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REVIEW

# Gut-brain connection: The neuroprotective effects of the anti-diabetic drug liraglutide

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## Abstract

Long-acting glucagon-like peptide-1 (GLP-1) analogues marketed for type 2 diabetes (T2D) treatment have been showing positive and protective effects in several different tissues, including pancreas, heart or even brain. This gut secreted hormone plays a potent insulinotropic activity and an important role in maintaining glucose homeostasis. Furthermore, growing evidences suggest the occurrence of several commonalities between T2D and neurodegenerative diseases, insulin resistance being pointed as a main cause for cognitive decline and increased risk to develop dementia. In this regard, it

has also been suggested that stimulation of brain insulin signaling may have a protective role against cognitive deficits. As GLP-1 receptors (GLP-1R) are expressed throughout the central nervous system and GLP-1 may cross the blood-brain-barrier, an emerging hypothesis suggests that they may be promising therapeutic targets against brain dysfunctional insulin signaling-related pathologies. Importantly, GLP-1 actions depend not only on the direct effect mediated by its receptor activation, but also on the gut-brain axis involving an exchange of signals between both tissues *via* the vagal nerve, thereby regulating numerous physiological functions (*e.g.*, energy homeostasis, glucose-dependent insulin secretion, as well as appetite and weight control). Amongst the incretin/GLP-1 mimetics class of anti-T2D drugs with an increasingly described neuroprotective potential, the already marketed liraglutide emerged as a GLP-1R agonist highly resistant to dipeptidyl peptidase-4 degradation (thereby having an increased half-life) and whose systemic GLP-1R activity is comparable to that of native GLP-1. Importantly, several preclinical studies showed anti-apoptotic, anti-inflammatory, anti-oxidant and neuroprotective effects of liraglutide against T2D, stroke and Alzheimer disease (AD), whereas several clinical trials, demonstrated some surprising benefits of liraglutide on weight loss, microglia inhibition, behavior and cognition, and in AD biomarkers. Herein, we discuss the GLP-1 action through the gut-brain axis, the hormone's regulation of some autonomic functions and liraglutide's neuroprotective potential.

**Key words:** Type 2 diabetes; Glucagon-like peptide-1; Gut; Brain; Insulin; Liraglutide; Alzheimer disease; Neuroprotection



**Core tip:** Glucagon-like peptide-1 (GLP-1) physiological responses are dependent on a gut-brain axis and receptor (GLP-1R) activation. GLP-1Rs are widely expressed throughout the body, including several brain areas. GLP-1 may readily diffuse across the blood-brain-barrier, activating neuroprotective pathways. Given the native GLP-1 short half-life, liraglutide has been developed with a highly increased half-life, allowing its use to treat type 2 diabetes (T2D). Given T2D patients increased risk for obesity and dementia [*e.g.*, Alzheimer disease (AD)], and evidence from preclinical studies, whereby liraglutide showed impressive neuroprotective effects, clinical studies are underway to test the role of liraglutide on weigh control and AD.

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## INTRODUCTION

The incretin effect was first discovered when experiments were conducted to evaluate the possibility that food ingestion would lead to hormone secretion by the gut into the bloodstream to modulate pancreatic insulin secretion and lower blood glucose levels[1-3]. Shortly after, glucose-dependent insulinotropic polypeptide (GIP) and gastrointestinal glucagon-like peptide-1 (GLP-1) were described as the incretin hormones secreted by intestinal cells that were responsible for a potent insulinotropic activity upon elevated plasma glucose (70% of the postprandial insulin secretion)[4-7]. More recently, in an increased number of studies directed to the analysis of incretins effects in patients with type 2 diabetes (T2D), impaired interactions between mediators such as insulin, glucagon and incretin hormones have been increasingly suggested to underlie the development of T2D[8].

In this review, we will focus primarily on the complex interaction between gut and central nervous system (CNS), particularly in the regulation of appetite and body weight. More specifically, we will briefly overview the role of the increasingly used anti-T2D drug from the incretin/GLP-1 mimetics class liraglutide in brain, with a special emphasis on its anorectic and potential neuroprotective effects on T2D-associated neurodegeneration.

## INCRETIN HORMONES IN BRAIN: A PIVOTAL ROLE FOR GLP-1

Despite the known GIP action in inhibiting gastric acid secretion and gastrointestinal motility, as well as in the stimulation of insulin release[6,7], it was observed that not only GLP-1 is more insulinotropic in hyperglycemic conditions than GIP[9,10], but also that GIP insulinotropic activity was diminished in T2D patients[11,12]. Thus, as the GIP secretion was maintained normal or even increased, such apparently reduced β-cell response to GIP might result from a down-regulation of GIP receptor expression/activity[13,14]. This was further reinforced by the observation that, despite no changes in GLP-1-related insulinotropic activity in diabetic patients, their impaired insulin secretion could be associated with a decreased incretin effect[15-17]. Importantly, in addition to its insulinotropic effects, GLP-1 has been also involved in the suppression of postprandial glucagon secretion, delaying gastric emptying, promoting early satiety (and the subsequent decrement in food intake), slowing the rate of endogenous glucose production and, ultimately, promoting weight loss, particularly in diabetic conditions[4,18,19]. Moreover, it has been reported that, by stimulating cell proliferation and protecting against apoptosis, GLP-1 also enhanced pancreatic β-cell mass[20,21]. In this perspective, it has been suggested that the combination of these effects may contribute to the normalization of blood glucose levels in T2D patients[19,22], thus rendering the GLP-1

hormone (instead of GIP) a very attractive target for the treatment of T2D.

### *The gut-to-brain GLP-1-dependent axis: GLP-1 synthesis and secretion*

As previously referred, GLP-1 is primarily synthesized and secreted from the intestine (ileum and colon) enteroendocrine L cells and, to a lesser extent, from pancreatic α-cells and from neurons located at the nuclei of brainstem [solitary tract nucleus (NTS), caudal brainstem and area postrema (AP)][23-25].

This hormone arises from the post-translational cleavage of proglucagon (catalyzed by the prohormone convertase) and, depending on the tissue, proglucagon may originate different products[26]. For instance, in pancreas the major products are glucagon, glycentin related polypeptide and a major proglucagon fragment, containing the GLP-1 and GLP-2 sequences, whilst in brain and gut proglucagon processing liberates GLP-1, GLP-2 (which is not an incretin, as it is deprived from insulinotropic and glucose lowering properties), IP-2, glicentin, and oxyntomodulin[23,26]. Additionally, recent studies showed that multiple forms of GLP-1 are secreted by humans, including GLP-1 (1-37) and GLP-1 (1-36) amides (synthesized as immature forms), as well as the bioactive forms glycine-extended form GLP-1 (7-37)-amide and the GLP-1 (7-36)-amide (this being the predominant form in plasma and brain)[23,27].

Most GLP-1 is secreted postprandially, particularly after fat- and carbohydrate-rich meals. Interestingly, this secretion is proportional to the size of the meal and may reach 10-30 pM[4,19]. Individual nutrients, including glucose and other sugars, fatty acids, essential amino acids and dietary fibers also stimulate GLP-1 release[28]. Amongst these, the glucose and fructose mechanism of stimulation have been the more explored and it has been shown that, in humans, oral (but not intravenous) glucose administration stimulates GLP-1 secretion[4,26]. Moreover, basal secretion of GLP-1 may even occur as a product of glucagon secretion in fasting state and reach 5-10 pM, being essential for maintaining glucose homeostasis[4,25]. Interestingly, plasma GLP-1 (7-36)-amide increases rapidly (within just a few minutes) through a biphasic pattern of secretion and release after oral glucose absorption, composed by an early phase within 10-15 min followed by a prolonged second phase at 30-60 min[28,29].

Although the majority of secreting L-cells are located in the distal small intestine, they can be found also throughout the entire length of the small intestine[30,31]. Interestingly, these cells may contact with different regions, being stimulated by a variety of mediators. For instance, L-cells can contact directly with nutrients at their luminal surface and with vascular tissue through their basolateral surface, as well as with the enteric and the CNS *via* the vagus nerve[31,32]. Hence, evidence suggests that early and late phases of GLP-1 secretion may be generated either through (1) the direct nutrient stimuli to L-cells (particularly those located in more proximal regions of the small intestine, being at least partially responsible to induce the first phase of GLP-1 secretion); or (2) *via* the indirect action of neural and endocrine factors[19,30,32]. More specifically, it has been hypothesized that the early GLP-1 secretion in rodents and humans may be indirectly regulated by the autonomic nervous system and neurotransmitters and peptides [*e.g.,* gastrin-releasing peptide, acetylcholine, γ-aminobutyric acid (GABA), calcitonin gene-related peptide and GIP], with the vagus nerve playing an essential role herein[31,33]. Additionally, others proposed that non-nutrient factors, as leptin and insulin, could also contribute to the rapid release of GLP-1[33,34].

