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Central Functions of Glucagon-like Peptide-1: Roles in Energy Regulation and Neuroprotection

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Abstract

The identification of the glucagon-like peptide-1 receptor in the central nervous system has led to an array of studies exploring the functions of central GLP-1 signalling. Originally identified as a gastrointestinal incretin hormone responsible for the potentiation of insulin secretion following ingestion of nutrients, the role of GLP-1 has been expanded to include specific neural activities. Two distinct actions of GLP-1 receptor activation in the brain have been identified, namely the regulation of appetite via promotion of satiety, as well as anti-inflammatory and anti-apoptotic activity to promote neuronal cell survival. Both of these features are now being exploited clinically, with GLP-1 receptor agonists, initially designed and marketed for the treatment of hyperglycaemia in type 2 diabetes, now being directed towards use in obesity and as potential neuroprotective agents. This review gives a summary of the functional role of GLP-1 in the central nervous system, in terms of promoting satiety, modulating food intake and aiding in the regulation of peripheral glycaemia. In addition, the molecular mechanisms underpinning the beneficial effects of central GLP-1 receptor agonist therapy in protecting against neuronal cell inflammation and death, including neurodegenerative processes, are described.

Keywords: Glucagon-like peptide-1; Central nervous system; Glucose metabolism; Satiety; Neuroprotection

Introduction

Glucagon-like Peptide-1

Glucagon-like peptide-1 (GLP-1) is a peptide hormone secreted from specific populations of cells in both the distal gut and central nervous system (CNS). In response to nutrient intake, GLP-1 exerts its insulinotropic activity via direct stimulation of pancreatic β-cells to potentiate insulin secretion in a glucose-dependent manner [1]. Thus, the principal metabolic function of GLP-1 is that of an incretin hormone. GLP-1 further lowers blood glucose levels by slowing gastric emptying, thereby reducing postprandial hyperglycaemia. In addition, GLP-1 participates in the gut-to-brain axis by transmitting nutritional signals to the CNS, resulting in increased satiety [2].

The GLP-1 peptide is produced through posttranslational processing of proglucagon in the intestinal L-cells and preproglucagon neurons in the hindbrain [3]. Native GLP-1 is 37 amino acids in length and is proteolysed by prohormone convertase 1/3 to give rise to the major active circulating peptide; GLP-1(7-36)-amide [4]. This peptide engages and activates the GLP-1R on the surface of pancreatic β-cells when plasma glucose levels ≥5 mMol/L, resulting in a rise in intracellular Ca2+ and consequent secretion of insulin. GLP-1 mediated signalling also reduces the expression of pro-inflammatory and pro-apoptotic mediators, leading to enhanced pancreatic β-cell viability [5,6].

Regulation of endogenous GLP-1 activity occurs through rapid proteolytic inactivation in the circulation by dipeptidyl peptidase-4 (DPP-4), such that GLP-1 has a half-life of approximately 3 minutes. While the short half-life of GLP-1 limits the therapeutic utility of the native protein as a diabetes treatment, the development of degradation resistant forms of GLP-1 and inhibitors of DPP-4 (DPP-4i) has proved an important therapeutic advance in the management of type 2 diabetes [7]. Furthermore, due to the glucose-dependent nature of incretin-mediated insulin release, GLP-1 receptor agonists and DPP-4i are associated with a minimal risk of inducing hypoglycaemia [8].

The GLP-1 receptor (GLP-1R) has been localised in tissues outside the pancreas, including the heart, kidney and brain [9]. It is widely distributed throughout the central nervous system (CNS), with expression in the thalamus, hypothalamus, hippocampal region, cerebellum, cortex and brain stem [10]. Interestingly, GLP-1 has also been identified as a neuropeptide, and is produced by preproglucagon neurons of the nucleus of the solitary tract (NTS) located in the caudal brainstem [11,12]. Furthermore, GLP-1 positive cells have been identified in the hippocampus and cortex in rodents and GLP-1 is secreted from microglial cells via a cyclic AMP (cAMP) dependent pathway [13]. It has also been observed that the GLP-1 peptide can cross the blood brain barrier [14].

