shown to be necessary for its anorectic actions [88].

Paraventricular nucleus

The PVH is also a region known to have a dense population of GLP-1R in rodents [89]. *In situ* hybridization (ISH) studies have revealed that GLP-1R mRNA is also expressed in the human brain PVH, with its expression significantly reduced in T2DM patients compared to controls, potentially contributing to homeostatic imbalance [90]. Direct injection of GLP-1, exendin-4, or liraglutide to the PVH indeed suppressed food intake [71, 80].

Single minded-1 (Sim1) is a transcription factor expressed in most PVH cells, and PVH Sim1 neurons are known to play a role in regulating satiety [91,92]. Some studies have reported that knockdown of GLP-1R in Sim1 neurons did not affect body weight, body composition, or food intake, nor did it significantly change the anorexic effects induced by i.p. exendin-4 injection [80]. Similarly, the blockade of GLP-1R in the PVH with antagonists failed to attenuate liraglutide-induced weight loss [57]. Yet GLP-1R knockdown in Sim1 neurons did result in a significant reduction in energy expenditure, in contrary to results from whole-body or hypothalamic GLP-1R knockout models. This suggests the presence of compensatory mechanisms involving other hypothalamic or extra-hypothalamic regions [80,93]. In addition, PVH GLP-1R knockout in juvenile mice led to increased adult body weight and food intake with no changes in energy expenditure, suggesting potential compensatory adaptation during development [94].

A study has shown that anticipation of food in the pre-ingestive stage, without ingestion and triggered solely by sensory detection of food, led to a rapid increase in calcium activity of PVH GLP-1R neurons. Chemogenetic activation and inhibition of PVH GLP-1R neurons were shown to reduce and increase food intake, respectively [95]. However, liraglutide did not directly activate Fos expression in the PVH, suggesting that the effects of GLP-1RA on this region may be indirect [95,96].

Other hypothalamic regions

The LH GLP-1R is also considered one of the hypothalamic targets in studies investigating central GLP-1R signaling. Injection of exendin-4 into the LH reduced lever-pressing behavior, while injection of exendin-9, a GLP-1R antagonist, increased food reinforcement. Additionally, liraglutide injection to the LH lowered food intake and body weight [71]. Interestingly, chronic LH GLP-1R knockdown resulted in increased nucleus accumbens (NAc) GLP-1R expression in male mice, which may be associated with compensation related to reward [97].

The ventromedial hypothalamus (VMH), a classically known satiety center, is also a brain area that has been studied [98]. Liraglutide injection into the VMH of mice induced weight loss and increased thermogenetic activity, as evidenced by elevated

uncoupling protein 1 expression in both BAT and white adipose tissue, with adenosine monophosphate-activated protein kinase (AMPK) signaling in the VMH required as a mediator [71]. Similarly, exendin-4 injection into the VMH of mice also reduced food intake and body weight, but, interestingly, decreased energy expenditure—unlike liraglutide injection—despite both acting via AMPK inhibition [99]. Furthermore, VMH GLP-1R deletion did not significantly affect the anorexigenic effects of systemically administered exendin-4, suggesting that the VMH may not be a critical site for mediating GLP-1RA driven appetite suppression [99]. Notably, GLP-1R has been reported to be absent in the VMH based on rat immunochemistry and non-human primates ISH studies, warranting caution when extrapolating these findings across species [66, 67].

Non-hypothalamic regions

A variety of non-hypothalamic regions are also studied for the neural circuitry targets of GLP-1RA actions. Nausea and vomiting are among the most common side effects of GLP-1R agonists. The area postrema (AP) is a circumventricular organ of the hindbrain with a leaky blood-brain barrier, previously identified as a region associated with nausea and vomiting [100,101]. GLP-1R is expressed in the AP and nucleus of the solitary tract (NTS) located in the hindbrain, and c-Fos expression after GLP-1RA injection was apparent in hindbrain GLP-1R cells, with further studies demonstrating these cells' role in mediating GLP-1RA actions [59,96,102,103].