### *Intracellular signaling pathways underlying brain GLP-1 synthesis, secretion and action*

Importantly, brain GLP-1 can be peripherally originated (from the intestine), reaching the CNS through leaks in the blood-brain barrier (BBB) (at the level of area postrema and subfornical organs), whereby it may readily diffuse across the BBB (GLP-1 is a relatively small molecule), and may also influence the activity of afferent vagal neurons[35]. However, as previously referred, GLP-1 synthesis can also occur locally in brain, in a process dependent on the complex brainstem-hypothalamic-preproglucagon system. More specifically, in preproglucagon neurons from the CNS, proglucagon is processed to GLP-1 in neuronal cell bodies[36]. First evidence showed that the largest population of GLP-1 immunoreactive innervations occurred in the dorsomedial and paraventricular nuclei of the hypothalamus, and to a lesser extent in the cortex and hindbrain[37,38]. Then, others reported that preproglucagon neurons are primarily located in the lower brainstem, particularly in the caudal NTS and AP, some cell bodies being also found in the dorsomedial part of the medullary reticular nucleus[37,39,40]. Besides this, both the NTS and AP appear to receive visceral sensory inputs generated by the vagal nerves that innervate the gastroduodenal tract[41]. Indeed, it has been described that sensors in the hepatic portal vein may activate the vagus nerve, initiating a neural signal to the NTS/AP in the brainstem, which in turn transmits the information through axons to the hypothalamic nuclei[42]. Intracellularly, GLP-1 secretion may be mediated by several signaling pathways. In general, these include the activation of protein kinases A (PKA) and C (PKC) and mitogen-activated protein kinase (MAPK), as well as an increase in intracellular calcium ($Ca^{2+}$)[43]. More specifically, upon a meal, the increase in blood glucose is accompanied by its uptake into the cells (namely *via* sodium/glucose transporters) and subsequent metabolization. As a result, the increment in ATP levels may lead to the closure of ATP-linked potassium channels and, ultimately, GLP-1 secretion[33,43]. Conversely, inhibition of GLP-1 secretion

in gut has been described to involve a negative feedback, probably *via* GLP-1-mediated stimulation of somatostatin secretion[34,44]. Interestingly, the neuropeptide galanin has been also identified as an inhibitor of GLP-1 secretion from intestinal L-cells, both *in vitro* and *in vivo*[26,34].

Physiological responses of GLP-1 are elicited upon binding of the hormone to its receptors belonging to the class B family of 7-transmembrane heterotrimeric expressed G-protein-coupled receptors, a family that also includes receptors for glucagon, GLP-2, and GIP[45,46]. Increasing evidence points towards an ubiquitous expression of GLP-1 receptor (GLP-1R), in tissues ranging from pancreas ($\alpha$, $\beta$, and $\delta$ cells), lung, heart, kidney, stomach, intestine, pituitary, skin and ganglion neurons of the vagus nerve, to multiple regions of CNS (including brainstem, hypothalamus, hippocampus and cortex)[26,30]. Importantly, GLP-1R expression was detected in mammalian brain neurons, astrocytes, microglia and endothelial cells[47] and, even more strikingly, GLP-1Rs have been identified in lipid rafts, where they interact with caveolin-1, thereby regulating receptor subcellular localization, trafficking, and signaling[48].

Interestingly, rat and human GLP-1Rs are polypeptiede chains with 463 amino acids and share 90% sequence homology[19]. Structurally, GLP-1R possesses a long N-terminal extracellular region responsible for peptide recognition and binding, and a cytoplasmic C-terminal containing the components for specific G protein coupling, thus having a major influence in signaling specificity and transmission[49,50]. Once activated, GLP-1R stimulates the adenylyl cyclase system, increasing intracellular cyclic adenosine monophosphate (cAMP) levels and, subsequently, activating the downstream PKA and exchange protein activated by cAMP-2 (Epac2) pathways[4,29]. Alternatively, GLP-1R activation may also increase intracellular $Ca^{2+}$ and phospholipase C levels, or stimulate other signal transduction pathways, depending on the activated tissues, including phosphoinositide 3-kinase (PI3K), insulin receptor substrate-2, epidermal growth factor receptor transactivation, PKC, MAPK, cyclic AMP response element binding protein (CREB), pancreatic duodenal homeobox-1, and glucose transporter-2[26,51,52].

Importantly, some authors suggested that at least part of GLP-1-associated endocrine effects (*e.g.,* GLP-1R-dependent insulin secretion) may be indirectly mediated by neural mechanisms[42]. This appears to be supported by the increasing notion that GLP-1R activation may generate new signals to guide the energetic flux towards tissues (*via* the autonomic nervous system) and ultimately regulating a diverse array of homeostatic functions (Figure 1)[23,53,54].

### *The short-half life of GLP-1: Inactivation by dipeptidyl peptidase-4*

Concerning the use of incretin-based anti-T2D therapy, we must bear in mind that a continuous GLP-1 administration would be required to effectively maintain glucose homeostasis. In fact, given the native GLP-1 short half-life of less than 2 min [the hormone is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4)][55,56], this would render its therapeutic use unfeasible, as we will discuss later.

DPP-4 is a ubiquitous and multifunctional enzyme that can be found either solubilized in blood or membrane-anchored in many cell types[57]. This glycoprotein is widely expressed in multiple tissues, including kidney, lung, adrenal gland, pancreas, liver, thymus, lymph node, uterus, placenta, prostate and on the surface of lymphocytes, macrophages and endothelial cells[58,59]. More relevant herein, DPP-4 appears to be also expressed in several brain areas (*e.g.,* hypothalamus, hippocampus, circumventricular organs, choroid plexus, and leptomeninges)[60,61]. And besides its well known role in GLP-1 inactivation, DPP-4 has been also implicated in numerous pleiotropic cellular processes involving cell cycle regulation, proliferation, adhesion, immunomodulation and apoptosis[62-64].

Molecularly, DPP-4 is able to specifically cleave different dipeptides possessing an alanine, proline or hydroxyproline in the penultimate N-terminal position. These substrates include fibronectin, substance P, chemokines, neuropeptide Y (NPY), peptide YY (PYY), and the best validated *in vivo* substrates: GLP-1, GLP-2 and GIP[62,63]. The resulting GLP-1 (7-36)-amide is metabolized to GLP-1 (9-37) or GLP-1 (9-36)-amide, which has a 1000-fold reduced affinity for GLP-1R and thus completely blunts its insulin-releasing activity[56,57]. Besides DPP-4, another relevant step in GLP-1 inactivation process can be catalyzed by the neutral endopeptidase (NEP), a membrane-bound zinc metallopeptidase expressed in both the periphery and CNS, that is responsible for GLP-1 (7-36)-amide hydrolysis into smaller peptides[65,66]. Therefore, as most of GLP-1 passing the portal circulation has been already degraded by DPP-4, GLP-1 (9-37) and GLP-1 (9-36)-amide constitute the major circulating forms of the hormone (with an estimated half-life of 8-10 min, as a result of renal clearance)[25]. Apparently, this suggests that, after GLP-1 secretion and release by intestinal L-cells, DPP4 starts to continuously degrade the incretin hormone, thus accounting for 50% of GLP-1 inactivation[30,67]. Then, after its passage through the liver, another large amount of the remaining intact bioactive form of the peptide is further inactivated, thus culminating in less than 10% of active GLP-1 reaching the blood circulation[30].

