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LEADING ARTICLE

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) in the Brain–Adipocyte Axis

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Abstract The complexity of neural circuits that control food intake and energy balance in the hypothalamic nuclei explains some of the constraints involved in the prevention and treatment of obesity. Two major neuronal populations present in the arcuate nucleus control caloric intake and energy expenditure: one population co-expresses orexigenic agouti-related peptide (AgRP) and neuropeptide Y and the other expresses the anorexigenic anorectic neuropeptides proopiomelanocortin and cocaine- and amphetamine-regulated transcript (POMC/CART). In addition to integrating signals from neurotransmitters and hormones, the hypothalamic systems that regulate energy homeostasis are affected by nutrients. Fat-rich diets, for instance, elicit hypothalamic inflammation (reactive activation and proliferation of microglia, a condition named gliosis). This process generates resistance to the anorexigenic hormones leptin and insulin, contributing to the genesis of obesity. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) have increasingly been used to treat type 2 diabetes mellitus. One compound (liraglutide) was recently approved for the treatment of obesity. Although most studies suggest that GLP-1RAs promote weight loss mainly due to their inhibitory effect on food intake, other central effects that have been described for native GLP-1 and some GLP-1RAs in rodents and humans encourage future clinical trials to explore additional mechanisms that potentially underlie the beneficial effects observed with this drug class. In this article we review the most relevant data exploring the mechanisms involved in the effects of GLP-1RAs in the brain–adipocyte axis.

Key Points

In addition to its well known action in glucose homeostasis GLP-1R can also modulate other important functions in the body, including cardiovascular, imune and nervous, and the control of caloric intake and energy expenditure.

Experimental studies show that GLP-1RA promotes increased activity of brown adipose tissue through the activation of hypothalamic neurons.

GLP-1RA are amongst the most promising agents that can act in the recruitment of brown adipose tissue in humans.

Subcutaneously administered GLP-1RA have established efficacy in the treatment of obesity in adult patients.

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1 Introduction

Intestinal hormones have become an important therapeutic target in the management of obesity due to their involvement in energy homeostasis and satiety [1]. Among the intestinal L cell peptides, glucagon-like peptide-1 (GLP-1) has been highlighted because of the success of its recent

clinical use in the treatment of diabetes mellitus and obesity [2]. GLP-1 receptor (GLP-1R) signaling contributes to increased glucose-dependent insulin secretion, β cell proliferation, islet size, portal glucose sensing, and postprandial lipid metabolism [3]. Moreover, it regulates cardiovascular function, glucose concentration, gut motility, immune function, neuronal physiology and repair, appetite, and energy expenditure, and therefore impacts on body mass control [3].

In addition to its extensively studied actions in peripheral tissues, studies have evaluated the distribution of GLP-1R in the central nervous system (CNS) of rodents, non-human primates, and humans, showing that it is widely diffused to multiple CNS neurons including neurons of the arcuate nucleus (ARC), which are crucial for the control of energy balance (Fig. 1) [4, 5]. Accordingly, one of the most remarkable central effects of GLP-1R signaling occurs in neuronal populations involved in the control of caloric intake by promoting anorexigenic effects. Furthermore, the activation of GLP-1R signaling in the ventromedial hypothalamus (VMH) can also control energy expenditure by promoting food intake-independent weight loss by inducing brown adipose tissue (BAT) thermogenesis and browning through a sympathetic drive to BAT [6]. BAT is a thermogenic mammalian organ composed of multilocular adipocytes specialized in generating heat instead of accumulating energy [7]. Besides the action of the GLP-1R agonist (GLP-1RA) on the brain–adipocyte axis, there is also recent evidence that its direct action (independent of its CNS actions) in the white adipose tissue induces browning and enhances the lipolytic capacity and mitochondrial biogenesis [8].

Despite the rapidly increasing understanding of the central regulation of whole-body energy homeostasis, translating this knowledge into more efficient therapies for obesity has proved challenging. Most effort has been directed towards development of anorexigenic drugs [9]; however, compounds that exert additional effects, such as regulation of energy expenditure, are expected to act with larger efficiency. Thus, following the identification of active BAT in adult humans and the demonstration that certain depots of white adipose tissue can undergo browning, there has been recent interest in the development of approaches that induce BAT activity and promote browning [10]. Such strategies have undergone a rapid development due to translational research, with the emergence of new pharmacological agents. Among the new agents, GLP-1RAs are the most promising.

