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Feature Review

# Glucagon-like Peptide-1 and the Central/Peripheral Nervous System: Crosstalk in Diabetes

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**Glucagon-like peptide-1 (GLP-1) is released in response to meals and exerts important roles in the maintenance of normal glucose homeostasis. GLP-1 is also important in the regulation of neurologic and cognitive functions. These actions are mediated via neurons in the nucleus of the solitary tract that project to multiple regions expressing GLP-1 receptors (GLP-1Rs). Treatment with GLP-1R agonists (GLP-1-RAs) reduces ischemia-induced hyperactivity, oxidative stress, neuronal damage and apoptosis, cerebral infarct volume, and neurologic damage, after cerebral ischemia, in experimental models. Ongoing human trials report a neuroprotective effect of GLP-1-RAs in Alzheimer's and Parkinson's disease. In this review, we discuss the role of GLP-1 and GLP-1-RAs in the nervous system with focus on GLP-1 actions on appetite regulation, glucose homeostasis, and neuroprotection.**

## Introduction

Type 2 diabetes mellitus (T2DM) has become a global health problem that is associated with considerable morbidity and mortality from both microvascular and macrovascular complications [1]. The epidemic surge of T2DM closely parallels that of obesity [2,3], with the link being tissue fat overload and lipotoxicity [4,5]. Neurologic complications involving the central nervous system (CNS) have assumed added importance, especially in elderly T2DM individuals who are more prone to develop cognitive dysfunction than the nondiabetic individuals [6].

The incretin glucagon-like peptide-1 (**GLP-1**; see Glossary) maintains glucose homeostasis by augmenting insulin secretion and inhibiting glucagon secretion [7–11]. In prediabetic and diabetic individuals, meal-stimulated GLP-1 secretion is impaired [12], and the diabetic beta cell is resistant to physiological levels of endogenous GLP-1 [13]. However, higher GLP-1 concentrations can overcome beta-cell resistance and produce a normal or near-normal insulin secretory response [14,15]. In rats, hyperglycemia causes downregulation of GLP-1 receptor (GLP-1R) expression on beta cells resulting in '**GLP-1 resistance**' [16]. In many T2DM patients, GLP-1 secretion is normal, particularly after an oral glucose tolerance test (OGTT), yet insulin secretion is impaired, indicating resistance to GLP-1 [17,18], which can be demonstrated by infusion of physiological amounts of GLP-1 [19]. Beta-cell resistance to the incretin hormone glucose-dependent insulinotropic polypeptide also has been demonstrated in T2DM individuals [14,15,19].

Recently, attention has focused on the role of GLP-1 in brain metabolism and function. Poorly controlled type 2 and type 1 diabetic patients frequently develop peripheral neuropathy that is associated with gray matter volume loss localized to regions involved in somatosensory

## Trends

Glucagon-like peptide-1 (GLP-1) is secreted in response to meals and maintains glucose homeostasis by augmenting insulin secretion and inhibiting glucagon secretion.

GLP-1 is important in the regulation of neurologic and cognitive functions.

The GLP-1 receptor is expressed throughout the human cerebral cortex and the hypothalamus, hippocampus, amygdala, caudate putamen, and globus pallidum.

GLP-1 receptor agonists that cross the blood–brain barrier can directly impact brain function independent of vagal afferent stimulation.

GLP-1 receptor agonists activate GLP-1 receptors on cranial and peripheral nerves improving both central and peripheral neuronal functions.

GLP-1 receptor agonists reduce cerebral infarct volume and ischemia-induced damage.

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perception [20]. T2DM patients may also develop cortical and subcortical atrophy involving multiple brain regions and functions [21]. These changes in cerebral histology and function have been related to chronic hyperglycemia and impaired cerebral glucose metabolism [22,23]. In the ACCORD-MIND study, a close association between increased HbA1c and cognitive impairment was documented [23], and patients with T2DM had an increased risk of developing neurodegenerative diseases such as Alzheimer's disease (AD) [24] and Parkinson's disease (PD) [25]. Diabetes-related changes in cardiovascular function (e.g., impaired endothelial function, left ventricular dysfunction, coronary artery disease, and atherosclerosis) also have been associated with reduced cognitive function [26]. Because GLP-1Rs are found diffusely throughout the CNS and peripheral nervous system (PNS) [27–30], it has been suggested that GLP-1 and GLP-1R agonists (**GLP-1-RAs**) might exert benefits on the CNS and PNS beyond the improvement in glycemic control. GLP-1Rs in the CNS are thought to be targets of GLP-1-producing neurons in the brain stem.

In this review, we will discuss the effects of GLP-1 and its analogs on the CNS and PNS, with emphasis on glucose metabolism, appetite regulation, and neuroprotection.

## Mechanism of Action of GLP-1: Role of CNS versus PNS

GLP-1 exerts its function through binding to GLP-1R, a member of the glucagon receptor family of G protein-coupled receptors [31,32]. Expression of GLP-1R in the human brain was first reported by Wei and Mojsov [29] using RT-PCR. GLP-1R expression has been detected throughout the human cerebral cortex and the hypothalamus, with particularly high density in the ventromedial hypothalamus, paraventricular nucleus (PVN), and arcuate nucleus (ARC), hippocampus, thalamus, amygdala, caudate putamen, and globus pallidum, using *in situ* hybridization [27,28,30,33]. Goke *et al*. [34] performed receptor autoradiography of tissue sections of the rat brain and demonstrated that the highest density of [$^{125}$I]GLP-1 binding sites was found in the lateral septum, subfornical organ, thalamus, hypothalamus, interpeduncular nucleus, posterodorsal tegmental nucleus, area postrema, inferior olive, and nucleus of the solitary tract (NST). They hypothesized that the central GLP-1Rs represent the same receptor isoforms as the peripheral GLP-1Rs [30,34] in agreement with the results of Wei and Mojsov [29].

Recently, GLP-1R mRNA expression was found in hypothalamic nuclei in humans, including the PVN and infundibular nucleus; in T2DM, cerebral GLP-1R activation was found to be decreased compared with control patients [35]. GLP-1Rs also have been found in the human pancreas, heart, stomach, intestine, lung, kidney, and enteric NS and CNS using *in vitro* autoradiography [36]. Again, pancreatic, cardiac, and brain GLP-1Rs share the same amino acid sequence and ligand-binding specificity [29].