A recent study distinguished the hindbrain neural circuits that mediate satiety and aversion. NTS GLP-1R neurons, sensitive to nutritive stimuli, induced satiety without aversion, whereas AP GLP-1R neurons elicited strong nausea-like behavior in mice. Ablation of AP GLP-1R neurons decreased aversion while maintaining appetite suppression, indicating the possibility of future incretin drugs that can reduce nausea by curbing the aversion pathway [104].

The lateral septum (LS) is also one of the regions known to have high expression of GLP-1R [105,106]. Direct injection of GLP-1RA into the LS reduced overnight chow and HFD intake [107]. Moreover, stimulation of LS GLP-1R neurons reduced food intake, both in an acute and chronic manner, while inhibition increased food intake [108,109]. Systemic liraglutide administration activated LS GLP-1R neurons, and the knockdown of GLP-1Rs in the LS mitigated the anti-obesity effects of liraglutide. Interestingly, unlike DMH GLP-1R neurons, calcium signals of LS GLP-1R neurons decreased at initiation of food consumption [109]. Recent studies have also shown that LS GLP-1R can play a role in mitigating cocaine-induced locomotion and cocaine conditioned place preference [110]. Indeed, i.p. injection of exenatide dampened cocaine-driven septal dopamine elevation, mediated by postsynaptic GLP-1R signaling that retrogradely regulates presynaptic dopamine transporter function [106].

ONGOING FUTURE STUDIES OF GLP-1R AGONISTS

Ongoing studies imply that the usage of GLP-1R agonists can be expanded to other areas, beyond their conventional roles in controlling food intake or energy balance. GLP-1RAs are being studied for their significant associations with reduced risks of various cardiovascular diseases, neuropsychiatric or substance use disorders, infectious illnesses and respiratory conditions, indicating their potential for broader therapeutic applications [111]. Notably, GLP-1R agonists have recently been suggested to have a role in mitigating reward-seeking. A vast number of preclinical and clinical studies have provided evidence for the potential role of GLP-1R agonists in modulating reward-seeking of food, alcohol, cocaine, and amphetamine, offering the possibility of a novel therapeutic alternative for treating addiction [112]. Randomized controlled clinical trials investigating the use of semaglutide in patients with alcohol use disorders (AUD) and comorbid obesity are currently underway, based on the potential of GLP-1R agonists for AUD treatment [113]. More studies are needed to clarify the underlying mechanism of drug and GLP-1 actions on reward circuits.

Recently, novel drugs combining GLP-1R agonism with other options, beyond the forementioned dual or triple agonist drugs, are being developed to maximize efficacy and minimize adverse effects in obesity and diabetes treatment. For instance, combinations of GLP-1R agonists with amylin analogues or peptide YY (PYY) analogues are currently undergoing clinical trials [114]. In addition, in preclinical stages, a combination of GLP-1R agonism with N-methyl-D-aspartate (NMDA) receptor antagonism (GLP-1-MK-801) has been developed [115]. Furthermore, small molecule oral agonists such as danuglipron are also under development, highlighting the potential for improved patient compliance through non-injectable delivery forms [116].

Several challenges remain to be addressed. The presence of

non-responders to GLP-1R therapy continues to complicate treatment outcomes, underscoring the need for a deeper understanding of individual variability in response [117,118]. Additionally, the issues of weight regain and altered metabolic outcomes following drug discontinuation emphasize the importance of long-term studies investigating the impacts of the hormonal and CNS on weight regain to optimize safety and efficacy [119,120].

In conclusion, the DMH is a key target of GLP-1RAs, mediating pre-ingestive satiation, which is a cognitive process. GLP-1R neurons in the DMH and other hypothalamic nuclei regulate multiple aspects of eating behavior, presenting potential therapeutic targets for GLP-1R-based therapies and other drug candidates.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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