In this review, we focus on the actions of GLP-1RAs in the CNS, with emphasis on the contribution of GLP-1 to reset energy balance by promoting BAT recruitment.

2 Structure and Physiology of Glucagon-Like Peptide-1 (GLP-1)

The incretin hormone GLP-1 is derived from the processing of proglucagon that occurs in ileal L cells and the nucleus tractus solitarius (NTS) [11]. During meals, GLP-1 is secreted in two stages: a first peak occurs approximately 15 min after the beginning of the meal, when food in the stomach and in the initial portions of the intestine stimulates the release of hormones, such as glucose-dependent insulinotropic polypeptide (GIP), which acts by vagal pathways to stimulate L cells [12]; a second peak occurs after direct stimulation of L cells by nutrients [13].

The active forms of GLP-1 have a half-life of less than 2 min. Immediately after being secreted, GLP-1 enters the capillaries and is rapidly degraded by dipeptidyl peptidase-4 (DPP-4). Despite the loss of its insulinotropic effect, the GLP-1 products of DPP-4 catalysis exert other actions, such as suppression of hepatic glucose production and antioxidant activity in the cardiovascular system [14]. The effects of the active forms of GLP-1 are mediated by a G protein-coupled receptor, GLP-1R, which is expressed in several sites, including enteric and vagal nerves, the stomach, pancreas, intestine, and various brain regions [15].

Because of its very short half-life, native GLP-1 cannot be used for therapeutic purposes. The GLP-1RAs are resistant to DPP-4 degradation, have longer half-lives, and have been developed for the treatment of patients with type 2 diabetes mellitus (T2DM) [15]. More recently, they have been used for the treatment of obesity [16]. Among the GLP-1RAs, exenatide is the synthetic version of exendin-4, a molecule identified in the Gila monster salivary gland whose amino acid sequence shares 53% identity with human GLP-1; its relatively short half-life requires twice-daily administration [17]. Lixisenatide is also a synthetic version of exendin-4 that has modifications consisting of the deletion of one proline residue and the addition of six lysine residues at the C-terminal end, which increases its half-life and its binding affinity to GLP-1R. Although lixisenatide is administered once a day, it is still considered a short-acting GLP-1RA [18].

Some of the molecules that are considered to be long-acting GLP-1RAs are briefly described here and in Table 1. Long-acting exenatide is formulated in microspheres of poly-(d,l-lactide-*co*-glycolide) for once-weekly administration [19]. Liraglutide is another long-acting GLP-1RA that is administered once daily. It is identical to the native GLP-1, except for the replacement of lysine with arginine at position 34 and