In the PNS and CNS of male C57Bl/6 mice, GLP-1Rs are primarily found in neurons [37], although GLP-1R mRNA also has been reported in astrocytes and microglia from the cerebral cortex of embryonic (E18) Wistar rats, using RT-PCR analysis [38]. GLP-1Rs are also highly expressed in the hindbrain, primarily in the dorsal vagal complex, and in the area postrema and NST, as well as in the lateral reticular nucleus and raphe nuclei [27,39]. This widespread cerebral distribution of GLP-1Rs suggests that GLP-1 might be involved in the regulation of multiple neurologic and cognitive functions that extend well beyond the regulation of glucose metabolism. However, as mentioned earlier, central GLP-1Rs are probably targets for GLP-1 produced by brain-stem neurons, which mainly are localized in NST. These neurons have projections to numerous regions of the brain including those expressing GLP-1Rs [30].

It has been suggested that many of the effects of GLP-1 are mediated indirectly via binding to GLP-1Rs in enteric or vagal sensory neurons [40]. GLP-1 is secreted by intestinal L cells as a full-length GLP-1 (7-36) amide, and is rapidly degraded and inactivated (plasma half-life, 1–2 min) by

### Glossary

**Glucagon-like peptide-1 (GLP-1):** an incretin hormone mainly secreted by the intestinal L cells and derived from the transcription/translation product of the proglucagon gene. It is released in response to meals and exerts an important role in the maintenance of normal glucose homeostasis, regulation of food intake, and body weight. Recent experimental studies suggest that GLP-1 may play a role in the regulation of multiple neurologic and cognitive functions in agreement with the widespread cerebral distribution of GLP-1 receptors.

**Glucagon-like peptide-1 receptor agonists (GLP-1-RAs):** antidiabetic drugs that act as agonists of glucagon-like peptide-1 receptor (GLP-1R). In type 2 diabetic patients, GLP-1-RAs exert a durable (up to at least 3 years) effect to improve glycemic control by stimulating insulin secretion in spite of compromised beta-cell function, suppressing fasting/postprandial plasma glucagon levels, and promoting weight loss, again through their appetite-suppressing effect on the brain. Recent experimental studies suggest that GLP-1-RAs also may be useful in treating neurodegenerative diseases and improving cognitive function.

**Glucagon-like peptide-1 (GLP-1) resistance:** decreased effect on insulin secretion of physiological concentrations of GLP-1 in patients with type 2 diabetes mellitus.

**Oxyntomodulin:** a gut hormone also derived from the proglucagon gene that has actions on both the glucagon-like peptide-1 and the glucagon receptor.

**Peptide YY (PYY):** secreted by the L intestinal cells. It belongs to the pancreatic polypeptide family and regulates appetite.

the endopeptidase diaminopeptidyl peptidase-4 (DPP-4), resulting in the formation of the metabolite GLP-1 (9-36) amide [41]. As a result, the concentration of intact endogenous GLP-1 in the circulation is very low and perhaps not sufficient to activate central GLP-1Rs [42]. In support of this hypothesis, RT-PCR analysis showed that in rats GLP-1Rs are expressed in both the nodose ganglion and the vagal nerve terminals innervating the portal vein [33,43–45]. Employing a specific antibody raised against the ectodomain of the GLP-1R, Pyke *et al.* [46] located GLP-1Rs to vagal sensory afferents in the gut of primates, however the signal was of low intensity. Richards *et al*. [33] found GLP-1Rs in afferent neuronal ganglia in a reporter mouse model expressing GLP1-R promoter-driven fluorescent proteins [33]. Thus, it was postulated that GLP-1R in the hepatoportal region could activate neurons in the nodose ganglion leading to downstream neural responses that activate brain circuits involved in the regulation of food intake. Both intraportal and intravenous GLP-1 administration stimulate vagal afferent fibers [47], while subdiaphragmatic denervation prevents the anorexic effect induced by intraperitoneal (IP), but not intraportal, GLP-1 infusion in rats.

Nishizawa *et al*. [47] showed in rats that portal administration of GLP-1 increased the firing frequency in the vagal afferents. These results are consistent with an important role of the vagus nerve in mediating the effects of peripheral GLP-1 [48,49]. The anorectic effect of exogenous GLP-1 on food intake has been shown to be decreased in truncally vagotomized male patients with pyloroplasty, providing further support for the importance of the vagus nerve in mediating GLP-1 function [50].

GLP-1-RAs used for the treatment of T2DM patients generally are resistant to DPP-4 degradation, allowing them to reach high concentrations in the circulation. This raises a question of whether they are able to cross the blood–brain barrier (BBB) and reach GLP-1Rs in the brain. Because some of the GLP-1 RAs are large and charged molecules, they would not be expected to cross the BBB. However, some (e.g., exenatide, liraglutide, and lixisenatide), but not others (e.g., albiglutide and dulaglutide) have been reported to penetrate into the CNS following peripheral administration [51,52]. Perhaps more relevant is the possibility that the smaller agonists (in terms of molecular size) can access the brain via the circumventricular organs, including the area postrema, subfornical organ [53], median eminence [54], and perhaps the choroid plexus. Since the concentration of long acting GLP-1-RAs remains high throughout the day, binding to both central and peripheral GLP-1Rs might promote the crosstalk between peripheral organs and the CNS.

## Effects of GLP-1 and GLP-1-RA on Peripheral and Hepatic Glucose Metabolism

In addition to their effects on the CNS and PNS, GLP-1 and GLP-1-RAs exert a number of extrapancreatic effects that are mediated by GLP-1Rs in the pancreas, liver, heart, lungs, kidney, and gastrointestinal tract [40,55]. Effects on adipose tissue and muscle also have been reported [55–61] but the mechanism remains unclear. It has been hypothesized that GLP-1Rs in muscle differ from those in the pancreas; in fact, they are not associated with any effect or any significant decrease in the cellular cAMP content, whereas they induced the immediate hydrolysis of glycosylphosphatidylinositols, indicating the generation of inositol phosphoglycan [62].

Diabetic hyperglycemia is associated with decreased insulin secretion, fasting and meal-related hyperglucagonemia, increased hepatic glucose production (HGP) secondary to accelerated gluconeogenesis, and decreased peripheral (muscle) glucose uptake [63]. GLP-1 and GLP-1-RAs improve all of these metabolic/hormonal disturbances, mainly by their pancreatic action. Beta-cell GLP-1R signaling is of paramount importance in the maintenance of normal glucose tolerance. Beta-cell-specific GLP-1R knockout results in impaired glucose tolerance [64] and transgenic rescue of the pancreatic GLP-1R normalizes glucose tolerance after both oral and IP

glucose load in Glp1r$^{-/-}$mice [65]. Through its action on pancreatic hormone secretion, GLP-1 increases insulin and reduces glucagon secretion. GLP-1 also appears to regulate hepatic and muscle glucose metabolism [61,66] but these effects are likely to be mediated via its effects on the pancreatic hormones and may be modulated via its effects on the vagus NS and CNS [67]. Studies in dogs showed that both portal and peripheral GLP-1 infusion similarly stimulated hepatic glucose uptake independent of insulin [68]. Denervation of the portal vein in a canine model resulted in a 50% increase in glycemia despite an increase in plasma insulin levels during an OGTT, without changes in peripheral insulin sensitivity, suggesting that activation of hepatoportal sensors is involved in the regulation of glucose tolerance independent of changes in pancreatic hormones [69]. However, in the same study, portal denervation did not change the effect of the GLP-1-RA exenatide that resulted in a decrease in gastric emptying and in overall glucose concentrations during OGTT [69].