The pleiotropic actions of GLP-1 to preserve β-cell function and reduce inflammation have led to the hypothesis that GLP-1 receptor activation could also have beneficial effects in the CNS. In addition to the regulation of satiety following a meal, experimental data also suggest an important role of GLP-1 in neuroprotection. An overview of these data is provided below, with a focus on the effect of GLP-1 receptor activation in the modulation of food intake and glucose

homeostasis, as well as the neuroprotective and anti-inflammatory properties of GLP-1 in ischaemic stroke and neurodegenerative disorders.

Central Activity of Glucagon-Like Peptide-1

Regulation of food intake

Ingestion of food leads to GLP-1 secretion from entero endocrine L-cells in the distal gut. As a consequence, insulin release from the pancreas is stimulated in a glucose-dependent fashion and satiety is increased through both central and peripheral effects [15]. There are several possible mechanisms through which GLP-1 modulates food intake. Firstly, GLP-1 transmits nutritional signals to the brain via activation of the enteric nervous system and/or vagus nerve in the gastrointestinal tract [16,17]. It has also been suggested that a small proportion of GLP-1 may escape degradation by DPP-4 and enter the systemic circulation to cross the blood brain barrier, where it may directly activate its receptor and increase satiety [18]. Moreover, food intake may lead to the release of GLP-1 from neurons in the nucleus of the solitary tract (NTS), and the activation the GLP-1R in the CNS [19]. GLP-1 additionally adds to the regulation of energy intake by decreasing gastrointestinal motility, thereby contributing to feelings of fullness [20].

In the absence of nutrient ingestion, central administration of GLP-1 limits food intake [18]. Intracerebro ventricular (ICV) injection of GLP-1 in rodents slowed gastric emptying, through non-adrenergic and non-cholinergic pathways [21]. The mechanisms through which this centrally mediated reduction in gastric motility occurs have not been completely elucidated, however a role for vagal afferent nerves has been proposed. Nutrient stimulated secretion of GLP-1 from the distal gut led to activation of hepatic vagal nerves [22], and the suppression of food intake mediated by peripherally administered GLP-1 was abolished in vagotomised individuals [23]. Targeted administration of GLP-1 receptor agonists in the hypothalamus and hindbrain diminished food intake, suggesting that both of these cerebral areas are important for GLP-1 mediated anorexia [24,25]. Furthermore, GLP-1 reactive nerve fibres extend from the NTS to the hypothalamus, a major centre in the brain for regulation of eating behaviour, and activation of hypothalamic GLP-1R inhibits feeding and promotes satiety [19,26]. In addition, ICV administration of the GLP-1 receptor agonist, exendin-4, gave rise to activation of neuropeptide Y, neurotensin, ghrelin and proopiomelanocortin neurons in the hypothalamus, leading to upregulated expression of appetite-regulating neuropeptides [27]. More recently, it was found that nestin-Cre mediated site-specific knockdown of the GLP-1 receptor in the hypothalamus and brain stem rendered high-fat fed rodents resistant to reductions in body weight and food intake induced by the long-acting GLP-1 analogue, liraglutide [28].

Several of the cellular pathways through which GLP-1R activation in the CNS modulates appetite have been identified. GLP-1 stimulates signalling cascades downstream of cAMP and protein kinase A (PKA) in the NTS, resulting in inhibition of food intake [29]. In particular, hindbrain GLP-1R activation suppresses energy intake via a PKA-mediated reduction in adenosine monophosphate protein kinase (AMPK) activity and concurrent upregulation of mitogen-activated protein kinase (MEK)/extracellular signal-related kinase-1/2 (ERK-1/2) pathways [24]. This has been proposed to ultimately lead to Ca2+-dependent depolarisation of GLP-1R expressing neurons, and long-term cAMP response element-binding protein (CREB)-mediated transcriptional changes in genes responsible for regulation of food intake [30]. Surprisingly, a role for the central cytokines interleukin-1β (IL-1β) and IL-6 was found in GLP-1 mediated suppression of food intake [31]. Ablation of IL-1β or IL-6 activity through either receptor blockade or knock-out gave rise to a reduction in GLP-1 mediated anorexia and loss of body weight in mice.