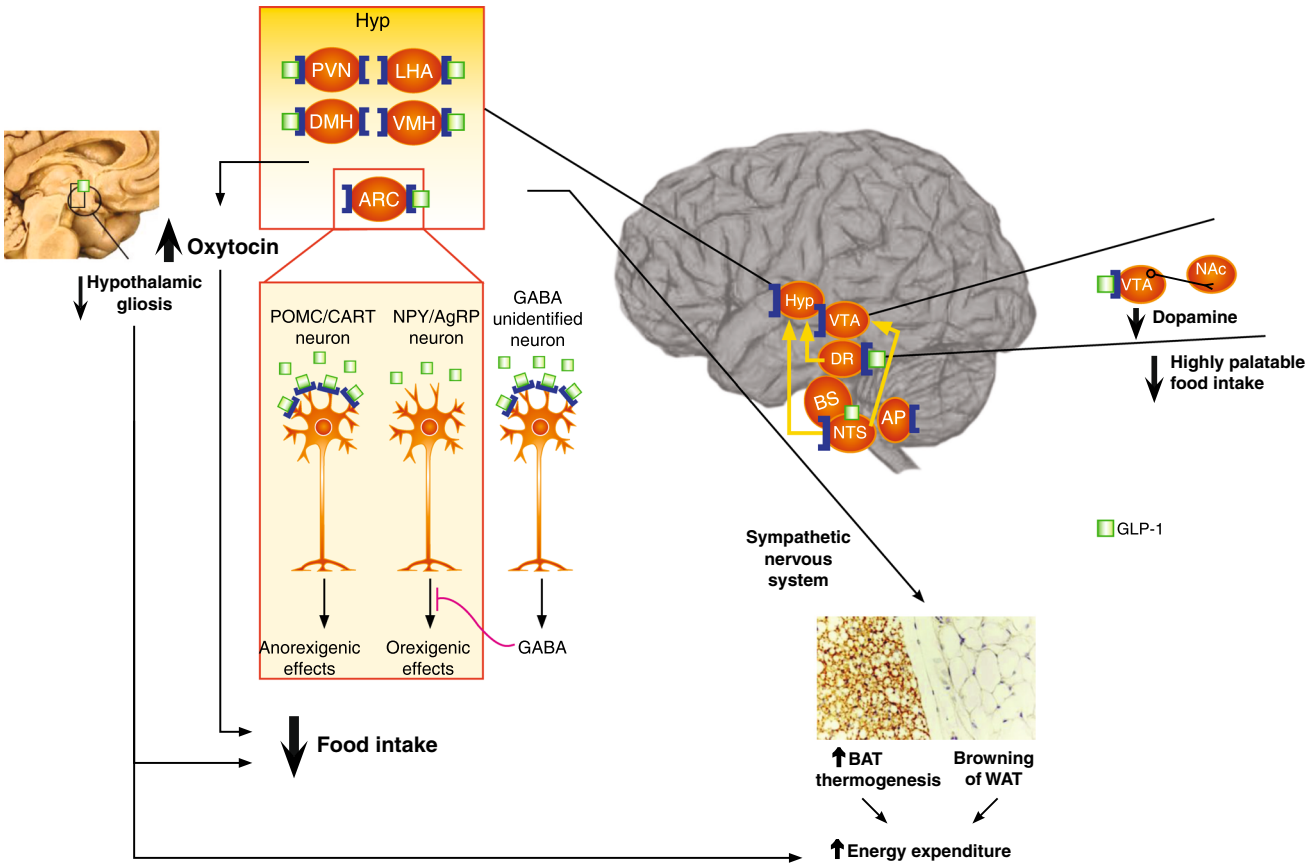

Fig. 1 Glucagon-like peptide-1 (GLP-1) action in the central nervous system. The illustration of the whole brain depicts the main regions containing binding sites (GLP-1 receptors [GLP-1R], shown in *blue*) for GLP-1 (shown in *green*): hypothalamus (Hyp), ventral tegmental area (VTA), dorsal raphe nucleus (DR), brainstem (BS), nucleus of the solitary tract (NTS), and area postrema (AP). In the Hyp (*upper box*), GLP-1R has been detected in the paraventricular nucleus (PVN), lateral hypothalamic area (LHA), dorsomedial hypothalamus (DMH), ventromedial hypothalamus (VMH), and arcuate nucleus (ARC). Acting in the Hyp, GLP-1 can increase oxytocin and reduce hypothalamic gliosis (details in the *right-hand side* of the figure). In the ARC (*box in the middle of the figure*), GLP-1 reduces food intake by acting directly in proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons and indirectly in neuropeptide Y (NPT)/agouti-related peptide (AgRP) neurons; the action in NPY/AgRP neurons is believed to occur through a hitherto unidentified γ-aminobutyric acid (GABA)-ergic neuron. In addition, acting in the Hyp, GLP-1 can increase energy expenditure by stimulating brown adipose tissue (BAT) activity and promoting browning of white adipose tissue (WAT) (details in the *bottom right-hand side* of the figure). The hypothalamic actions of GLP-1 increasing oxytocin and reducing gliosis can also contribute to reduction of food intake and increasing energy expenditure. In the VTA, GLP-1 can reduce dopamine, which contributes for reduction of consumption of highly palatable foods (details in the *right-hand side* of the figure). ↑ indicates increase, ↓ indicates decrease

the attachment of a palmitic acid to lysine at position 26. These modifications result in increased self-association, binding to albumin, and a longer half-life [20]. Dulaglutide is a once-weekly GLP-1RA consisting of the fusion of two identical sequences (the N-terminal portion of the native GLP-1) covalently bound by a peptide linker to the Fc component of a modified human immunoglobulin G4 heavy chain [21]. Albiglutide is also a once-weekly GLP-1RA consisting of two copies of a 30 amino acid sequence of modified human GLP-1 (replacement of alanine with glycine at position 8) fused with human albumin [22]. The most relevant metabolic effects expected from the GLP-1RA are summarized in Table 2.