In humans, it has been demonstrated that GLP-1 infusion inhibits HGP [8–10] during a pancreatic clamp [61], providing further support that GLP-1 might exert an effect on the liver. Hvidberg *et al*. [9] acutely infused natural GLP-1 at rates of 25 and 75 pmol/kg/h in eight healthy volunteers and measured plasma concentrations of glucose, insulin, and glucagon and glucose turnover using a glucose tracer [9]. They found a significant 75% reduction in the rate of glucose appearance (Ra), that is, HGP during GLP-1 infusion [9]. Similar results were obtained in 12 obese T2DM participants studied with a mixed-meal tolerance tests – double tracer technique (i.v. [3-$^{3}$H]glucose and oral [1-$^{14}$C]glucose) [8]. In this study, the acute intravenous administration of exenatide (0.05 μg/min started 15 min before the meal and decreased to 0.025 μg/min 45 min after meal ingestion) enhanced by 28% the postprandial suppression of HGP, compared with the decrease observed after saline infusion [8]. Cersosimo *et al*. [10] provided similar results following 2 weeks of exenatide treatment (5 μg b.i.d.) in 17 type 2 diabetic patients studied with a double tracer during a mixed meal. To investigate whether the effect of GLP-1 on the liver was mediated by insulin and/or glucagon or represented a direct hepatic effect, GLP-1 (7-37) amide (0.4 pmol/min/kg) was infused during a pancreatic clamp (maintenance of basal insulin and glucagon concentrations with somatostatin) in 14 healthy volunteers (3 females and 11 males aged 18–60 years; BMI, 25.5 ± 3.7 kg/m$^{2}$) [61]. It was found that the liver released less glucose after GLP-1 compared with saline infusion, even though the plasma insulin and glucagon concentrations were not allowed to change. Additional groups have found that GLP-1 and GLP-1-RA significantly inhibited HGP [45,60,70], indicating either a direct effect on hepatocytes, or neurally mediated inhibition. Consistent with this, several groups have shown that the human liver cells express GLP-1Rs [59,71–73], and Glp1r$^{-/-}$mice display impaired suppression of endogenous glucose production [74], although others have failed to detect GLP-1R expression in the human liver [29,72,75,76]. There was no effect on peripheral glucose uptake after infusion of native GLP-1 [61], in agreement with previous results obtained with the pancreatic clamp technique [77] in healthy volunteers. Toft-Nielson *et al.* [77] studied the rate of glucose clearance after intravenous glucose infusions in healthy volunteers during pancreatic clamp conditions and i.v. infusions of GLP-1 in 'therapeutic doses'. They found that conventional pancreatic clamping was unable to fully suppress insulin/C-peptide responses to GLP-1; only very high somatostatin doses were able to do so and in that case there was no effect of GLP-1 on glucose clearance [77].

Several animal studies have shown that the CNS might mediate the peripheral effects observed by GLP-1. Injection of GLP-1 into the ARC has been shown to augment glucose-stimulated insulin secretion and to reduce HGP and glycemia in mice [78], while intracerebroventricular (ICV), but not peripheral, administration of the specific GLP-1R antagonist, exendin-9, caused hyperglycemia. The effect of GLP-1 on HGP was observed only with injection into the ARC and not into the PVN of the hypothalamus [78]. In mice, ICV administration of exendin-4 during a hyperglycemic–hyperinsulinemic clamp increased hepatic utilization and favored glycogen

storage, while it reduced muscle glucose uptake; conversely, ICV administration of the GLP-1R antagonist exendin-9 reduced insulin-stimulated muscle glucose utilization [79]. In mice fed a high-fat diet, ICV administration of GLP-1 enhanced insulin-mediated suppression of HGP and hepatic phosphorylation of Akt, while GLP-1R blockade impaired hepatic insulin action [80]. Although these studies clearly demonstrate that in mice GLP-1 can regulate hepatic glucose metabolism via a central mechanism, it remains to be explained how the signal is transmitted from the brain to the peripheral tissues. Since the majority of native GLP-1 secreted by the L cells is degraded locally by DPP-4, this limits the amount of endogenously secreted GLP-1 that can reach and bind to GLP-1Rs in the brain. Because of the location of the L cells and access of their secretory products to branches of the enteric and autonomic nervous systems and to the portal circulation, the metabolic effects of endogenously secreted GLP-1 are likely to differ significantly from those of exogenously administered GLP-1-RAs, which are resistant to degradation by DPP-4 and, therefore, circulate at much higher concentrations with the potential to activate different receptors, for example, those of the circumventricular organs.

## Effect of GLP-1 and GLP-1-RA on Cerebral Glucose Metabolism

Some of the GLP-1-RAs (exenatide, liraglutide, and lixisenatide) have been reported to be able to cross the BBB, and thus, can directly impact brain function independent of vagal afferent stimulation [51]. Positron emission tomography with $^{18}$F-fluorodeoxyglucose has been used to study cerebral glucose metabolism. In healthy volunteers studied with the pancreatic clamp technique, Lerche *et al*. [81] demonstrated that GLP-1 (7-36) amide infused at a rate of 1.2 pmol/kg/min reduced brain glucose uptake in multiple areas of the brain [81]. During a hyperglycemic pancreatic clamp, Gejl *et al.* [82] demonstrated that the infusion of synthetic GLP-1 (7 to 36) amide at a rate of 1.2 pmol/kg/min increased peripheral glucose clearance, but reduced the increase in cerebral glucose concentration, protecting the brain against excess glucose uptake under conditions of hyperglycemia. The acute effect on cerebral glucose metabolism of exenatide injected subcutaneously before an OGTT has been studied recently [83]. Exenatide increased glucose metabolism in areas of the brain related to glucose homeostasis, appetite, and food reward, despite lower plasma insulin concentrations; however, glucose uptake was reduced in the hypothalamus [83]. Whether these actions are exerted directly or indirectly remains unclear.