## INCRETIN-BASED THERAPIES: THE FUTURE OF ANTI-T2D AND NEURODEGENERATIVE DISEASES?

The management of T2D through a patient's lifetime is often difficult and frequently renders the achievement of therapeutic goals unsuccessful. However, this

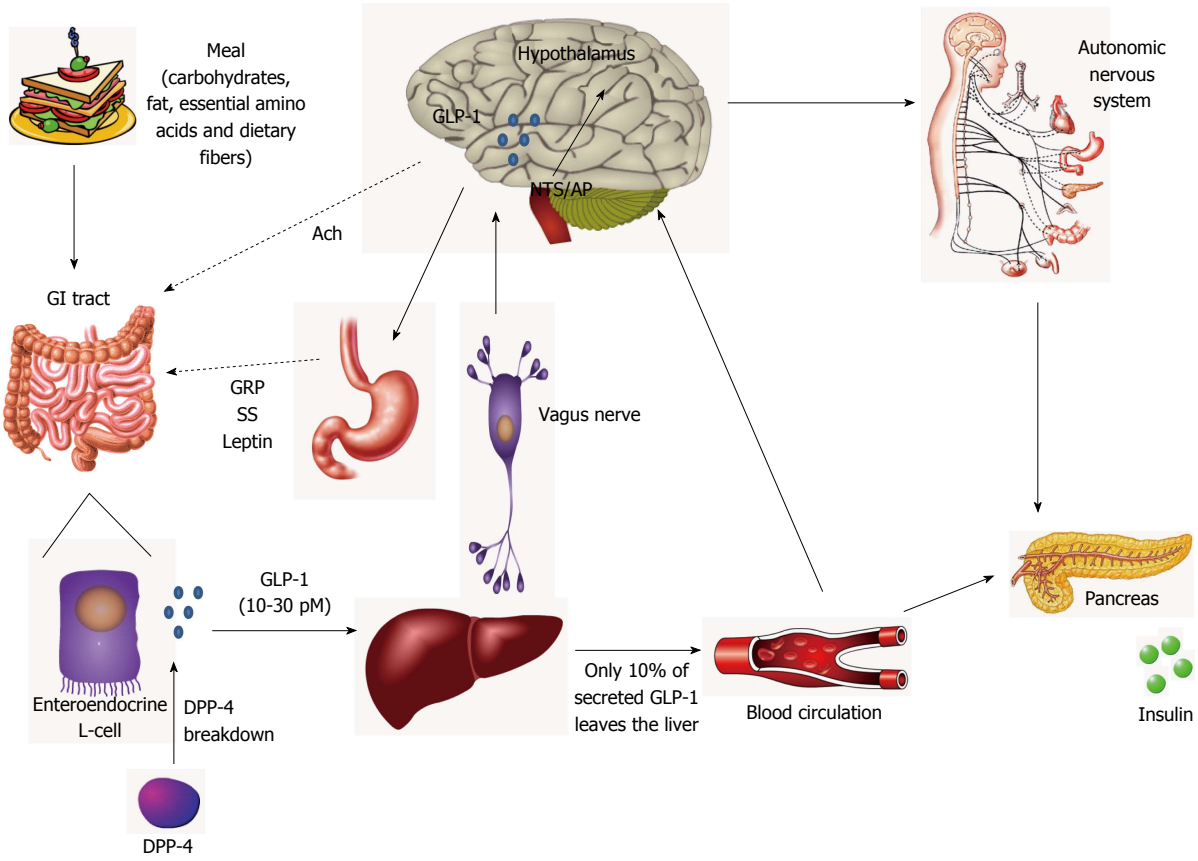


**Figure 1 The gut-brain axis for the actions of glucagon-like peptide-1.** After a meal ingestion, gastrointestinal (GI) tract is rapidly stimulated and glucagon-like peptide-1 (GLP-1) is secreted in the gut lumen by enteroendocrine L-cells. Besides the direct interaction of nutrients with L-cells, neural (acetylcholine) and endocrine (gastrin-releasing peptide, somatostatin and leptin) mechanisms are also involved in the control of GLP-1 secretion after food intake. Bioactive GLP-1 diffuses into the capillaries, immediately beginning to be degraded by dipeptidyl peptidase-4, so that more than 50% of the hormone is inactivated before reaching the portal circulation. In the liver, a further large amount is truncated, thus only 10% of the secreted GLP-1 leaves the liver and enters the systemic circulation and may reach the pancreas, the brain and other tissues *via* the endocrine pathway. However, the passage of GLP-1 through the hepatoportal vein activates vagal afferents nerves that initiate a neural signal towards the brain. In the central nervous system, the metabolic information is received by the solitary tract nucleus and the AP in the brainstem, which synthesize and project the GLP-1 to the hypothalamus. The GLP-1 receptor signaling is involved in the central control of energy homeostasis and food intake, and several autonomous functions, such as glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion in the pancreas, cardiovascular effects, regulation of gastric emptying and of endogenous glucose production in liver and glucose uptake and storage in muscle and adipose tissue. GRP: Gastrin-releasing peptide; Ach: Acetylcholine; SS: Somatostatin; DPP-4: Dipeptidyl peptidase-4; AP: Area postrema.

scenario has been increasingly challenged in the recent years, due not only to the promising results obtained with GLP-1-related therapy in T2D, but also to its widespread beneficial effects on body weight and metabolic parameters where other promising anti-T2D approaches failed[68]. Altogether, this rendered the GLP-1R-mediated intracellular signaling one of the most appealing targets in the development of therapies for diabetes management. Importantly, and despite GLP-1's pharmaceutical promise, the first crucial step was the need to overcome its rapid degradation by DPP-4, thereby enhancing the hormone's action time[69-71]. In this regard, two novel classes of glucose lowering agents, the DPP-4-inhibitors and the GLP-1R agonists (GLP-1RAs) have been intensively developed over the last years[72].

### *DPP-4-inhibitors and GLP-1R agonists: The future therapeutic dream team?*

DPP-4-inhibitors are orally-given small molecules that compete with DPP-4 substrates for the active site of the enzyme, thus avoiding the inactivation of native bioactive GLP-1 and, therefore, extending its half-time and increasing its levels in circulation[73,74]. Currently, there are three inhibitors approved for treatment of T2D in the United States and Europe: sitagliptin, saxagliptin and linagliptin[74]. Besides these, vildagliptin is another DPP-4 inhibitor also available only in Europe[73].

On the other hand, given the peptidic nature of GLP-1RAs, it is necessary to administer them by subcutaneous injection[75]. These molecules have been developed based on the effects of native GLP-1 (binding to GLP-1R and activating similar glucoregulatory effects), but with a high resistance to DPP-4 degradation, thereby increasing the systemic GLP-1 activity[73]. Currently, three GLP-1RAs are commercially available: exenatide twice daily (EBID), liraglutide once daily, and exenatide once weekly (EQW)[74]. Importantly, most of these incretin-based therapies

have been approved as a second line therapy, in dual or triple combination with other anti-diabetic therapies, including metformin, sulphonylureas (SU) and thiazolidinediones (TZD)[75].

Since the endogenous levels of incretin hormones appear to be reduced in T2D patients, increasing evidence points towards a higher effectiveness of GLP-1RAs-based therapies in glycemic control than the use of DPP-4-inhibitors, particularly in reducing glycated hemoglobin $A_{1C}$ ($HbA_{1C}$) and postprandial glucose levels[8,11]. Furthermore, contrary to GLP-1RAs, DPP-4-inhibitors appear to be weight neutral, with no effect in gastric emptying, and with less described positive cardiovascular effects[76,77]. And although some adverse events have been reported in both therapeutic subclasses [namely an increased risk for infections with DPP-4 inhibitors and common gastrointestinal side effects (predominantly nausea) with GLP-1RAs], the overall tolerability was comparable and general positive results were described for both classes of incretin-related therapy, with no episodes of major hypoglycemia documented in patients on either therapy[8,78]. Thus, it is not surprising that, in the last years, the incretin-based therapies (and particularly GLP-1RAs) have been increasingly faced as the potential "dream team" not only for the treatment of T2D and its associated complications, but also for other disorders involving changes in glucose homeostasis and metabolism [*e.g.,* neurodegenerative diseases, as Alzheimer disease (AD)].