3 GLP-1 Receptor Agonists (GLP-1RAs) in the Central Nervous System and the Energy Balance in Rodents

GLP-1 is synthesized in NTS neurons that project to GLP-1R-expressing regions, such as the paraventricular nucleus (PVN) and ARC [23]; in the latter, proopiomelanocortin (POMC) neurons are present and it is believed that endogenous GLP-1 induces satiety, affecting both anorexigenic and orexigenic signaling pathways. Activation of GLP-1R in the PVN stimulates the release of oxytocin, which exerts anorexigenic effects [13]. There are also NTS neurons projecting to the ventral tegmental area, which is a reward center. Endogenous GLP-1 acts in GLP-1Rs located

Table 1 Glucagon-like peptide-1-based therapies available on the market for the treatment of diabetes mellitus and obesity

GLP-1-based therapies	Usual dose
Short-acting GLP-1RAs	
Exenatide twice daily	5.0 μg/10.0 μg [57]
Lixisenatide once daily	10.0 μg/20.0 μg [58]
Long-acting GLP-1RAs	
Liraglutide once daily	1.8 mg/3.0 mg[a] [59]
Exenatide once weekly	2.0 mg [60]
Albiglutide once weekly	30.0 mg/50.0 mg [61]
Dulaglutide once weekly	0.75 mg/1.5 mg [62]

GLP-1 glucagon-like peptide-1, *GLP-1RA* glucagon-like peptide-1 receptor agonist

[a] Liraglutide was approved as an adjunct treatment for long-term weight management in adults. The recommended dose is 3.0 mg daily, other than the maximum dose of 1.8 mg for the treatment of diabetes

in this region and reduces the intake of highly palatable foods by suppressing mesolimbic dopamine signaling, which controls the pleasure-directed acquisition of food [24].

The GLP-1 derived from intestinal L cells may also communicate with the CNS through GLP-1Rs located in fibers innervating the portal vein or in the vagus nerve. However, the contributions of the peripheral nervous system and the CNS in the mediation of the anorexic effects of the GLP-1RAs is still not completely understood [23]. Experimental studies suggest that liraglutide exerts its anorexigenic but not hypoglycemic effects through CNS receptors, rather than through vagus nerve receptors [25]. Secher et al. [26] showed that liraglutide-dependent weight loss relies on its binding to GLP-1Rs located mainly in POMC/CART (cocaine- and amphetamine-regulated transcript) anorexigenic neurons in the ARC, but an indirect inhibitory effect of agouti-related peptide (AgRP) orexigenic neurons via γ-aminobutyric acid (GABA)-ergic signaling was also observed.

In addition to the studies demonstrating the central effects of GLP-1 and its analogs on satiety and reduction of energy intake, there are studies showing other central effects of GLP-1 involving BAT. BAT regulates energy expenditure through a process known as adaptive thermogenesis, in which uncoupling protein-1 (UCP1, a BAT marker) uncouples mitochondria respiration to generate heat instead of adenosine triphosphate [7].

Intracerebroventricular (ICV) infusion of native GLP-1 promotes not only a reduction in food intake and body weight, but also an increase in BAT thermogenesis induced by increased sympathetic nervous system (SNS) activity [6]. In addition, the ICV infusion of exendin-4 increases CNS activity, promotes BAT activation and white adipose tissue browning, and increases BAT glucose and triglyceride uptake [27]. Peripheral exendin-4 administration also increases energy expenditure and BAT thermogenesis [28]. Similarly, the ICV infusion of liraglutide stimulates BAT thermogenesis and white adipose tissue browning. These effects depend on the reduction of 5′ adenosine monophosphate-activated protein kinase (AMPK) activity in the VMN [29]. Together, these results suggest that GLP-1R signaling contributes to BAT thermogenic capacity. However, the increase in BAT recruitment apparently does not induce weight loss during long-term subcutaneous treatment with liraglutide in mice (Fig. 1) [30].

In addition to the expression in areas related to satiety, GLP-1R is present in several other areas in the CNS. Glial cells only express GLP-1R when activated, in response to inflammation [31]. Farr et al. [4] evaluated the distribution of GLP-1R in human brains and demonstrated its presence in all neurons of the parietal cortex, in the ARC, PVN, VMN, area postrema, dorsal motor nucleus of the vagus in the medulla oblongata, and in the NTS. They also confirmed the lack of expression of GLP-1R in glial cells [4].