## Effect of GLP-1 and GLP-1-RA on Appetite and Food Intake

GLP-1 has been reported to have a direct effect on appetite and food intake due to its ability to reach the brain stem through the subfornical organ, the area postrema, and the median eminence [53,54]. In the brain, GLP-1 binds to GLP-1Rs that are expressed in multiple areas of the human brain, including centers involved in the regulation of appetite and satiety [55,84–86]. ICV injection of GLP-1 inhibits food intake in a dose-dependent manner [87,88], while blocking cerebral GLP-1 action with ICV administration of exendin-9 increases food intake and weight gain [89]. This effect of GLP-1 is mediated through the brain-stem and hypothalamic circuits, and is thought to reflect the actions of GLP-1 produced locally in the brain (Figure 1). Central injection of exendin-4 has been shown to increase the expression of interleukin-6 (IL-6) in the hypothalamus and hindbrain and to increase IL-1β in the hypothalamus in rats [90]. The cytokines IL-6 and IL-1β may exert an antiobesity effect in the CNS. Burmeister *et al.* [91] have proposed a model in which activation of the central GLP-1Rs reduces food intake via glucose metabolism-dependent inhibition of central 5′ AMP-activated protein kinase (AMPK).

As previously stated, intestinally secreted GLP-1 is, in large part, rapidly degraded by DPP-4, and therefore, its direct role in appetite regulation remains to be defined [42]. By contrast, the GLP-1 concentration in the gut region of the L cells is very high and could contribute to the hormone's anorectic effect by activating vagal nerve fibers that transmit a signal to the brain stem and hypothalamic centers involved in appetite regulation [40,48,49]. However, GLP-1-positive

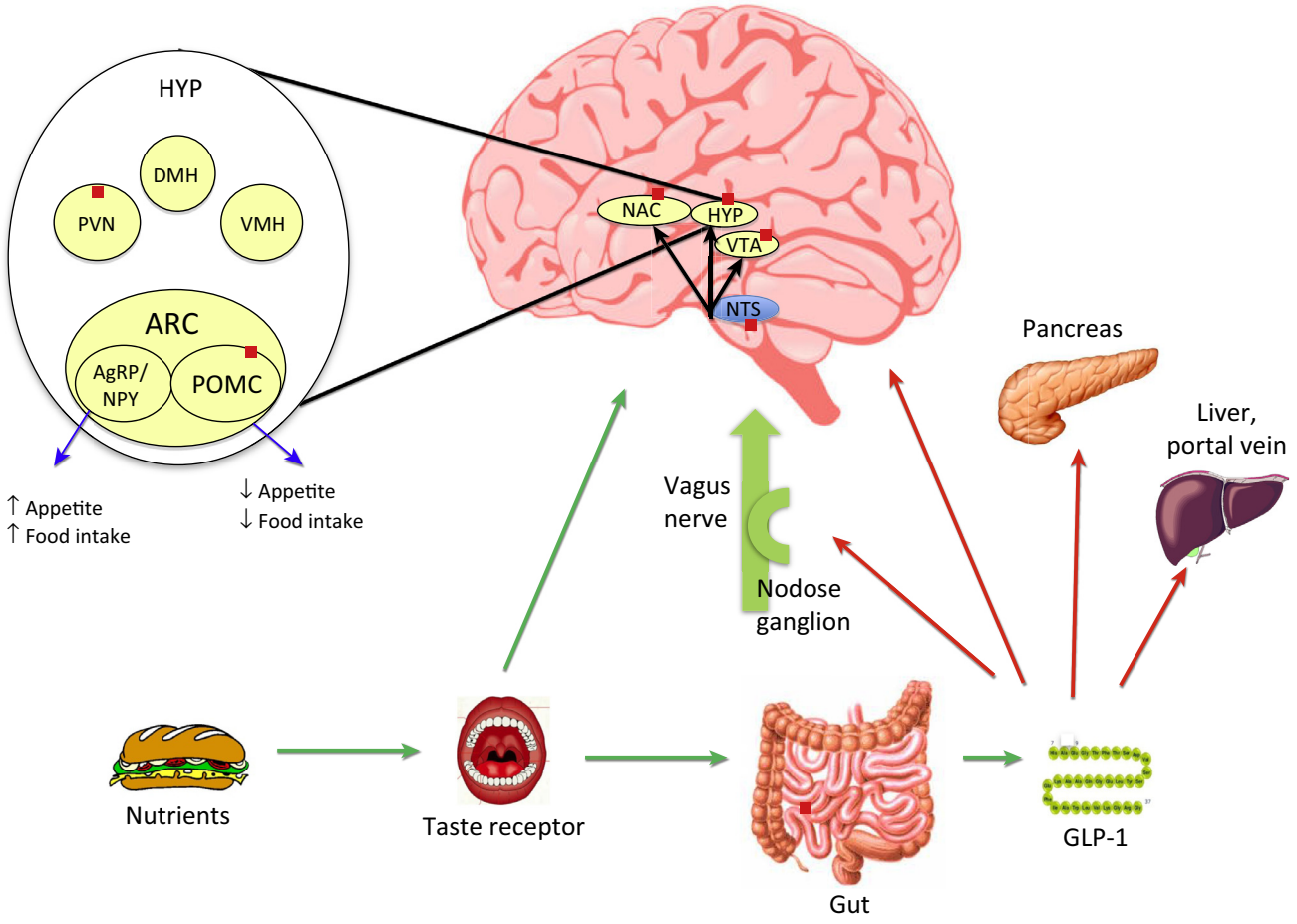


Figure 1. Mechanisms of Action of Glucagon-like Peptide-1 (GLP-1) in the Central Regulation of Feeding. GLP-1 secreted from intestinal L cells in response to meal ingestion may communicate with the brain by accessing GLP-1 receptors (GLP-1Rs) within fibers innervating the portal vein or the nodose ganglion of the abdominal vagus nerve. Subsequently, endogenous GLP-1 through intestinal vagal afferents activates GLP-1-producing neurons in the nucleus tractus solitarii (NTS). These neurons project to several food-intake regulating areas, most of which contain GLP-1Rs, such as the ventral tegmental area (VTA), the nucleus accumbens (NAC), and the hypothalamus (HYP). The GLP-1Rs are present, throughout the HYP, particularly in the paraventricular nucleus (PVN) and the arcuate nucleus (ARC), with a greater density on pro-opiomelanocortin (POMC) neurons (anorexigenic neurons). GLP-1 signals may also start in the oral cavity and may affect taste function and food intake. Abbreviations: AgRP, Agouti-related protein; DMH, dorsomedial hypothalamus; NPY, neuropeptide Y; VMH, ventromedial hypothalamus.

cells have been reported to be present in the cerebral cortex and hippocampus and were significantly reduced in insulin-resistant obese (ob/ob) mice compared with normal C57 black mice [92]. The same authors found that microglia, surprisingly, also represent a possible central source of GLP-1. In conditions of insulin resistance and inflammation, mRNA expression of proglucagon and GLP-1 secretion by microglial cells was decreased [92]. A decrease in GLP-1-positive cells was also detected in the cerebral cortex and hippocampus of adult ob/ob male mice in which the number of GLP-1-positive cells is reduced, compared with normal C57 black mice [92].