### *GLP-1R agonists: Exenatide and liraglutide*

As previously referred, the main advantage of GLP-1RAs over DPP-4 in terms of T2D treatment appears to be the fact that these patients often present lower circulating incretins' levels[8,11]. Although comparative clinical efficacy data are still limited to support the use of one GLP-1RA molecule over another, some comparative studies have already shown some differences between the two main GLP-1RAs, exenatide and liraglutide. First, liraglutide has been considered a true GLP-1 agonist, sharing 97% sequence identity with human GLP-1, while exenatide is a mimetic isolated from the saliva of the Gila monster (Heloderma suspectum) that shares only 53% structural similarity with native GLP-1[79-83]. Additionally, the long-acting GLP-1 analog liraglutide, $Arg^{34}$,$Lys^{26}$-{N-ε-[γ-Glu(N-α-hexadecanoyl)]}-GLP-1 (7-37), has a substitution of a lysine residue with arginine at position 34 and a 16-carbon fatty acid chain *via* a glutamic acid spacer attached to lysine at position 26, thereby promoting the noncovalent binding of liraglutide to serum albumin that not only confers its DPP-4 enzyme resistance and protection from renal clearance, but also allows liraglutide molecules to form heptamers, slowing its absorption rate from injection site and increasing its half-life in plasma to 13 h (in contrast with the 2 h half-life of exenatide)[84-86]. And although the efficacy of peptide injection into the organism may be partially compromised by the formation of antibodies against GLP-1RAs, given its protein sequence differences liraglutide appears to be less immunogenic than exenatide[75,87,88]. Indeed, the Liraglutide Effect and Action in Diabetes-6 (LEAD-6) study reported that 61% of T2D patients treated with exenatide developed antibodies compared to only 2.6% of patients given liraglutide[89,90]. Importantly, this trial also showed that, during the 26-wk study, liraglutide was significantly more efficient than exenatide BID in reducing HbA1c levels (1.12% *vs* 0.79% respectively) and in improving HOMA-β (homeostasis model assessment of β-cell function) index in T2D patients, thereby suggesting that liraglutide may also induce a better improvement in β-cell function[89,90]. But, to us, the most striking point from the LEAD-6 clinical trial was that, in a 14-wk extension, patients who started and responded well to exenatide BID treatment could even further ameliorate some parameters when switching to liraglutide. For instance, these patients further reduced $HbA_{1C}$ levels by 0.32%, body weight by 0.9 kg and systolic blood pressure by 3.8 mmHg[89,90]. In another comparative study between liraglutide and exenatide QW - the DURATION-6 trial -, the first was shown to decrease $HbA_{1C}$ levels by 1.48% in T2D patients compared to the 1.28% lowering achieved with exenatide QW[91]. Additionally, in this study more patients submitted to liraglutide therapy were able to achieve $HbA_{1C}$ < 7% than with exenatide QW[91]. And, as in LEAD-6, weight loss was greater among patients receiving liraglutide (-3.58 kg *vs* -2.68 kg). Interestingly, 94% of the liraglutide-treated T2D patients from the DURATION-6 trial were satisfied with their treatment compared with 86% of those receiving exenatide[91]. To further complete this comparative overview on both drugs, we must refer that, since the primary route of exenatide clearance from the body is through renal excretion, this may pose some risk of accumulation in patients with renal disease, and, thus, exenatide is not recommended for patients with hepatic impairment[79,92,93]. Conversely, liraglutide (as GLP-1) is almost exclusively enzymatically degraded by DPP-4 and NEP, and therefore, renal impairment should not affect liraglutide efficacy[94].

**The actions of liraglutide in peripheral diseases:** T2D is mainly characterized by hyperglycemia and an impaired insulin action. However, T2D most dangerous and devastating consequences may arise from the development of long-term complications (*e.g.,* retinopathy, nephropathy, cardiovascular disease, stroke, neuropathy, cerebrovascular disease), which in most cases are already installed by the time of diagnosis[95].

As previously discussed, the first characteristic that turned GLP-1 into an ideal candidate for T2D treatment was its property to enhance glucose- induced insulin release and overcome insulin desensitization[6,7]. However, over time GLP-1 has been shown to exert

**Table 1 Studies assessing the effects of liraglutide in different organs and/or conditions**

| Liraglutide effects | Study | Ref. |
|---|---|---|
| Pancreas | Review | Davies *et al*[99] |
| | Preclinical | Shao *et al*[97] |
| | | Yosida *et al*[98] |
| Heart | Review | Davies *et al*[99] |
| | | Martín-Timón *et al*[100] |
| | | Vilsbøll *et al*[101] |
| | | Seufert and Gallwitz[104] |
| | Preclinical | Liu *et al*[103] |
| | | Noyan-Ashraf *et al*[106] |
| | | Shiraki *et al*[107] |
| | Clinical | Russell-Jones *et al*[102] |
| | | Marso *et al*[105] |
| Kidney | Preclinical | Fujita *et al*[114] |
| | Clinical | Armstrong *et al*[110] |
| | | Davidson *et al*[111] |
| Liver | Clinical | Eguchi *et al*[116] |
| | | Armstrong *et al*[117] |
| Muscle | Preclinical | Ji *et al*[109] |
| | | Li *et al*[118] |
| Weight and appetite | Review | Davies *et al*[99] |
| | | Seufert and Gallwitz[104] |
| | | Rigato and Fadini[119] |
| | | Sjoholm[121] |
| | | van Bloemendaal *et al*[123] |
| | | Ng and Wilding[135] |
| | Clinical | Toft-Nielsen *et al*[17] |
| | | Horowitz *et al*[133] |
| | | Wadden *et al*[136] |
| | | Wadden *et al*[137] |
| | | Senda *et al*[138] |
| | | [139] |
| | | Astrup *et al*[140] |
| | | Rosenstock *et al*[141] |
| Neuroprotection/ T2D brain | Review | Hölscher[205] |
| | | Duarte *et al*[206] |
| | | Hölscher[210] |
| | Preclinical | Hou *et al*[47] |
| | | Hunter *et al*[204] |
| | | Hamilton *et al*[207] |
| | | Agrawal *et al*[208] |
| | | Cummings *et al*[209] |
| | | Parthsarathy *et al*[212] |
| AD | Preclinical | McClean *et al*[213] |
| | | Han *et al*[214] |
| | | McClean *et al*[215] |
| | | Long-Smith *et al*[216] |
| | | McClean *et al*[217] |
| | | Parthsarathy *et al*[218] |
| | | Yang *et al*[219] |
| | Clinical | [220] |
| | | [221] |
| | | [222] |
| Stroke | Preclinical | Sato *et al*[227] |

T2D: Type 2 diabetes; AD: Alzheimer disease.

many other interesting (and potentially therapeutically relevant) effects in the organism[96] and, in this perspective, the GLP-1RA liraglutide may have also a significant impact (rather than the "mere" GLP-1R activation), not only in periphery, but also in CNS and in other pathologies besides T2D (Table 1), as we will further discuss.

Regarding the role of liraglutide in the periphery and the progressive loss and dysfunction of pancreatic β-cells that constitutes one of the key features of T2D, several recent studies have shown that the drug was able not only to protect (through anti-apoptotic effects), preserve and enhance β-cell mass, but also to improve β-cell function [seen in the *db/db* and in the transient receptor potential melastatin 2 (TRPM2)-deficient mice models], thereby improving glucose control, and insulin secretion and sensitivity[97-99].

It is well known that chronic hyperglycemia and poor blood glucose control may also underlie cardiovascular dysfunction and development of cardiovascular disease, thus rendering T2D a risk factor for cardiovascular disease[100]. Therefore, it is not surprising that emerging data from animal and human studies also point towards a liraglutide-mediated reduction in systolic blood pressure and improvement in lipid profiles (decreased low-density lipoprotein cholesterol and triglycerides levels, and increased high-density lipoprotein cholesterol)[99,101,102]. Moreover, Liu *et al*[103] demonstrated that liraglutide improves cardiac function in diabetic rats, probably due to a decreased expression of proteins involved in the endoplasmatic reticulum stress pathway. Accordingly, recent studies also associated liraglutide treatment with a significant decrease in several cardiovascular risk biomarkers, such as plasminogen activator inhibitor-1, B-type natriuretic peptide [104-106], interleukin-6 (IL-6) and tumor necrosis factor-α[107,108]. Besides cardiovascular function, liraglutide was also shown to reduce endothelial cell dysfunction in a process probably mediated by its anti-oxidant and anti-inflammatory effects[107]. Moreover, other tissues can be directly or indirectly affected by GLP-1RA therapies, including muscle, liver and kidney[109-111], thus rendering them highly promising against other pathologies than T2D. However, some caution must be used and further clarification is needed as, *e.g.,* was recently reported that, albeit rare the aggravation of an existing nephropathy in T2D patients submitted to GLP-1RA treatment may be due to external factors (*e.g.,* other medications), but if related with this therapy it may probably arise from gastrointestinal problems[112,113]. Nevertheless, recent data also showed that liraglutide was able to counteract renal impairment in a mouse model that also displayed chronic hyperglycemia and increased renal oxidative stress[114]. According to these authors, such protection was due to liraglutide-mediated inhibition of NAD(P)H oxidase and activation of cAMP-PKA pathway, thus suppressing the progression of renal failure[114].

Concerning the effects of GLP-1 analogues in hepatic impairment, there is currently an increasing interest mostly due to the lack of effective therapies against hepatic diseases. Amongst them, the non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver diseases, being strongly related with insulin resistance, metabolic syndrome, cardiovascular disease, cerebral vessel

disease and T2D[115]. In a recent pilot study involving patients diagnosed with diabetes complicated by NAFLD/non-alcoholic steatohepatitis (NASH), liraglutide (0.9 mg/body per day) was given for 24 wk[116]. Data suggested that liraglutide significantly improved liver function (as given by the decreased serum levels of alanine aminotransferase, aspartate aminotransferase, ferritin and C-reactive protein) and histological changes in NASH patients[116]. Besides this, data from LEAN-2 study demonstrated that liraglutide combined with metformin also exerted positive effects in liver enzymes and hepatic steatosis in T2D patients[117].