The identification of GLP-1R in other regions of the CNS provided a further advance in the understanding of the role played by GLP-1/serotonin cross-talk in the regulation of homeostatic control of body mass. Anderberg et al. [32] demonstrated that long-term stimulation with GLP-1RAs promoted an increase in the expression of serotonergic receptors in the hypothalamus. In addition, they showed that the 5-hydroxytryptamine 2A (5-HT_{2A}) receptor is crucial for GLP-1RA-induced weight loss after exendin-4 ICV injection, such as peripheral injection of liraglutide in rats. The authors identified that the dorsal raphe nucleus (DR) has serotonergic neurons that secrete serotonin to hypothalamic nuclei and that GLP-1R activation promotes the activity of DR serotonin neurons. Thus, they provided evidence that serotonin is crucial for controlling feeding and weight loss induced by GLP-1R activation [32].

The first studies evaluating the effects of GLP-1 and exendin-4 in neuronal cells demonstrated their ability to promote neurite outgrowth (a similar effect to that observed with the neurotrophic nerve growth factor) and to protect cultured neurons against glutamate-induced apoptosis [33]. Such reports inspired further studies to evaluate the effects of GLP-1RAs in animal models of degenerative neurological diseases.

Parkinson disease is characterized by the degeneration of nigrostriatal dopamine-producing neurons. Intraperitoneal exendin-4 was shown to interrupt and even revert the progression of drug-induced nigrostriatal lesions [34]. In a rodent model of stroke, exendin-4 interrupted microglia infiltration and increased the stem cell proliferation elicited by middle cerebral artery transient occlusion [35].

The ability of exendin-4 and liraglutide administered subcutaneously to promote proliferation of progenitor cells

Table 2 Expected metabolic effects of the glucagon-like peptide-1 receptor agonists[a]

Biological effects	Clinical benefits/comments
Pancreatic effects	
↑ Insulin and ↓ glucagon secretion (not during hypoglycemia)	There is robust evidence of enhancement of β cell function [63–66]
↑ β cell proliferation (in rodents)	GLP-1RA preserves the β cell mass and decreases susceptibility to cytokines [67, 68]
↓ β cell apoptosis (in rodents; needs confirmation in humans)	GLP-1RA protects β cells by suppressing tacrolimus-induced oxidative stress and apoptosis [69, 70]
↓ Oxidative stress-induced β cell damage (in rodents)	GLP-1RA treatment decreased ROS production through Nrf2 signaling [71]
↓ Glucagon secretion	The mechanisms are not completely understood. GLP-1 inhibits glucagon secretion through somatostatin-dependent mechanisms [72]
Extra-pancreatic effects	
Cardiovascular protection	GLP-1 promotes a myriad of cardiovascular actions (vasodilatation, plaque stability, decrease platelet aggregation, lipid profiles, ischemic injury, blood pressure, and inflammation) and increases endothelial function and left ventricular function [73, 74]
Delay gastric emptying	↑ Satiety and improve postprandial glycemia. The deceleration of gastric emptying is subject to rapid tachyphylaxis, which results in an attenuation of the effect on glycemic control after long-term use in humans [75]
Control of ovarian cancer cells proliferation	GLP-1RA inhibited growth of ovarian cancer cells through inhibition of the PI3K/Akt pathway [76]
Inhibition of apoptosis of renal tubular epithelial cells and increased natriuresis	GLP-1RA infusion stimulates natriuretic response [77]; in addition, GLP-1RA impairs apoptosis induced by high glucose in renal tubular epithelial cells [78]
↓ Hepatic steatosis and ↑ hepatic insulin sensitivity	GLP-1RA improves hepatic insulin sensitivity, impairs hepatic glucose production. and inhibits hepatic steatosis [79, 80]
↓ Inflammation	There is GLP-1R mRNA expression in many subpopulations of immune cells such as regulatory T cells and thymocytes, suggesting that GLP-1R signaling has a role in the regulation of immune response [81]
Central effects	
Stimulus of reward centers	↓ Intake of highly palatable foods [82–84]
Stimulatory effect on anorexigenic neurons and inhibitory effect on orexigenic neurons	↑ Satiety and consequent weight loss [26]
Increase brown adipose tissue thermogenesis (in rodent; needs confirmation in humans)	↑ Energy expenditure and consequent weight loss [29]
Neuroprotective action on degenerative diseases, which should be an important use in the coming years	Growing evidence has shown that GLP-1RA has neuroprotective action in NDs. These two reviews assess their promising role as a new treatment for NDs [31, 85]

GLP-1 glucagon-like peptide-1, *GLP-1R* glucagon-like peptide-1 receptor, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *mRNA* messenger RNA, *NDs* neurodegenerative diseases, *Nrf2* nuclear factor erythroid 2-related factor 2, *ROS* reactive oxygen species, ↑ indicates increase, ↓ indicates decrease

[a] It is not the purpose of this review to detail the biological actions of GLP-1 in multiple sites, for which there are recent good reviews [3]

located in the dentate gyrus in the hippocampus has been tested. Both GLP-1RAs further increased progenitor cells proliferation, suggesting that they may be promising drugs for the treatment of neurodegenerative diseases [36]. Lixisenatide administered intraperitoneally has also been shown to increase neurogenesis in the dentate gyrus [37].