In clinical studies, infusion of GLP-1 led to increased satiety and reduced energy intake in obese individuals and also in patients with type 2 diabetes [32,33]. Similarly, GLP-1 dose-dependently reduced nutrient intake in lean and overweight individuals [34]. Interestingly, functional magnetic resonance imaging (fMRI) of the brain has shown that infusion of GLP-1 attenuates blood-oxygen level dependent signal changes in fasted individuals who were presented with images of food [35]. Likewise, continuous administration of exenatide, a GLP-1 analogue, reduced food intake in obese men which correlated with enhanced hypothalamic activity, as measured by fMRI [36]. The favourable effects of GLP-1 on reducing appetite and food intake have been exploited in a recent clinical trial, where liraglutide therapy for 56 weeks resulted in clinically significant weight loss in non-diabetic obese individuals [37] With additional human studies underway [38,39], it is highly likely that a new therapeutic indication for GLP-1 will be established in the coming years, to aid in the reduction of excess body weight in obese individuals through augmentation of central GLP-1R mediated appetite suppression.

Glycaemic Control and Peripheral Glucose Homeostasis

While the chief physiological function of GLP-1 is in the glucose-dependent stimulation of insulin secretion to regulate systemic glycaemia, a glucose lowering effect of GLP-1 has also been recognised in the brain. In healthy male subjects administered glucose via IV infusion, GLP-1 leads to decreased glucose concentrations in all cerebral areas with an increase in glucose metabolism through enhanced hexokinase activity during hyperglycaemia [40]. Similarly, glucose transport across the blood brain barrier (BBB) is down-regulated by GLP-1 in healthy individuals with normal blood glucose levels [41]. In the presence of hypoglycaemia, GLP-1 does not affect brain-glucose concentrations, nor does it influence glucose metabolism or transfer across the BBB [42].

A further role of central GLP-1 is to regulate peripheral glucose homeostasis (Figure 1). As evidenced in animal studies, stimulation of the GLP-1R in the CNS leads to increased insulin secretion and greater hepatic glycogen storage, during hyperglycaemia [43]. Interestingly, GLP-1 signalling in the CNS facilitates glucose-uptake into skeletal muscle in an insulin-dependent and non-insulin dependent manner, as seen in MIRKO mice, a muscle insulin receptor knock-out model. In another study, ICV administration of GLP-1 in rodents augmented glucose-dependent insulin release, and decreased glucose production in the liver [44]. Moreover, it was demonstrated that antagonism of arcuate GLP-1 receptors in the rat brain increased the magnitude of glycaemic excursion during a glucose tolerance test. GLP-1 regulates peripheral glucose levels via activation of the afferent nervous system, through slowed gastric emptying and a concomitant reduction in absorption of glucose into the bloodstream [45]. Furthermore, GLP-1 can promote enhanced energy expenditure, through CNS signalling pathways; ICV administration of GLP-1 gave rise to increased thermogenesis in brown adipose tissue of C57BL/6 mice, which the authors suggest contributes to the mechanisms by which GLP-1 regulates energy balance [46].