There is general agreement that GLP-1 is expressed in the brain stem, particularly in the nucleus tractus solitarii (NTS) [30,92–94]. It has been suggested that GLP-1 released by neurons is involved in the regulation of feeding, as well as in digestion and nutrient absorption, and that these effects differ from the incretin effects that are mediated by intestinal GLP-1 [95]. Activation of GLP-1Rs in the hindbrain, either by endogenous GLP-1 [96] or by GLP-1-RAs [97], has been

shown to play an important role in diminishing food intake and reducing body weight. Further, experimental evidence to support a role for CNS secretion of GLP-1 in the regulation of food intake is derived from knockout of the proglucagon gene in the NTS, which leads to hyperphagia and weight gain [43].

The action of GLP-1 on food intake may depend not only on its effect on hypothalamic and brainstem circuits, but also on its effect on cortical food reward centers that are located in the mesolimbic reward system, that is, the ventral tegmental area (VTA) and nucleus accumbens (NAc). Infusion of exendin-4 into both the VTA and into the NAc reduces food intake in rats [98]. Activation of GLP-1Rs in the VTA decreases nutrient intake, especially of highly palatable food, while blockade of endogenous GLP-1Rs in the VTA increases food intake [98,99]. Infusion of exendin-4 (0.025 and 0.05 μg/min) into the VTA of male Sprague Dawley rats allowed *ad libitum* access to both normal chow and a high-fat diet, decreased sucrose and fat intake at 6 and 24 h, and reduced 24-h body weight gain [99]. The NAc receives dopaminergic projections from the VTA, but it is less sensitive to exendin-4 than the VTA, since higher doses were required to decrease chow diet intake in both fasted and *ad libitum*-fed rats [98,99]. Native GLP-1 decreases chow intake when locally administered into the NAc, while infusion of the GLP-1 antagonist exendin-(9-39) into the NAc causes hyperphagia in rats, suggesting a regulatory role of GLP-1Rs in the NAc on food intake [100]. The two regions of NAc, core and shell, modulate food reward differently; exendin-4 reduces fat intake only when locally injected into the NAc shell [99,100].

It is still debated if GLP-1 RAs exert their activity through the CNS or the PNS. Two recent studies [54,101] have helped to clarify the mechanism, peripheral versus central, via which the GLP-1 RA liraglutide controls food intake and promotes weight loss. Sisley *et al*. [101] created either selective CNS or vagal knockout of GLP-1R; only the former reduced food intake and body weight in response to liraglutide. Secher *et al*. [54] administered fluorescently labeled liraglutide peripherally in rats and demonstrated uptake in all circumventricular organs and in the ARC and PVN of the hypothalamus [54]. Direct injection of exendin-(9-39) into the ARC, but not into the PVN, abolished the effect of liraglutide on food intake and body weight. These investigators demonstrated that neurons that produced pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript (POMC/CART) in the ARC also expressed GLP-1R and were, therefore, likely to mediate the weight loss effect of liraglutide. These results are in direct conflict with those of Sandoval *et al*. [78] who reported that GLP-1Rs in the PVN, but not in the ARC, mediated the anorexigenic effect of intracerebrally administered GLP-1 in rats. Secher *et al*. [54] also demonstrated that peripherally administered liraglutide is taken up and internalized by the POMC/CART neurons in the ARC. Collectively, the studies by Sisley *et al*. (mice) [101], Secher *et al*. (rats) [54], Flint *et al*., and van Can *et al*. (humans) [102–104] all agree that reduced energy intake, rather than increased energy expenditure, is responsible for GLP-1-RA-induced weight loss. Krieger *et al*. [105], by contrast, created a virus-induced knockdown of GLP-1R in the afferent neurons of the vagal nodose ganglion, and found that this diminished the effects of IP GLP-1 and, importantly, influenced feeding behavior and glycemic regulation.

Food intake has been suggested to be affected by GLP-1 through the regulation of taste sensation. Production of GLP-1 in oral taste cells, as well as GLP-1R expression on adjacent taste nerve fibers, has been reported and this suggests that GLP-1 signaling may affect taste function [35,106]. Consistent with this, GLP-1R knockout mice show dramatically reduced responses to sweeteners in behavioral assays, indicating that GLP-1 acts to maintain or enhance sweet taste sensitivity [107]. Further, Thiele *et al*. [108] demonstrated that central administration of GLP-1 elicited a conditioned taste aversion to saccharine in rats.

In humans, neuroimaging techniques, that is, positron emission tomography and functional magnetic resonance imaging (fMRI), have been used to examine the effects of GLP-1 and GLP-1 analogs on the CNS and PNS, on the gut–brain axis, and on the mechanisms involved in the regulation of body weight and food intake [35]. fMRI studies in humans showed that exenatide infusion in obese type 2 diabetic and nondiabetic individuals during a somatostatin pancreatic–pituitary clamp activated multiple brain areas (insula, amygdala, putamen, and orbitofrontal cortex), indicating that it may play a role in the regulation of appetite [86]. The combined administration of GLP-1 (7-36 amide) (0.8 pmol/kg/min) plus **peptide YY (PYY)** (3-36 amide; 0.3 pmol/kg/min) in 16 healthy fasted nondiabetic individuals resulted in a reduction in energy intake that was equivalent to the summed effects of the single hormones, and decreased brain activity in food-sensitive areas (amygdala, caudate, putamen, insula, NAc, orbitofrontal cortex, and putamen) [109]. GLP-1 (7-36 amide) infusion (1.2 pmol/kg/min) during a mixed-meal test inhibited ghrelin secretion in a study of 14 healthy lean male volunteers, prompting the investigators to postulate that the anorexigenic effect of GLP-1 is mediated also by ghrelin [110].