Liraglutide was evaluated in a mouse model of Alzheimer disease in an intermediate stage of disease progression; it improved learning and memory and decreased amyloid deposition and chronic inflammation [38]. In another study conducted in mice with Alzheimer disease in the final stage, intraperitoneal liraglutide improved spatial memory, reduced amyloid deposition and inflammation, and increased dentate gyrus neurogenesis, suggesting that, besides exerting preventive effects, this GLP-1RA may reverse some of the key pathological findings of Alzheimer disease. Currently, liraglutide is being evaluated in humans with mild cognitive impairment [39].

A recently published study explored the neuroprotective effects of subcutaneous liraglutide in the ARC neuronal damage (gliosis and upregulation of the pro-apoptotic gene *Bax*) induced by a high-fat diet (HFD). In addition to

promoting weight loss, activating POMC anorexigenic neurons, and increasing leptin sensitivity, liraglutide reduced gliosis and increased expression of the anti-apoptotic gene *Bcl2*. These effects could be attributed to treatment with liraglutide and not to weight loss, since they were not observed in the group of animals that lost weight without receiving the GLP-1RA [40]. Similar results of gliosis reduction have been shown after subcutaneous administration of exendin-4 to mice on HFDs [41]. These results demonstrate the potential of GLP-1RAs not only to promote weight loss and metabolic improvement but also to act directly on the hypothalamic inflammation.

4 Clinical Effects in Humans

4.1 Peripheral Effects

In 1998, Flint et al. [42] demonstrated in healthy volunteers that infusion of native GLP-1 during breakfast increased satiety and fullness and reduced the caloric intake in the next meal by 12%. The clinical trials conducted with GLP-1RAs in T2DM patients have demonstrated these beneficial effects. A meta-analysis of 21 clinical studies showed a weighted mean difference in body weight of –2.9 kg (95% confidence interval [CI] –3.6 to –2.2) with the maximum dose of each one of the GLP-1RAs [43]. These positive effects on weight loss together with the experimental evidence suggesting that liraglutide exerts its effects directly in the CNS raise the question of whether GLP-1RAs of higher molecular weights, such as dulaglutide and albiglutide, would be as effective as liraglutide in promoting weight loss [23].

A phase III, randomized, double-blind, placebo-controlled trial, which was open-label for the comparator liraglutide group, evaluated dulaglutide monotherapy (0.75 mg) versus placebo versus once-daily liraglutide in individuals with T2DM. Despite the positive results regarding glycemic control, in which dulaglutide was superior to placebo and non-inferior to liraglutide, there was no significant weight loss in any group after 26 weeks. This could be explained by the leanness of the Japanese population at the baseline, by the anabolic effect of improved β cell function, or even because of the low dose employed in this trial [44].

Another phase III, randomized, open-label, non-inferiority, head-to-head trial, AWARD-6, evaluated dulaglutide (1.5 mg) versus liraglutide (1.8 mg) in patients with T2DM. The once-weekly dose of dulaglutide was non-inferior to once-daily liraglutide in relation to glycemic control. There was significant weight loss in both groups; however, the magnitude of the body mass reduction was significantly greater in the liraglutide group [45]. Similar results were seen in the non-inferiority HARMONY 7 trial, which compared liraglutide versus albiglutide [46]. Thus, two head-to-head trials demonstrated that liraglutide was superior for weight loss. However, the explanation for this is not clear. One possibility is that the difference in efficiency in weight loss is due to a higher uptake of liraglutide in the CNS. Another possibility is the existence of differences in the effect of high molecular weight versus low molecular weight peptides on GLP-1R signaling in the CNS [23]. Experimental evidence indicated that while peptides bound to albumin do not penetrate the CNS, peripheral activation of the GLP-1R system would be coupled to neuronal activation and central effects of gastric emptying and decreased food intake, independent of direct exposure on the CNS [47].