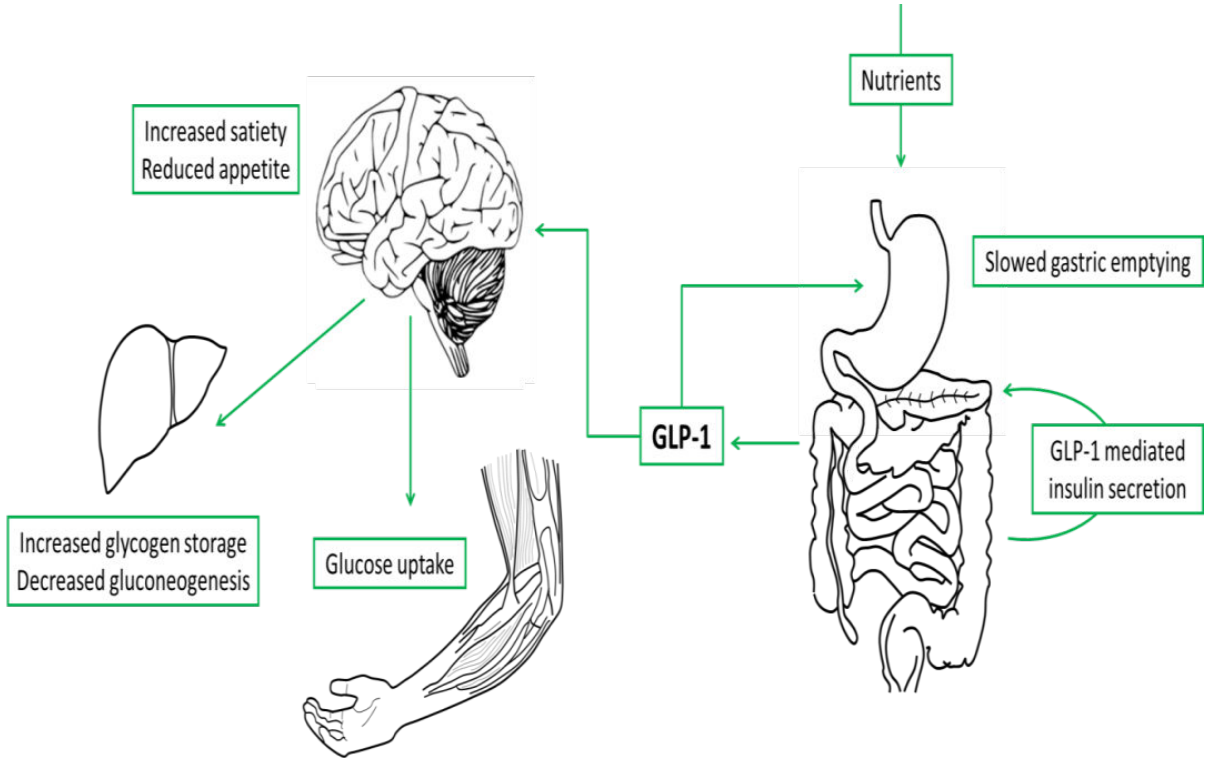

Figure 1: Functions of GLP-1 in the regulation of glycaemia. Upon ingestion of food, GLP-1 is secreted from the L cells in the lower gut and potentiates (glucose-dependent) insulin secretion from pancreatic β-cells, whilst also stimulating centrally mediated signals that give rise to a reduction in appetite, and peripheral uptake of glucose in both liver and muscle.

Sisley et al. recently observed that CNS expression of the GLP-1R is not necessary for peripheral glucose regulation, as administration of liraglutide reduced glucose excursions in the absence of neuronal GLP-1R [28]. This implies that pancreatic GLP-R activation is sufficient for the glucose lowering activity of GLP-1; however previous evidence suggests a direct role of central GLP-1R activation in the modulation of systemic glucose homeostasis [43,44]. Finally, administration of the GLP-1 receptor agonist liraglutide to patients with type 2 diabetes gave rise to a decrease in fasting endogenous glucose release due to a reduction in hepatic glycogenolysis, although the role of central GLP-1R signalling in this process is unclear [47].