To investigate if the hypothalamic response to GLP-1 might explain why some individuals lose weight during exenatide treatment (responders), while others do not (nonresponders), Schlogl *et al*. [111] examined the effect of exenatide infusion versus placebo on hypothalamic connectivity (measured by fMRI) and energy intake in 24 male obese Caucasian volunteers. Rated food and nonfood images were shown during fMRI. Those who, in response to exenatide, decreased their caloric intake more than 10% (responders) showed significantly higher connectivity of the hypothalamus when they watched food pictures during exenatide infusion compared with placebo, while nonresponders did not show any significant exenatide-induced change [111].

## Effect of GLP-1 and GLP-1-RA on Body Weight and Body Fat

Chronic administration of GLP-1-RAs to overweight diabetic individuals has been associated not only with a decrease in total body weight and fat mass [112,113] but also with a specific decrease in visceral and liver fat [60,114]. There is general agreement that the anorectic effect of GLP-1, resulting in reduced food intake, is the primary cause of weight loss. Of note, obese individuals generally display impaired GLP-1 secretion in response to a meal [12,115,116]. Treatment with GLP-1-RAs of smaller molecular size (i.e., liraglutide, exenatide) causes greater weight loss than treatment with GLP-1-RAs of larger size (albiglutide, dulaglutide) when administered at maximal doses in head-to-head studies [117–119]. However, because of widely different pharmacokinetic profiles, it is difficult to compare the doses. Since larger GLP-1-RAs exert a modest effect to promote weight loss, do not cross, or poorly cross, the BBB, and are unlikely to enter via the leaks in the circumventricular organs, it has been questioned whether their appetite-suppressive effect is mediated exclusively through binding to central GLP1-Rs. Studies in animals have provided conflicting results. A study in rodents demonstrated that both central (ICV) and peripheral (IP) administration of albiglutide modulated gastric emptying and reduced food intake [120], indicating a possible role of PNS. As discussed earlier, the vagus nerve may play an important role in mediating these effects as demonstrated in animals and humans [121–123]. Further, GLP-1 has been shown to directly interact with and activate GLP-1R on enteric neurons in mouse models [122]. GLP-1 has been reported to exert different effects on the stomach and on the colon; infusion of GLP-1 directly into the cerebral ventricles of rats resulted in the inhibition of gastric emptying [88]. In humans, delayed gastric absorption of glucose after OGTT correlated with GLP-1 activation of cerebral areas involved in glucose homeostasis and food reward [83]. By contrast, GLP-1 accelerated colonic transit, an effect mediated via the parasympathetic nervous system [124,125]. Short- and long-acting GLP-1-RAs have different effects on gastric emptying: short-acting agonists have a more pronounced inhibition of gastric emptying causing a greater reduction in postprandial glucose excursions [126,127], while long-acting GLP-1-RAs primarily affect the fasting plasma glucose, as their effect on gastric emptying rapidly wanes due to tachyphylaxis [126–128].

## Effect of GLP-1 and GLP-1-RA on Energy Expenditure

The effect of GLP-1 on energy expenditure is unclear. Studies in animals have demonstrated that ICV administration of liraglutide produced greater weight loss than peripheral injection, and that ICV administration was associated with activation of CNS areas involved with the regulation of energy expenditure [129]. Liraglutide also has been shown to stimulate brown adipose tissue thermogenesis and browning of white adipocytes, independent of food intake, through activation of AMPK in the hypothalamus [129]. Intact GLP-1 does not appear to have a direct effect on thermogenesis, but has been proposed that other peptides, derived from GLP-1 (7-36) amide, might play a role. A recent study in diet-induced obese mice demonstrated that GLP-1 (32-36) amide, derived from cleavage of the GLP-1 (9-36) amide, increases basal energy expenditure, reducing weight gain, and improves insulin resistance, glucose control, and hepatic steatosis [130]. Whether this also applies to humans remains to be seen.

Studies in humans have demonstrated that weight loss after GLP-1-RA primarily results from reduced caloric intake rather than from increased resting energy expenditure (REE) or increased total energy expenditure. A 4-h infusion of GLP-1 (50 pmol/kg for an hour) in normal-weight healthy male volunteers decreased REE, which was associated with a reduction in carbohydrate oxidation without change in fat or protein oxidation [104]. Similar findings have been reported in nondiabetic obese male participants with GLP-1 infusion following ingestion of a breakfast meal [103]. Since weight loss usually is associated with a reduction in both REE and total energy expenditure due to a decrease in lean body mass and thermic effect of food [131], it is difficult to discern whether GLP-1 exerts a direct effect to reduce energy expenditure. Energy expenditure, quantitated under resting conditions, has been reported either to be unchanged or slightly, but not significantly, increased after both liraglutide and exenatide [112,113,132]. GLP-1-RA treatment is associated with a reduction in respiratory quotient (RQ), consistent with increased fat oxidation [102] and the preferential loss of fat versus lean body mass.

Harder *et al*. [112] studied 33 type 2 diabetic patients randomized to either liraglutide (0.6 mg; $n = 21$) or placebo ($n = 12$) for 8 weeks. The authors did not observe any change in 24-h energy expenditure (measured with the calorimetric chamber) but this result is not surprising given the low dose of liraglutide (0.6 vs. 1.8 mg approved for diabetes and 3.0 mg approved for obesity) and the absence of significant weight loss. Using the doubly labeled water technique (gold standard for measurement of free-living total energy expenditure), Bradley *et al*. [113] found that 3 months of treatment with exenatide decreased fat mass in nondiabetic individuals without diminishing weight-adjusted total energy expenditure or lean body mass. Interestingly, the authors also found a decrease in physical activity, without change in either REE or thermic effect of food, and suggested that an exercise program, combined with GLP-1-RA treatment, might be particularly effective in promoting loss of fat mass [113].

## GLP-1 and Other Hormones

The PVN has been shown to participate in the regulation of food intake by modulating the interaction between GLP-1 and hormones involved in weight regulation, including oxytocin (OT) and corticotrophin-releasing hormone [99,133]. Injection of a GLP-1R antagonist into the third ventricle blunted the anorexigenic effect of OT, while an OT antagonist did not alter the anorexigenic effect of GLP-1, suggesting that NTS GLP-1-producing cells mainly acting through OT–GLP-1R-positive cells modify OT cell signaling or OT release [133]. Corticotrophin-releasing hormone neurons also have been implicated in the reduction in food intake following GLP-1R activation [134]. **Oxyntomodulin**, which has been reported to increase energy expenditure (but surprisingly only activity-related EE, not REE) [135], exerts its action through the GLP-1R, and mimics the effects of GLP-1 and GLP-2 on gastric acid secretion and gut motility [136]; further, the anorectic effect of oxyntomodulin was blocked by the GLP-1R antagonist exendin (9-39) in rats [137].