Regarding the impact of liraglutide on muscle, Li *et al* [118] showed recently that this drug increases cAMP and AMP-activated protein kinase (AMPK) signaling pathways, which may in turn induce GLUT4 translocation in mouse skeletal muscle cells.

**The role of liraglutide in appetite and weight loss: A centrally-regulated peripheral anorectic effect:** Unhealthy lifestyle, weight gain and obesity are intimately related with the increased prevalence of T2D worldwide, being estimated that 60%-90% of T2D patients are overweight[119-121]. Importantly, weight gain has been also described as a common side-effect of standard anti-T2D therapies. Therefore, weight management should be an important issue herein, as it not only may interfere with treatment, but may also increase the risk for the development of long-term complications (*e.g.,* cardiovascular disease)[120,122]. However, the control of body weight and energy balance is a complex process, involving different tissues and pathways, such as gut, adipose tissue, pancreas and brain[30,123]. For instance, gut-derived hormones (*e.g.,* GLP-1, PYY, ghrelin, cholecystokinin and oxyntomodulin) are known to play a major role in feeding regulation, at least partially by relaying to the CNS information on nutritional status[123]. On the other hand, GLP-1's well known anoretic properties have been suggested to arise from the combination of both central and peripheral effects, *via* another gut-brain connection[23,124]. More specifically, GLP-1-mediated satiating effect requires primarily the activation of peripheral GLP-1Rs located on vagal sensory afferents in the gut and in the hepatoportal region of the liver; after the transmission of the metabolic signals into the brain c-fos expression is increased in NTS neurons[124,125]. Once activated, these neurons act on brain neuronal circuits from the brainstem and several other areas involved in appetite control, where GLP-1R are also expressed. These include the ventral tegmental area (VTA), nucleus accumbens (NAc) and hypothalamus[37,39,123]. In the hypothalamus, GLP-1R are highly expressed in the paraventricular nucleus, dorsomedial hypothalamus and the arcuate nucleus (ARC) [where they overlap with the pro-opiomelanocortin (POMC) neurons (anorexigenic neurons)], being present at a lesser extent in agouti-related peptide (AgRP)/NPY neurons (orexigenic neurons)[23,126,127]. At this respect, Seo *et al*[128] demonstrated that intracerebroventricular (icv) infusion of GLP-1 stimulates the synthesis of anorexigenic peptides (POMC and cocaine- and amphetamine-regulated transcript), and simultaneously decreased the synthesis of NPY and AgRP in rodents. Accordingly, while effects on hypothalamic and brainstem circuits may regulate food intake, the inhibitory effect of GLP-1 on the rewarding value of food appears to be regulated by the regions of VTA and NAc (mesolimbic reward system)[123,124]. This hypothesis was supported by the finding that the administration of the GLP-1R antagonist, exendin 9-39, into the NAc promoted hyperphagia in rats[129]. After hypothalamic and brainstem (dorsal motor nuclei) stimulation, efferent impulses depart from these brain areas to regulate the gastrointestinal tract, pancreas and other peripheral organs, by slowing gastric emptying and acid secretion, and decreasing gut motility, thereby further controlling the feeding behavior and glucose metabolism[39,124]. Although such slowed gastric emptying may also arise from a direct activation of gastric inhibitory GLP-1Rs, this appears to be more visible with long-acting GLP-1RAs, particularly liraglutide (whose potent gastric emptying capacity has been increasingly described)[104]. Importantly, the rate of gastric emptying may also influence stomach distension, thereby stimulating gastric mechanoreceptors, with the subsequent activation of the nodose ganglion (inferior ganglion of vagus nerve) that may *per se* culminate in the activation of NTS neurons to induce satiety[123]. Besides this, a direct central action of GLP-1 in satiation signaling was also demonstrated by an inhibition of food intake by pathways independent of the vagal afferents[130-132].

As T2D-associated postprandial hyperglycemia may be further aggravated by an accelerated gastric emptying, it is not surprising that GLP-1RAs drugs have been successful in attenuating postprandial blood glucose levels also by slowing gastric emptying[133]. And although this is not considered the main mechanism by which these drugs regulate appetite and weight loss, it has been widely described that the incidence of gastrointestinal adverse events (such as nausea and vomiting, which albeit transient may affect nearly 50% of treated patients) is often accompanied by a decrease in food intake and body weight. Despite the limited knowledge on the mechanisms involved, it is plausible that a direct effect on gastrointestinal system and a central action producing conditioned taste aversion may play a role herein[104,123,134].

In recent clinical trials, T2D patients treated with liraglutide (either as a monotherapy or in combination therapies) have shown a weight loss, in contrast with the weight gain associated with SU, TZD and insulin[119,121]. More strikingly, both people with or without T2D, treated with clinically relevant doses of liraglutide for 20 to 30-wk presented significant reductions in body weight (from 1 to 3 kg)[99,135].

Importantly herein, despite the increased GLP-1 levels in response to the amount of nutrient intake, obese people were shown to have lower basal GLP-1 levels[136]. Accordingly, a negative relation was also established between body mass index (BMI) and GLP-1 oral stimulation[17]. Moreover, the SCALE Maintenance study reported a loss of 5.9 kg in obese patients treated with 3.0 mg liraglutide for 56-wk *vs* placebo-treated ones[137]. Interestingly, even a study case involving the Prader-Willi syndrome (PWS) (a rare genetic disorder characterized by an extreme and insatiable appetite that ultimately leads to morbid obesity), described that a 25-year-old female hyperglycemic PWS patient submitted to liraglutide therapy, not only improved her glycemic control, but was also able to control hyperphagia and to decrease plasma ghrelin levels and her BMI[138].

From the above, such consistent weight loss observed with liraglutide and other GLP-1RAs, not only in T2D patients, but also in non-T2D people has aroused the interest for the use of GLP-1RAs as promising pharmacotherapies for weight management. To further potentiate this interest, we must bear in mind that, to date, only one medical therapy against obesity is approved in Europe, with most current anti-obesity pharmacological drugs having serious undesirable side effects[135]. In this regard, the use of these drugs in obese people is currently being tested in several clinical trials[139-141].

**The neuroprotection in type 2 diabetic and degenerative brain: Insulin and liraglutide:** (1) Pathological commonalities between T2D and neurodegenerative diseases: neuroinflammation and brain dysfunctional insulin/ insulin-like growth factor-1 (IGF-1).

Obesity, hypertension, dyslipidemia and T2D all constitute risk factors, particularly vascular, for cognitive dysfunction[142]. Numerous experimental data indicated a decrease in cognitive function in T2D patients, which is often accompanied by impairments in memory, attention, intelligence, processing speed and executive functions, as well as by brain atrophy (particularly in cortical, subcortical and hippocampal areas) and white matter abnormalities[143,144]. Interestingly, the well described cell loss that occurs in T2D pancreas appears to be accompanied by cell loss also in the CNS upon disease progression[145,146]. Indeed, the pathological progression of T2D and, more specifically, its associated glucose toxicity, insufficient insulin action, neuroinflammation and general aging, amongst others, can slowly lead to nervous damage and may ultimately result in diabetic neuropathy and diabetic encephalopathy, thus increasing the risk for dementia in diabetes[147-149]. In line with this, chronic inflammatory response in brain has been suggested to play a pivotal role in propagating T2D-mediated injury. This may probably occur *via* activation of microglia and other immune cells, with the subsequent release of neurotoxic amounts of proinflammatory cytokines and free radicals and ultimately leading to neurodegeneration and brain disease upon T2D progression[150-152]. Additionally, similarly to desensitization of IR from peripheral tissues of T2D patients, increasing evidence also point towards the impairment of brain insulin signaling in AD[153,154]. As a consequence, it has been increasingly suggested that brain insulin resistance could be a potential link between T2D and AD[95,151]. This hypothesis has been supported by numerous evidences, *e.g*., (1) a decrease in IR expression in brains from AD patients; (2) an inverse correlation found between AD Braak stage and the levels of such receptors; (3) the accumulation of hyperphosphorylated tau (a neuropathological hallmark of AD) upon insulin signaling impairment and the consequent inhibition of GSK-3β phosphorylation and of tau protein phosphatase 2A[155,156]; (4) the increased Aβ accumulation and decreased insulin degrading enzyme (IDE) levels in AD patients displaying also brain insulin resistance[157]; and (5) the memory enhancement and protection against Aβ toxicity in AD patients submitted to insulin therapy[158]. These and other *in vivo* and *in vitro* findings have been also corroborated and extended by epidemiological studies showing an increased risk for T2D patients to develop AD and *vice versa*. According to a very recent study, T2D patients have a 65% increased risk to develop AD later in their life[155], whereas others found that 85% of AD patients had either T2D or increased fasting glucose levels[159].