Glucagon-like Peptide-1 and Neuroprotection

Anti-inflammatory properties of GLP-1 in the brain

The cytoprotective and anti-inflammatory effects of GLP-1 have been demonstrated in several cell types, including pancreatic islets and endothelial cells [48-50]. In addition, a recent study has shown that stimulation of the GLP-1 receptor reduces the inflammatory response in the kidneys of diabetic rodents, independent of GLP-1 blood-glucose lowering activity [51]. In each of these studies, improvements in cell viability and a concomitant reduction in the expression of pro-inflammatory adhesion molecules and cytokines was observed.

In vitro experiments initially revealed that GLP-1 exerts neuroprotective activity in neuronal cell culture, [52] promotes cell survival and proliferation, and prevents apoptosis and oxidative-stress-associated cell death in mammalian glial and hippocampal cells (Figure 2). The pathways involved in GLP-1 mediated neuronal cell proliferation are downstream of protein kinase A and phosphoinositide 3-kinase activity, and enhanced cell survival arises through modulation of apoptotic signal expression (decreased bax and caspase-3, and increased bcl-2; Figure 3) [53-56]. GLP-1 further regulates inflammatory cytokine expression in the brain; lipopolysaccharide (LPS) challenge in activated microglia and astrocytes gave rise to a significant increase in IL-1β, and this increase was attenuated in the presence of GLP-1 [57]. This finding is in contrast to that observed by Shirazi and colleagues, who showed that GLP-1 promotes IL-1β expression in the brain, to reduce food intake and appetite. Thus, GLP-1 may differentially influence the expression of central cytokines, dependent on the initial stimulus or upon which signalling pathway is activated. More recently, it was found that the GLP-1 receptor agonist liraglutide enhanced cell viability and prevented cytotoxicity and apoptosis in human neuroblastoma cells exposed to methylglyoxal stress [58]. The mechanisms through which this increase in cell viability occurs include activation of the transcription factor p90RSK, which modulates the expression of genes associated with the cellular response to stress.

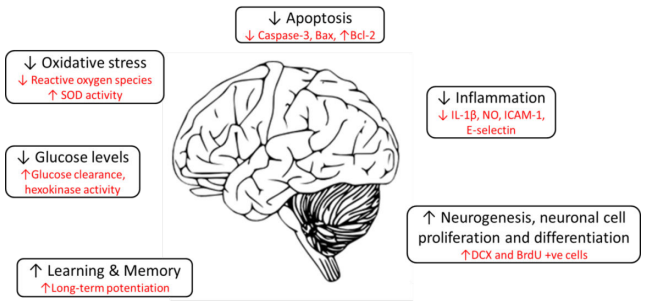

Figure 2: Glucagon-like peptide-1 activity in the brain gives rise to neuroprotection, through various molecular mechanisms. The mechanisms through which GLP-1 elicits a neuroprotective effect in the brain are outlined. General mechanisms are indicated in black, with specific molecular pathways in red. GLP-1 enhances neurogenesis, neuronal cell proliferation and differentiation, as evidenced by increases in the cell proliferation markers DCX and BrdU. Stimulation of the GLP-1 receptor prevents apoptosis, with a decrease in pro-apoptotic signalling molecules caspase-3 and bax, as well as greater levels of anti-apoptotic bcl-2 observed. Favourable effects on learning and memory are also seen, as reflected by enhancements in long-term potentiation, a marker of synaptic plasticity and a major mechanism underlying the processes of memory and learning in the brain. Oxidative stress is ameliorated through a reduction in reactive oxygen species. Finally, GLP-1 lowers blood glucose levels in the brain, preventing hyperglycaemia associated inflammation and cell death during ischaemia [40].