The effects of GLP-1 and its analogs on energy expenditure are still inconsistent [48]. An evaluation of T2DM patients using liraglutide for 4 weeks detected a trend towards an increased basal energy expenditure [49], but this effect was not confirmed in subsequent longer studies [50, 51].

A randomized, double-blind, placebo-controlled, crossover study investigated the effects of liraglutide 1.8 and 3.0 mg for 5 weeks in obese non-diabetic patients. One-hour gastric emptying was 13 and 23% slower than placebo, respectively. Liraglutide doses similarly increased postprandial satiety and fullness and reduced hunger and prospective food consumption [52]. Additional studies are needed to define the participation of increased energy expenditure on the weight loss induced by GLP-1RAs.

4.2 Brain Effects

Neuroimaging studies have been employed in attempts to explore the central mechanisms of action of GLP-1 and its analogs. Increasing GLP-1 in the postprandial period correlates with the increase in blood flow in brain areas related to satiety, such as the hypothalamus and areas of the prefrontal cortex [53]. De Silva et al. [54] employed functional magnetic resonance imaging (fMRI) and showed that GLP-1 infusion in fasting healthy volunteers of normal weight attenuated neuronal activity in areas related to reward processing and hedonic feeding to the same extent as a meal (Table 3).

fMRI was also used to evaluate the central effects of GLP-1RAs. van Bloemendaal et al. [55] demonstrated that obese subjects presented increased activation in appetite and reward-related brain areas in response to food images. This was attenuated by an intravenous injection of exenatide [55]. Farr et al. [4] treated 21 T2DM patients with increasing doses of liraglutide (up to 1.8 mg) for 17 days. In comparison to placebo, liraglutide reduced activation of the parietal cortex and of insula and putamen (areas

Table 3 Effects of glucagon-like peptide-1 receptor agonists on the central nervous system in humans—imaging studies

Compound	Area	Imaging/sample	Comparison	Summary	References
Endogenous GLP-1	Homeostasis	fMRI with food pictures to assess brain activity in reward system areas/ $n = 40$	Fasted condition vs. fed condition	Dietary intake and the consequent increase in endogenous GLP-1 levels reduced the activation of the insula region comparing diabetic subjects versus lean subjects	[86]
Exenatide	Homeostasis	fMRI with food pictures to evaluate hypothalamic connectivity/$n = 24$	Responders vs. non-responders after exenatide infusion	Among obese volunteers who had an anorexigenic effect after exenatide, the treatment with exenatide promoted higher hypothalamic connectivity than did placebo	[82]
	Homeostasis	fMRI in response to chocolate milk or tasteless solution to study brain responses to anticipation/ $n = 48$	Obese individuals with T2DM, and obese individuals and lean individuals with normoglycemia	GLP-1 activation decreased food reward	[84]
	Homeostasis	fMRI with food pictures to evaluate cerebral activity in reward-related brain areas/$n = 48$	Obese subjects with T2DM, and obese individuals and lean individuals with normoglycemia	Exenatide blunted food-related brain activation in T2DM patients and obese subjects in reward-related brain areas	[55]
	Homeostasis	[(18)F]2-fluoro-2-deoxy-d-glucose-PET/CT/$n = 15$	Effect of single dose of exenatide on cerebral glucose metabolism	Exenatide increased glucose metabolism in brain areas related to glucose homeostasis, appetite, and food reward	[87]
	Homeostasis	fMRI with food pictures/ $n = 20$	Obese vs. lean individuals with and without exenatide infusion during the test	Exenatide blunted the fMRI signal in amygdala, insula, hippocampus, and frontal cortex in obese individuals but not in lean individuals	[88]
	Homeostasis	fMRI with food pictures to assess emotional eating and reward system/$n = 48$	Obese subjects with T2DM, and obese individuals and lean individuals with normoglycemia	Emotional eaters had a modified pattern of responses to food cues in areas of the reward system, and exenatide did not modify those responses	[83]
	Parkinson disease	$^{[123I]}$FP-CIT SPECT scans to assess presynaptic dopaminergic deficit/ $n = 10$	Before and after 12 weeks of exenatide	Exenatide promoted minimal changes in all ganglia subregions in $^{[123I]}$FP-CIT activity[a]	[89]
Liraglutide	Homeostasis	fMRI with food pictures/ $n = 21$	Individuals with T2DM treated with liraglutide vs. placebo during 17 days	Liraglutide decreased brain activation in parietal cortex and areas of the reward system (insula and putamen) after food cues	[4]
	Homeostasis	fMRI in response to food cues/$n = 20$	Individuals with T2DM treated with liraglutide vs. placebo during 17 days	Liraglutide reduced activation of the attention- and reward-related insula in response to food cues and this change was positively correlated with increased GIP levels	[90]
	Homeostasis	fMRI in response to food cues/$n = 20$	Obese and diabetic subjects treated with liraglutide or insulin glargine during 12 weeks	Liraglutide promoted reduced responses to food cues in insula and putamen in relation to insulin after 10 days but not after 12 weeks	[91]