Parkinson disease (PD) is the second most common neurodegenerative disorder after AD, the most common form of parkinsonism (motor syndrome) and, pathophysiologically, is the predominant form of synucleinopathies, which are characterized by an abnormal accumulation of α-synuclein (α-syn) protein[160]. PD is characterized by the neuronal accumulation of Lewy bodies (containing deposits of α-syn) and the progressive loss of dopaminergic neurons (particularly in substantia nigra) that may culminate in multiple motor (tremor, rigidity, slowness of movement, and postural instability) and non-motor (autonomic dysfunction and neuropsychiatric problems) symptoms occurring throughout the course of the disease[161]. Nowadays, an increasing amount of evidence points towards several similar biochemical changes between PD and T2D, leading to the idea that dysfunctional insulin signaling might be at the center of those alterations[162]. Amongst such commonalities are, *e.g*., the increased serum IGF-1 levels in PD patients[163,164], both the insulin and IGF-1 resistance found in basal ganglia and substantia nigra from PD[165,166], the impaired dopaminergic signaling observed in a rat model of T2D[167], and the observation that activation of PI3K/Akt pathway was able to rescue α-syn toxicity *in vitro*[168].

Stroke (or cerebrovascular accidents) is considered the third most common cause of death in

developed countries and may develop as a long-term complication in comorbid diseases, such as T2D[169,170]. Indeed, epidemiological studies point towards a 2- to 6-fold increased risk of T2D patients to development of stroke, whereas stroke victims often present impaired glucose tolerance[171,172]. It is well known that this disease arises from a disturbance in the blood supply to the brain (due to ischemia or hemorrhage), thus resulting in neurological deficits and a loss of brain function[173]. Interestingly, stroke has been regularly associated with increased neuroinflammation markers[174], thereby rendering GLP-1 analogues an appealing therapeutic strategy, as we will discuss later.

Strikingly, such correlation between T2D, AD, PD and stroke appears to be also applicable to a wide range of other neurodegenerative diseases, including vascular dementia or Huntington disease (HD)[95,170], thereby suggesting that T2D is a risk factor for at least some of these brain pathologies.

(2) Brain insulin/IGF-1 as metabolic and body weight regulators.

As it is well known, the primary regulators of glucose homeostasis and metabolism involve insulin/IGF-1 signaling pathways responsible for the control of both peripheral signals and CNS effects[155]. Although most of the brain insulin is primarily secreted by the pancreas (whereas IGF-1 comes from the liver), being then transported by cerebrospinal fluid (CSF) and crossing the BBB into the brain, numerous evidence also points towards their local synthesis (particularly in brain cortex, olfactory bulb, hippocampus, hypothalamus, and amygdala)[175]. Once bound to their receptors, the insulin and IGF-1 receptors (IR and IGF-1R, respectively) that are ubiquitously expressed in brain (particularly neurons), many physiological functions are activated, such as neuronal outgrowth and survival, enhancement of attention, memory formation and cognition, food intake and weight maintenance, synaptic protection and sexual regulation[170,176,177]. Of these, food intake and energy homeostasis are the most directly related also with GLP-1R-mediated signaling, being mediated by a specialized group of hypothalamic glucosensing neurons that appear to be able to detect and respond to even small variations in glycemia[130]. Such anorexigenic effect of insulin signaling depends on a strict control of the hypothalamic PI3K/protein kinase B (Akt) signaling pathway, on the inhibition of NPY and AgRP expression and on the induction of POMC neurons[178,179].

From the above, it is not surprising that changes in body weight, hyperinsulinemia and insulin resistance may arise from alterations in the homeostatic balance, thus culminating in injurious effects on the organism[180,181]. Indeed, hyperinsulinemia has been widely associated to a downregulation of insulin transport across the BBB, thus decreasing its uptake and levels in the brain, as well as the subsequent IR activity, ultimately leading to a brain insulin resistance[182,183]. Moreover, insulin resistance and subsequent impairment in glucose supply, transport and utilization may lead to glucose dysmetabolism that may be also accompanied by a decrease in cerebral flow and damaging effects to intracellular organelles, including mitochondria[184-186]. As brain mitochondria are particularly susceptible to metabolic impairment, situations like brain insulin resistance may lead to dysfunctional respiratory chain and phosphorylation system, and alterations in mitochondrial dynamics and biogenesis that may significantly compromise ATP production and mitochondrial membrane potential. As a result, mitochondrial permeability transition pore may open and ultimately activate apoptotic cell death[184]. Thus, defects in brain insulin/IGF-1 signaling may raise a deleterious vicious cycle involving metabolic impairment and mitochondrial dysfunction, that in turn generate a wide range of harmful effects (*e.g.,* increased oxidative stress, advanced glycation end-products formation, inflammatory response, excitatory neurotransmitter release)[175,187]. Altogether, these alterations can be responsible for a decrease in neuronal function and survival, and impaired synaptic activity and plasticity, that may be also accompanied by a decrease in neurogenesis, leading to impaired memory formation and storage, and learning potential, culminating in cognitive decline[188]. To further intricate this subject, as we detailed above, both T2D and neurodegeneratives diseases share several common features that together with the neuroprotective effects demonstrated by many of the already marketed anti-T2D therapeutic agents have potentiated the recent investigations worldwide on the potential beneficial role of such drugs also in the context of neurodegeneration[96,189].

(3) Restoration of insulin/IGF-1 action as a potential therapeutic target in neurodegenerative diseases: what can we count on in a near future?

Preclinical studies involving insulin and IGF-1 to treat animal models of neurodegenerative diseases revealed promising results. In this regard, our group showed that insulin was able to protect against oxidative stress and a decline in mitochondrial oxidative phosphorylation efficiency induced by the amyloid β-peptide (Aβ, one of the main players in AD pathology) in streptozotocin (STZ)-induced type 1 diabetic rats[190]. Similarly, Quesada *et al*[191] reported that IGF-1 treatment significantly increases tyrosine hydroxylase (TH) positive neurons and improves motor performance of the medial forebrain bundle 6-hydroxydopmaine (6-OHDA) lesion rat model of PD, in a PI-3K/Akt-dependent manner. Additionally, we and others showed that by increasing blood insulin and brain IGF-1 levels, the *in vivo* peripheral administration of IGF-1 was not only able to protect against peripheral glucose intolerance[192], but also to rescue motor deficits and brain glucose dysmetabolism upon HD[193]. Molecularly, these observations were further supported and extended by a recent study using an *in vitro* model of human HD, in which insulin- and IGF-1-mediated

PI3K/Akt activation was able to improve mitochondrial function and decrease mitochondrial reactive oxygen species (ROS) formation[194].

Even though insulin therapy can be very useful to prevent or slow the progression of long-term complications of diabetes and others pathologies, as diseases progress not only the hormone's beneficial effects may be lost (including glycemic control), but also it may increase the risk for severe hypoglycemic episodes, which have been also associated with increased brain damage. As a result this may further increase neuronal and cognitive dysfunction[195]. Alternatively, the use of insulin sensitizers (another commonly prescribed class of anti-T2D drugs, whose most widely used member is metformin, a first line pharmacological approach against the pathology) could provide a reliable therapeutic alternative also in the context of neurodegenerative diseases[154,196]. Indeed, metformin was demonstrated to protect the brains of the non-obese T2D Goto-Kakizaki rat models against oxidative imbalance, by decreasing oxidative stress markers and increasing antioxidant defenses[197]. Additionally, Gupta *et al*[198] reported that metformin ameliorates neuronal insulin resistance and AD-associated characteristics in an *in vitro* model of the so-called "type 3 diabetes". Nevertheless, we must bear in mind that metformin presents several controversial side effects, and some authors suggested that metformin therapy and subsequent AMPK activation may even exacerbate previously existing impairments[199-201].

From all the above, and given also the previously mentioned actions in the brain, the native GLP-1 hormone would be considered the "almost perfect" alternative to restore insulin action in CNS, either in T2D, neurodegenerative diseases or simply in normal aging. And this has been widely corroborated by its rapid capacity to cross the BBB when injected peripherally, acting as a growth factor in brain, whereby the hormone has been shown to stimulate the metabolism, the expression of genes associated with cell growth, repair and replacement and to protect against oxidative injury, neuroinflammatory response and apoptosis, thus exerting beneficial effects in neuronal health and cognition[155]. However, given the previously described limited half-life of the native GLP-1, recent research interests have been mostly focused on the neuroprotective potential of DPP-4 inhibitors and GLP-1RAs.