The role of GLP-1 in attenuating neuroinflammation has been also demonstrated using animal models. Both liraglutide and its metabolite GLP-1 (9-36) decreased the expression of pro-inflammatory markers such as ICAM-1 and E-selectin after intracerebral haemorrhage in mice [59]. Indeed, it was also found that liraglutide reduced the number of neutrophils in the perihaematoma region, further downregulating neuroinflammation. In addition, chronic irradiation-induced inflammation in rodent brains was ameliorated by treatment with GLP-1, with lower levels of markers such as interleukin-6 and nitrite observed [60,61]. GLP-1 receptor stimulation through treatment with the GLP-1 analogue exendin-4 minimised mild traumatic brain injury induced deficits in mice, again through reduction of oxidative stress associated inflammation [62]. This study demonstrated that administration of GLP-1 gave rise to increased levels of neuronal cell survival in response to challenge with the oxidative stress mediator hydrogen peroxide, and also protected cells against glutamate-induced toxicity.

Due to the modulatory effects of GLP-1 on neuroinflammation, a key process in the pathogenesis of neurodegenerative disorders and cerebral injury, it has been proposed that GLP-1 may be a viable treatment option for targeting inflammation in the brain, and as such, further clinical studies in this area are warranted

GLP-1 and Ischaemic Stroke

Diabetes is an established risk factor for the development of ischaemic events, such as stroke. Persistently high blood glucose after stroke correlates with larger infarct volume, and hyperglycaemia is an independent predictor for increased functional impairment, disability and mortality [63-66]. The mechanisms through which hyperglycaemia may exert a deleterious effect in ischaemic stroke include heightened lactic acidosis, enhanced production of free radicals, oxidative stress and augmentation of inflammation. As previously described, GLP-1 effectively lowers hyperglycaemia in the brain and furthermore, ameliorates oxidative stress and inflammation in preclinical models of brain injury and inflammatory challenge [40]. In addition, GLP-1 therapy resulted in favourable effects in a rodent model of ischaemic stroke and concomitant type 2 diabetes, with a dose-dependent reduction in hyperglycaemia, inflammation and neuronal tissue damage [67]. Treatment of mice with the DPP-4 inhibitor linagliptin significantly enhanced circulating levels of GLP-1, and lowered both fasting and fed blood glucose levels. Treated mice also showed a marked decrease in ischaemic brain damage [68].

In a recent clinical study, patients with acute ischaemic stroke were given subcutaneous exenatide for glycaemic control. It was observed that blood glucose levels were effectively regulated, with minimal incidence of hyperglycaemia and no symptomatic hypoglycaemia [69]. These promising preliminary results suggest that GLP-1 therapy may be a viable treatment option for individuals with hyperglycaemia in ischaemic stroke, with negligible glycaemic variability, and low risk of hypoglycaemia. This may lead to improved outcomes for patients with acute stroke, as hypoglycaemia has been associated with poorer outcomes and an increased risk of morbidity and mortality [70].

The mechanisms through which GLP-1 exerts its beneficial effects in stroke, in addition to glycaemic control, have been determined in a variety of preclinical models. Administration of exendin-4 was shown to reduce brain damage and improve functional outcome in a transient middle cerebral artery occlusion stroke model, independent of its blood glucose lowering activity [71,72]. Likewise, treatment of rats with exendin-4 confers significant neurological protection following cerebral ischemia as a consequence of middle cerebral artery occlusion with a reduction in infarct size, oxidative stress levels and neurological deficit [73]. In particular, exendin-4 was found to increase the levels of superoxide dismutase (SOD), an antioxidative enzyme that reduces the concentration of harmful superoxide within cells. More recently, GLP-1 treated rats showed an improvement in behavioural score and smaller infarct volumes after stroke [74]. A reduction in reactive oxygen metabolites and an increase in the levels of vascular endothelial growth factor (VEGF) were seen, reinforcing the premise that GLP-1 down-regulates oxidative stress and promotes oxygenation. It has also been observed that administration of exendin-4 to rodents protects against ischaemia-induced activation of microglial cells, thereby preventing premature microglial cell death [75].