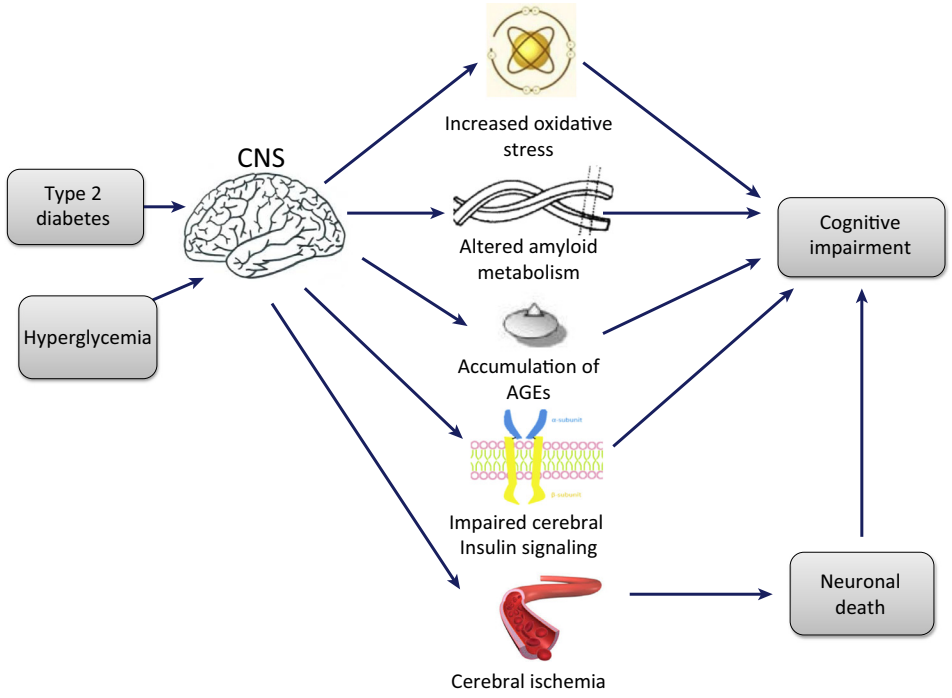


Figure 2. Type 2 Diabetes and Cognitive Dysfunction. Type 2 diabetes has been associated with an impairment of the central nervous system (CNS). Chronic hyperglycemia triggers several pathogenic mechanisms such as impaired cerebral insulin signaling, altered amyloid metabolism, accumulation of advanced glycation end products (AGEs), and increased oxidative stress that collectively contribute to the onset of cognitive impairment.

## Neuroprotective Effects of GLP-1 and GLP-1-RA

Chronic diabetic hyperglycemia is associated with cognitive impairment [138]. Proposed mechanisms for the cognitive impairment (Figure 2) include impaired cerebral insulin signaling, altered amyloid metabolism, accumulation of advanced glycation end products within the CNS, and oxidative stress [139].

GLP-1 has been proposed as a neuroprotective hormone [140]. GLP-1Rs are expressed in various brain regions involved in cognitive function, including the hypothalamus, hippocampus, and cortex. GLP-1R-deficient mice have a phenotype which is characterized by a deficit in cognitive function and impaired synaptic plasticity and memory formation [141] that is restored after hippocampal GLP-1R gene transfer [142]. GLP-1-deficient mice are also characterized by a learning deficit, enhanced seizure severity, and increased neuronal injury after kainate administration, while mice overexpressing GLP-1R in the hippocampus show improved learning and memory [142]. In the same study, ICV administration of GLP-1 and [Ser(2)]–exendin-(1-9) was associated with enhancement of associative and spatial learning likely mediated via GLP-1R. Although [Ser(2)]–exendin-(1-9) exerted its effect when administered peripherally, GLP-1 did not [142].

GLP-1-RAs have been shown to exert a neuroprotective effect in animal models by improving cognitive performance [143], stimulating neurogenesis [144,145], and improving synaptic plasticity [146]. Treatment with GLP-1-RAs also reduces ischemia-induced changes, oxidative stress, neuronal damage, and apoptosis [147,148] and attenuates cerebral infarct volume and

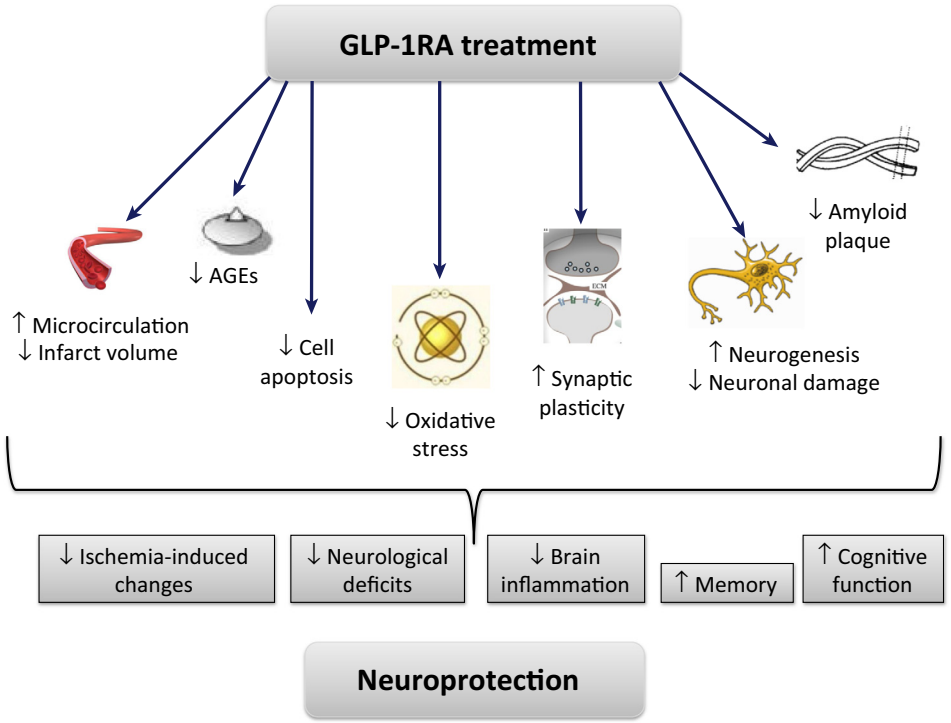


Figure 3. Positive Effects of Glucagon-like Peptide-1 Receptor Agonist. Both exenatide and liraglutide have been shown to exert their neuroprotective effects by reducing central nervous system oxidative stress, enhancing antioxidative mechanisms, reducing apoptosis and inflammatory responses in the brain, and increasing microcirculation after middle cerebral artery occlusion. Both liraglutide and lixisenatide reduce amyloid plaque volume, prevent loss of synapses, and improve neuronal plasticity in association with improved object recognition tasks. Further, both exenatide and liraglutide promote neurogenesis by increasing progenitor cell division, while lixisenatide increases progenitor cell proliferation and the number of immature neurons in the hippocampal gyrus, thus improving recognition memory. Abbreviation: AGE, advanced glycation end product.