Regarding DPP-4 inhibitors, their beneficial roles in CNS have been intensively analyzed and appear to constitute promising candidates for the treatment of CNS disorders. In this regard, sitagliptin (the first DPP-4 inhibitor approved for T2D treatment), has been recently shown to positively affect working and reference memories, and to increase the hypothalamic acetylcholine content and adiponectin receptor 1 expression in T2D Sprague-Dawley rats[202]. Additionally, vildagliptin (another DPP-4 inhibitor)-mediated decrease in Aβ, tau protein phosphorylation and neuroinflammatory markers levels were also accompanied by an amelioration in memory retention capacity in a STZ-induced AD rat model[203].

On the other hand, and similarly to the native GLP-1, liraglutide and the other synthetic GLP-1RAs are able to readily cross the BBB, reaching the brain almost intact and thereby exerting neuroprotective effects[204]. Therefore, it is not surprising that most of the preclinical studies that reported such protective effects were performed in T2D, AD, PD and also in stroke models[205]. For instance, liraglutide has been increasingly suggested to prevent or attenuate T2D-associated neuronal and cognitive deficits[206]. Although the underlying mechanisms remain unclear, Hamilton *et al*[207] proposed that such protection could rely on the activation of stem cells and neuronal progenitor cells to counteract T2D-induced neurodegeneration. Indeed, these authors reported that liraglutide was able to promote neurogenesis [as given by the increase in the number of 5'-bromo-2'-deoxyuridine (BrdU)-positive cells dividing progenitor cells and doublecortin-positive young neurons] in the dentate gyrus of three different types of obese T2D mouse models. Additionally, other authors observed that liraglutide administration in 2 mo-old pre-diabetic UCD-T2D rats (a polygenic obese model of T2D) reduced energy intake and body weight, improved insulin sensitivity and reduced triglycerides, thus delaying diabetes onset by about 4 mo compared to controls[208,209]. Moreover, these authors reported that liraglutide normalized brain metabolic homeostasis (as given by TFAM, SIRT1, and AMPK phosphorylation), decreased hippocampal lipid oxidation (upon determination of 4-hydroxynonenal levels), improved brain mitochondrial regulation (*via* PGC-1α) and preserved synaptic plasticity (as given by the BDNF-TrkB signaling) in the UCD-T2D rats over the disease progression[208,209]. These results appear to be in line with previous evidences that GLP-1R activation may be involved in memory and learning[210]. In fact, During *et al*[211] demonstrated that GLP-1R activation was correlated with an enhancement of associative and spatial learning, as GLP-1R-deficient mice exhibited a learning deficit phenotype. Strikingly, liraglutide (25 nmol/kg, once daily *i.p.*, for 30 d) has been also demonstrating potent anti-inflammatory effects in brains from a mouse model irradiated with 6Gy (X-ray, a model of chronic inflammation), as given by a reduction in microglia activation in cortex and dentate gyrus, and a decrease in mean astrocyte load after irradiation (by massively reducing the total GFAP load), in pro-inflammatory cytokines (IL-6, IL-12p70, IL-1β) and in total nitrite levels[212]. Moreover, liraglutide was able to decrease cerebral edema, and to ameliorate both neurobehavioral deficits (in modified Garcia test and wire hanging test) and inflammatory parameters (given by an increased brain phosphorylated AMPK and reduced neutrophil infiltration) in an intracerebral hemorrhage-induced

brain injury mouse model (strongly associated with inflammatory mechanisms)[47].

Therefore, given also the pathological commonalities between T2D and AD, it is plausible that a therapeutic approach involving incretin analogues might be beneficial against the cognitive deficits occurring in AD.

The neuroprotective potential of liraglutide in AD has been increasingly analyzed. In one of the first studies, McClean *et al*[213] reported that liraglutide significantly affects brain neurotransmission and modulates synaptic plasticity by enhancing long-term potentiation (LTP) mechanisms. More recently, Han *et al*[214] observed that pre-treatment with liraglutide dose-dependently protected against the impairment in learning and memory (as given by the dysfunctional spatial memory and hippocampal late-phase LTP) induced by a bilateral intrahippocampal injection of Aβ in adult male Sprague-Dawley rats, suggesting a possible preventive strategy against the development of AD in T2D patients. Strinkingly, McClean *et al*[215], Long-Smith *et al*[216] and McClean *et al*[217] described that once daily intraperitoneally (*i.p.*)-injected liraglutide for 8 wk was able to reduce brain amyloid plaque formation by 30%-50%, as well as the levels of soluble amyloid oligomers (by 25%) and amyloid precursor protein (APP) in the APP/PS1 AD mouse model (which expresses the human Swedish mutated form of APP and a mutated human form of presenilin-1). Additionally, these authors observed that chronic liraglutide administration blunted the Aβ-associated changes in neuronal IR localization and IRS-1 phosphorylation at serine 616 (a key marker of insulin resistance), increased IDE levels, reduced microglia activation by up 50%, decreased the Aβ-associated astrocytic activation, enhanced LTP and synaptophysin levels, and increased hippocampal neuronal progenitor cells, thus indicating a protection against neuroinflammation, synapse loss and deterioration of synaptic plasticity that may culminate in the restoration of memory function, particularly in object recognition and water maze tasks. Interestingly, Parthsarathy *et al*[218] also reported that chronic treatment with liraglutide-mediated increase in neurogenesis in an AD mouse model was accompanied by an increased differentiation of newly generated cells into mature neurons. Concerning abnormal tau protein phosphorylation (another neuropathological hallmark of AD), liraglutide treatment has been able to reduce both brain tau protein phosphorylation at different residues (Ser199, Ser202, and Ser396) and phospho-tau immunoreactivity in T2D rats, which also displayed a reduction of HOMA-IR close to control levels and a normalization of brain insulin signaling (as given by the activation of Akt and subsequent inhibition of GSK-3β at Ser9)[219]. Altogether, these results strongly suggest that liraglutide may be able to prevent and/or reverse the major pathological hallmarks of AD. In line with this, two clinical trials are underway to assess the effects of liraglutide in AD. In a small randomized clinical trial at the University of Aarhus (Denmark)[220], 17 early-onset AD patients were treated with liraglutide (1.8 mg, once a day, 26 wk) and the already available results point towards an effect of liraglutide on cerebral amyloid deposits in the brain (assessed by Pittsburg compound B PET scan), but more novelties are expected soon. The second trial, at the Imperial College of London and launched in June 2013[221], is a large-scale Phase 2 clinical trial involving 206 early AD patients treated with liraglutide (1.8 mg/d, for 12 mo), that aims to use fluorodeoxyglucose-PET scan to detect changes in cerebral glucose metabolic rate, microglia activation, CSF markers, and amyloid and tau levels, to correlate with eventual Alzheimer Disease Assessment Scale Executive (ADAS) and Magnetic resonance imaging (MRI) changes. Interestingly, another ongoing, Phase 2, randomized, double-blind clinical trial sponsored by the National Institute on Aging and aiming at analyzing the action of the long-acting GLP-1RA exendin-4 (Ex-4) in AD[222] will end by December 2015 and involves the evaluation of patients' performance in the Clinical Dementia Rating scale sum-of-boxes, ADAS (cognitive sub-scale), behavior and cognition, changes on structural and functional MRI and magnetic resonance spectroscopy, hormonal and metabolic changes, as well as alterations in CSF and plasma AD biomarkers.

Regarding the protective potential of GLP-1 analogues against PD, evidences are still relatively scarce and mostly relying on preclinical assessing the role Ex-4 in PD. Upon a 3 wk, twice daily i.p administration of Ex-4, it was observed a significant increase in the number of TH-immunoreactive neurons and of dopamine levels that, together with a reduction of amphetamine-induced rotations in the 6-OHDA rat model of PD, suggest that Ex-4 may have beneficial cellular and functional properties in this model of PD[223,224]. Similar effects were also reported in another rat model of PD involving a lipopolysaccaride-induced lesion to substantia nigra[224]. Moreover, Li *et al*[225] observed that Ex-4 protected against the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, another PD-like phenotype inducer)-associated loss of nigral neurons and striatal dopaminergic fibers, preserved dopamine levels and improved motor function. With all this in mind, in a recent randomized Phase 2 clinical trial, Ex-4 safety and efficacy was evaluated in 21 PD patients, which received 5 mg b.i.d for 1 mo or 10 mg b.i.d for 11 mo[226]. The main observations herein included a good tolerability to Ex-4, improved motor scores [from the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)] at 12 mo (a mean improvement of 2.7 *vs* a 2.2 point decline in control group) and cognitive efficiency (using the Mattis dementia rating scale 2) (a mean improvement of 2.8 *vs* a 3.5 point worsening in control group)[226].