Interestingly, GLP-1 exerts cardioprotective activity in patients with myocardial infarction (MI) and ischaemic heart disease. In a small cohort of non-diabetic patients, treatment with GLP-1 led to an improvement in left ventricular function (LVF) and a reduction in ischaemic dysfunction after coronary balloon occlusion during percutaneous coronary intervention [76]. Infusion of GLP-1 to patients after acute MI enhanced LVF and increased recovery in the peri-infarct area, and exenatide was shown to improve myocardial salvage after ST-segment elevation MI [77,78]. Epidemiological data has further found that individuals taking exenatide had a lower incidence of cardiovascular disease, including stroke [79]. These results, taken together with the above animal data, suggest that GLP-1 therapy may lead to favourable outcomes after ischaemic injury, both in the heart and CNS. Indeed, GLP-1 may exert a dual protective effect in the ischaemic brain, in terms of preventing hyperglycaemia

associated neurological damage, and directly ameliorating neuro inflammation and oxidative stress associated cell death.

Protective Role of GLP-1 in Neurodegenerative Disorders

The risk of developing neurodegenerative disorders such as dementia and Parkinson's disease is significantly increased in individuals with diabetes [80,81]. The pathogenesis of neurological impairment and injury in these disorders includes premature neuronal cell death, oxidative stress and neuro inflammation, processes that may be attenuated by GLP-1 signalling in the brain. Interestingly, GLP-1 receptor knockout mice demonstrated impaired learning, memory and cognitive ability, as well as a reduction in recovery after neurological insult, suggesting an intrinsic role for endogenous GLP-1 in maintaining normal brain activity [82,83].

Pre-clinical models of neuro degeneration have been used to show that GLP-1 therapy is beneficial in preserving neurological function. In a mouse model of Alzheimer's disease, both short- and long-term administration of the GLP-1 receptor agonist, liraglutide, resulted in increased neuronal cell survival and proliferation, and enhanced neurogenesis [84]. Furthermore, several studies have demonstrated that GLP-1 preserves synaptic plasticity and further reduces the accumulation of the pathogenic β-amyloid protein in the brain of preclinical models of Alzheimer's disease [61,85]. Administration of GLP-1 dose-dependently conserved spatial memory in rats exposed to β-amyloid, by protecting hippocampal long-term potentiation between neurons. Similarly, GLP-1 was found to be protective against neuro degeneration in a Parkinson's disease model; administration of exendin-4 reduced functional impairment and also increased the number of neuronal precursor cells, showing protection against loss of neurons [86,87]. Treatment with exendin-4 increased levels of L-DOPA and tyrosine hydroxylase after challenge with 6-OHDA (a selective inducer of Parkinsonism), suggesting that GLP-1 can rescue dopaminergic neurons after damage has occurred. Finally, GLP-1 improves motor performance and extends survival in a murine model of Huntington's disease [88].

GLP-1 is currently being explored as a potential neuroprotective agent in patients with dementia and Parkinson's disease [89]. A recent pilot study investigated the effect of exenatide treatment in addition to regular therapy on neurological function in non-diabetic individuals with Parkinson's disease. Exenatide was well tolerated and patients in the treated group showed a significant reduction in disease progression and improvements in motor and cognitive skills [90]. Phase 1 studies have also been completed for a novel GLP-1 delivery system, where CellBeads® containing mesenchymal stem cells that overexpress GLP-1 are inserted directly at the site of injury in patients with haemorrhagic stroke, with the aim of eliciting GLP-1 mediated protection against neuronal cell damage [91]. Two further clinical trials have been described, where the effect of liraglutide on glucose metabolism and functional outcome in Alzheimer's disease, and in reducing reperfusion injury after acute stroke will be studied [92,93]. Moreover, GLP-1 has also been suggested as a prospective treatment option for the cognitive impairments observed in individuals with mood disorders [94].