fMRI functional magnetic resonance imaging, *GIP* glucose-dependent insulinotropic polypeptide, *GLP-1* glucagon-like peptide-1, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *T2DM* type 2 diabetes mellitus, *[(18)F]2-fluoro-2-deoxy-d-glucose-PET/CT* [18F]-2-fluoro-2-deoxy-d-glucose–positron emission tomography/computed tomography, *$^{[123I]}$FP-CIT SPECT* 123 55 I-Fluoropropyl-2-beta-carbomethoxy-3-beta(4-iodophenyl) nortropane/single photon emission computerized tomography

[a] GLP-1RAs have demonstrated important effects in pre-clinical models of Parkinson disease and other neurodegenerative diseases not reviewed here [92]

involved in the reward system) in response to pictures of highly palatable foods [4].

The observation that liraglutide promotes relevant weight loss led to the approval of the daily dose of 3.0 mg for the treatment of obesity [16]. The efficacy of liraglutide 3.0 mg was evaluated in T2DM patients with a body mass index (BMI) $\geq$27 kg/m^2 treated with diet and exercise alone or in combination with antidiabetic drugs. This was a randomized, double-blind study with three arms of treatment: placebo and liraglutide 1.8 and 3.0 mg. The primary endpoints were relative change in weight and the proportion of participants losing $\geq$5 or $\geq$10% of baseline weight at week 56. Weight loss was significantly greater with both doses of liraglutide than with placebo for all three primary endpoints. Weight loss was 6.0% (6.4 kg), 4.7% (5.0 kg), and 2.0% (2.2 kg) with liraglutide 3.0 mg, liraglutide 1.8 mg, and placebo, respectively. A weight loss $\geq$5% occurred in 54.3, 40.4, and 21.4% of patients, respectively, and a weight loss $\geq$10% occurred in 25.2, 15.9, and 6.7% of patients, respectively. The safety profile was similar to that described in other clinical trials [56].

The efficacy of liraglutide 3.0 mg as an adjunct to diet and exercise was also evaluated in 3731 non-diabetic patients presenting with a BMI $\geq$27 (in the presence of dyslipidemia or hypertension) or $\geq$30 kg/m^2 treated for 56 weeks. The primary endpoints were the change in body weight and the proportions of patients losing at least 5% and $\geq$10% of their initial body weight. Weight loss was significantly greater with liraglutide than placebo for all primary endpoints. At week 56, the mean weight loss was 8.4 $\pm$ 7.3 kg in the liraglutide group and 2.8 $\pm$ 6.5 kg in the placebo group. Weight loss of at least 5% was observed in 63.2 and 27.1% of the patients, respectively, and weight loss $\geq$10% was seen in 33.1 and 10.6% of the patients, respectively. The most frequently reported adverse events with liraglutide were mild or moderate nausea and diarrhea, both of which were transitory [16].

5 Concluding Remarks

It is believed that GLP-1RAs promote weight loss mainly because of their inhibitory effect on food intake [42]. However, the numerous central effects described for native GLP-1 and for some of the GLP-1RAs in rodents and in humans encourage future clinical trials exploring additional mechanisms that could potentially underlie the beneficial effects observed with this drug class. Among the aspects that deserve special attention, we highlight three: (i) the increased thermogenesis by activation of BAT or browning of the white adipose tissue; (ii) the neuroprotective properties, including the ability to reduce hypothalamic inflammation triggered by HFD; and (iii) the effects on damaged neurons in neurodegenerative diseases. Considering that hypothalamic inflammation directly interferes in neural circuits controlling food intake and energy balance, its reversal could contribute to the restoration of the hypothalamic energy set point.

Authors' contributions BG, JCL, and LAV participated in the concept and drafting of the manuscript, and performed the critical review for intellectual content. All authors read and approved the final manuscript.

Compliance with Ethical Standards

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