Given the previously mentioned increasing interest on the potential therapeutic use of GLP-1 analogues

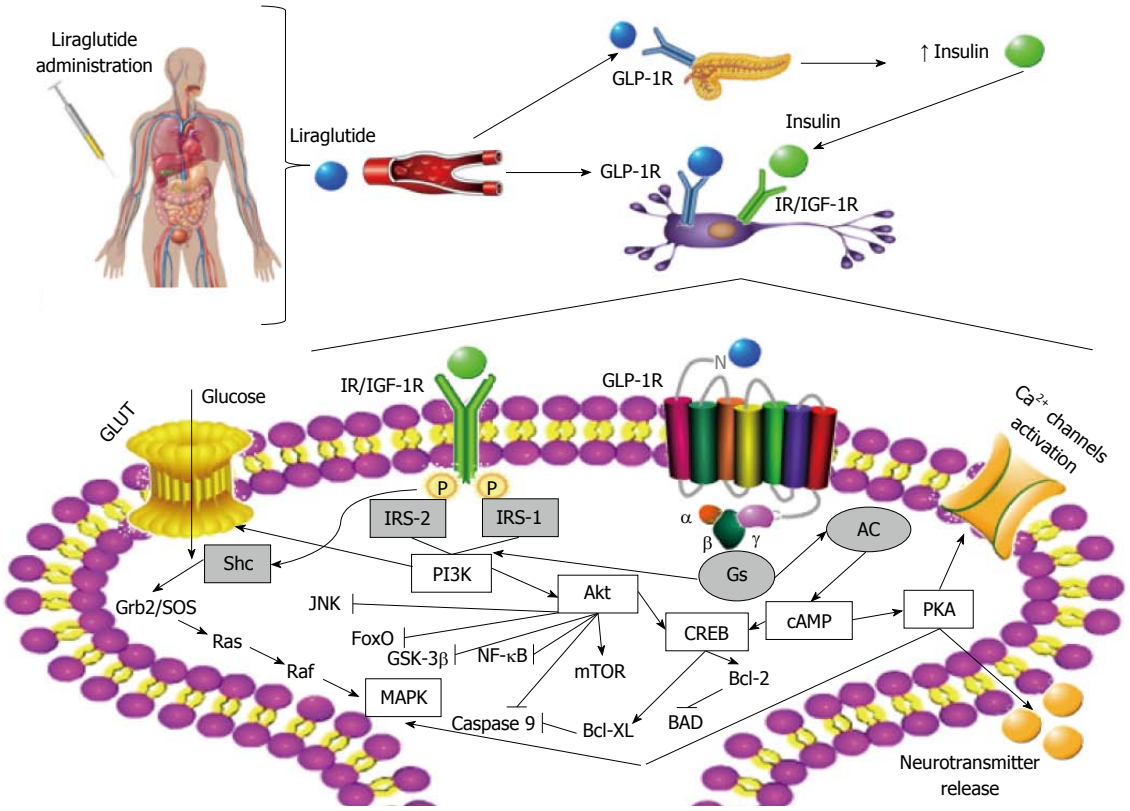


**Figure 2 Overview of the main pathways induced by a peripheral administration of liraglutide in neurons.** When liraglutide enters the body, it will move through the bloodstream and activate glucagon-like peptide-1 receptors (GLP-1R) widely expressed throughout tissues. In pancreas, GLP-1R activation exert insulinotropic effects, thus increasing insulin levels, which may migrate into the brain, crossing the blood-brain-barrier (BBB) and will activate insulin receptor (IR) or insulin-like growth factor-1 receptors (IGF-1R) expressed in neurons. Liraglutide by itself may also cross the BBB and activate GLP-1R present in the brain. Neuronal IR/IGF-1R and GLP-1R mediated intracellular signaling transduction pathways show several overlapping downstream targets. Activation of these pathways may mediate several biological responses in the central nervous system, such as control of cell metabolism and energy homeostasis, inhibition of apoptosis, reduction of inflammatory responses, modulation of synaptic neurotransmission, regulation of gene transcription, cell growth, synapse growth, cell repair and regeneration, facilitation of long-term potentiation and memory formation, among others. AC: Adenyl cyclase; Akt: Protein kinase B; Bcl-2: B-cell lymphoma 2; BAD: (Bcl-2) antagonist of death; Bcl-XL: B-cell lymphoma extra-large; $Ca^{2+}$: Calcium; cAMP: Cyclic adenosine monophosphate; CREB: cAMP response element-binding protein; Foxo: Forkhead box O; GLUT: Glucose transporter; GRB2/SOS: Growth factor receptor-bound protein 2/son of sevenless; GSK-3β: Glycogen synthase 3 beta; GTP: Guanosine triphosphate; IRS-1: Insulin receptor substrate 1; IRS-2: Insulin receptor substrate 2; JNK: C-Jun N-terminal kinase; MAPK: Mitogen associated protein kinase; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: Phosphoinositide 3-kinase; PKA: Protein kinase A; Shc: Src homology-2/a-collagen-related protein.

for stroke treatment, in a recent study Sato *et al*[227] demonstrated that liraglutide was able to ameliorate behavioral scores, to reduce brain infarct volumes at 24 h, to decrease the levels of ROS derivatives and to upregulate vascular endothelial growth factor in brain cortex of a rat model for stroke (90 min transient middle cerebral artery occlusion and 1 h reperfusion). Similarly, neuroprotective effects upon stroke and ischemia were also reported for Ex-4[225,228,229].

From the above, as exenatide and liraglutide are the currently marketed GLP-1RAs for the treatment of T2D, and since preclinical studies have demonstrated remarkable and consistent neuroprotective effects, some clinical trials are underway to assess the effect and efficacy of Ex-4 and liraglutide in AD and PD patients. And although the underlying molecular mechanisms (particularly those focused on the liraglutide's neuroprotective and anti-inflammatory potential) remain mostly unknown, a recent study on human neurons shed some light on this issue. Indeed, Sharma *et al*[230] suggested that liraglutide-mediated neuroprotection may involve the PI3K/Akt pathway and its subsequent regulation of mammalian target of rapamycin; however, it is also plausible that GLP-1R activation under such circumstances may also activate the alternative extracellular signal-regulated kinase signaling. Traditionally, liraglutide-mediated activation of GLP-1R may further activate adenylyl cyclase and increase cAMP content, leading to the subsequent activation of PKA and CREB, and ultimately contributing to cell survival, inhibition of apoptosis, activation of $Ca^{2+}$ channels, cell growth, repair and regeneration, as well as regulation of translation/transcription processes in response to stress (Figure 2).

## CONCLUSION

As the quote "the key to one's heart is through his stomach", the gut hormone GLP-1 (and, more specifically, its long-lasting synthetic analogs) may

hold the key for promising therapeutic effects against diseases affecting such different tissues, as the heart, pancreas, kidneys, liver, brain, and all the other tissues where we can find GLP-1Rs. It is plausible that this hormone, mainly secreted from L-cells, may exert its influence on the activities of several organs *via* complex axis involving the gut. And despite the still limited knowledge on this matter, we believe that the clarification of the molecular mechanisms involved herein might be of the outmost relevance in the context of the promising preventive/therapeutic potential of the long-acting GLP-1RAs against the development of long-term complications of several diseases. As a novel GLP-1RA and already marketed anti-T2D drug, and given the strong association between T2D and numerous neurodegenerative pathologies, liraglutide has been extensively investigated for such purpose in the recent years and has shown remarkable effects, not only peripherally, but also in CNS upon a wide range of diseases, including T2D, AD, PD and stroke. As liraglutide's positive effects in brain, we emphasize its promotion of neuronal survival, protection from apoptosis, regulation of neuroinflammatory response and modulation of stress response, thereby suggesting a strong neuroprotective potential. And this might be of a pivotal relevance, in our ever increasingly aged world and societies, characterized by an exponential increase in age-related diseases that still lack effective (or at least with a minimum of serious side-effects) preventive or therapeutic approaches, thereby posing an enormous socio-economic burden and urging the seek for an effective cure or delay in such diseases. Thus, the limited preclinical and clinical findings already available strongly suggest that liraglutide may emerge as a potential mono- or combined therapy against most of the common diseases afflicting the brain.

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