neurologic damage in rats [149]. Both exenatide [147,148] and liraglutide [148,149] exert a neuroprotective effect following a cerebral ischemic insult, reduce CNS oxidative stress [149], decrease hypoxia-inducible factor-1$\alpha$ expression [150], enhance antioxidative mechanisms [151], and increase blood flow in the microcirculation after middle cerebral artery occlusion [148] (Figure 3). In a rat model of middle cerebral artery occlusion, subcutaneous injection of liraglutide (100 μg/kg/day) for 7 days reduced infarct volume, improved neurologic deficits, and inhibited cell apoptosis [152]. These beneficial effects may be related to decreased reactive oxygen species generation and activation of the phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase pathways [152]. Further, exenatide protects neuroprogenitor cells from apoptosis induced by amyloid beta oligomers [153] and lixisenatide (an analog of exendin with a C-terminal hexa-lysine extension) improves recognition memory in association with augmented progenitor cell proliferation and increased number of immature neurons in the hippocampal gyrus [154]. Both exenatide and liraglutide have been shown to promote neurogenesis by increasing progenitor cell division in the dentate gyrus in ob/ob mice, db/db mice, and high-fat-diet-fed mice. Thus, they could represent a promising approach for the treatment of neurodegenerative diseases [155] (Figure 3). A neuroprotective effect of GLP-1R activation also has been demonstrated in cranial and peripheral nerves, as demonstrated by an increase in retinal ganglion cell survival after experimental damage to the optic nerve [156], and by prevention of diabetic peripheral nerve degeneration in streptozotocin-induced diabetic rats [157]. GLP-1R

expression has been also detected by immunofluorescence in the white and gray matter of the spinal cord and was profoundly upregulated after peripheral nerve injury [158].

Exenatide binding to GLP-1R has been associated with endorphin release from both the spinal cord and cultured microglia [158]. In human neuroblastoma cell lines, liraglutide improved cell viability and reduced cytotoxicity and apoptosis in response to methyl glyoxal stress [159]. The GLP-1-RA liraglutide also reduced hippocampal neuron toxicity induced by advanced glycation end products, which play a role in the development of both microvascular and macrovascular complications [160]. Further, pretreatment with liraglutide has been reported to prevent beta amyloid-induced neurotoxicity in the human neuroblastoma cell line SH-SY5Y. This mechanism seems to be mediated by activation of the PI3K/Akt signaling pathway [161].

In humans, clinical trials have been initiated to investigate the neuroprotective effect of exenatide and liraglutide in PD and AD. After 12 months of treatment with exenatide, patients with PD showed a clinically relevant improvement in motor and cognitive functions that persisted after a 2-month drug washout period [162]. Trials[i] examining the efficacy and safety of GLP-1 mimetics in AD are ongoing (Clinical Trial.gov Identifiers: NCT01255163, NCT01469351, and NCT01843075). In animal models, both liraglutide and lixisenatide have been shown to reduce amyloid plaque volume after intracerebral administration, prevent loss of synapses, improve neuronal plasticity, and reduce oxidative stress and inflammatory response in the brain, in association with improved object recognition tasks [163–165]. Accumulating evidence that GLP-1-RAs can improve central and peripheral neuronal function supports their therapeutic potential in neurological and neurodegenerative diseases in humans [164,166].

In addition to intact GLP-1, the metabolite of GLP-1 has been reported to have neuroprotective effects. Ma *et al.* [167] demonstrated that GLP-1 (9-36) (amide) prevented long-term potentiation and enhanced long-term depression induced by exogenous amyloid β peptide Aβ[(1-42)] in hippocampal slices of amyloid precursor protein/presenilin-1 mutant mice, a model of AD. Treatment with GLP-1 (9-36) (amide) at an age at which individuals display impaired spatial and contextual fear memory reversed their memory defects. This may be explained by the ability of GLP-1 (9-36) (amide) to decrease elevated levels of mitochondrial-derived reactive oxygen species and to restore dysregulated Akt-glycogen synthase kinase-3β signaling in the hippocampus of APP/PS1 mice [167]. GLP-1 (9-36) has been also reported to reduce neuroinflammation and improve neurologic outcome through AMPK phosphorylation in a mouse model of brain injury after intracerebral hemorrhage [168].

## Concluding Remarks and Future Perspectives

GLP-1-RAs represent an established therapeutic option for T2DM patients because of their durable effects to reduce HbA1c, stimulate insulin, inhibit glucagon secretion, and promote weight loss. Most recently, studies have also shown improved cardiovascular outcome and reduced mortality [169,170]. Much evidence has accumulated to indicate that GLP-1-RAs also exert clinically relevant neuroprotective effects. Neuroimaging techniques have provided important insights about the mechanisms via which the GLP-1-RAs modulate CNS and PNS function. Further, GLP-1-RAs may play a role in preventing/reducing deleterious cerebrovascular events related to diabetes [169]. Although emerging evidence suggests a beneficial effect of GLP-1-RAs in the management of diabetic and nondiabetic neurological disorders, additional studies to definitively establish their efficacy are needed and no guidelines have been established to recommend the GLP-1-RAs specifically for the treatment of neurological disease in either diabetic or nondiabetic individuals. Large clinical trials are needed to evaluate whether GLP-1-RAs are effective in the treatment of neurological disease (see Outstanding Questions).

### Outstanding Questions

To what extent is the use of glucagon-like peptide-1 (GLP-1) receptor agonists effective in improving cerebral ischemia in type 2 diabetes?

What are the mechanisms by which GLP-1 receptor agonists exert neuroprotective effects?

What are the features of GLP-1 receptor agonists that allow them to cross the blood–brain barrier?

The role of GLP-1 receptor agonists on cerebral ischemia has mostly been studied in animal models. What role could they play in the treatment of cerebral ischemia in humans? Do they have the same effect on cerebral ischemia in diabetic and nondiabetic patients?

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## Resources

[i] Clinical Trial.gov Identifier: NCT01255163, NCT01469351, and NCT01843075.

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