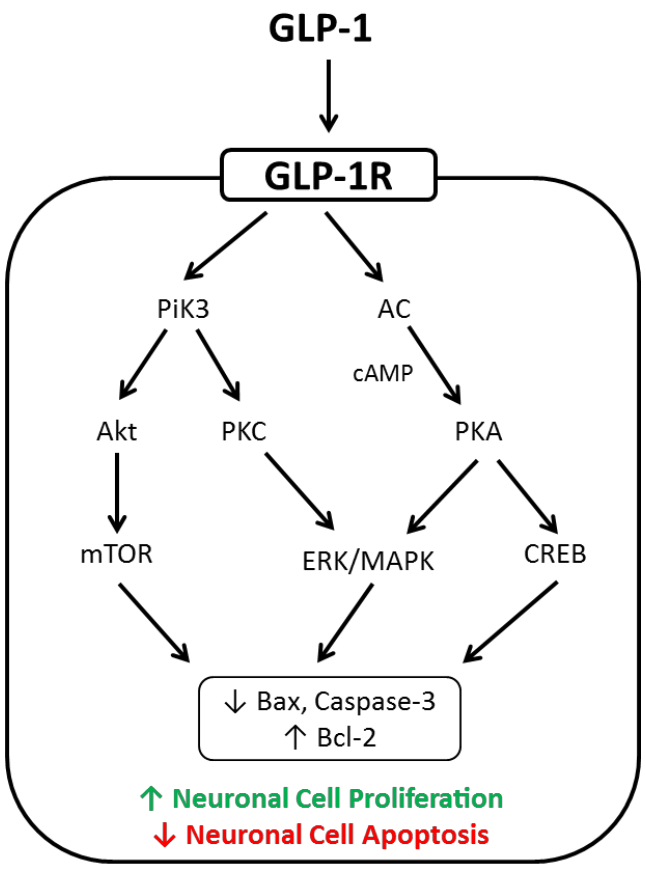

Figure 3: Summary of the principal signalling pathways through which glucagon-like peptide-1 receptor activation promotes neuronal cell survival. Stimulation of the GLP-1R on the surface of neuronal calls activates protective signalling pathways, downstream of phosphoinoside kinase 3 (PiK3) and adenylate cyclase (AC) [63]. Activation of protein kinase A (PKA) leads to modulation of pro-survival gene expression via the extracellular signal-related kinase/mitogen-activated protein kinase (ERK/MAPK) and cAMP response element-binding protein (CREB) pathways [52,56]. Similarly, protein kinase C (PKC) and Akt signal through ERK/MAPK and mTOR (mammalian target of rapamycin), respectively, to promote neuronal cell proliferation and modulate levels of apoptotic gene expression (decreased Bax and Caspase-3; increased Bcl-2).

Conclusions

Characterisation of GLP-1R activation in the CNS, in both in-vitro and pre-clinical models has enabled an understanding of the dual regulatory activities of central GLP-1 signalling. First, GLP-1R activation leads to increased satiety and a reduction in food intake [95]. Second, GLP-1 signalling in the brain regulates peripheral glucose metabolism, through modulation of glucose uptake. Thus, GLP-1 has an important role in energy homeostasis; initially to regulate food intake limiting nutrient ingestion and further to influence how nutrient-derived energy is metabolised peripherally.

Another consequence of central GLP-1R activation is in the protection of neuronal cells against damage and premature cell death. This neuroprotective activity of GLP-1 is achieved through ameliorating inflammation and oxidative stress, processes that occur in the brain after an ischaemic event and also during neurodegeneration. In addition, GLP-1 may additionally protect against the neurological consequences of hyperglycaemia. In turn, this could potentially lead to improved outcomes in acute stroke and neurodegeneration with several studies showing a correlation between stress hyperglycaemia and functional outcome, morbidity and mortality [96]. Furthermore, it has recently been hypothesised that GLP-1 agonists could lower blood glucose levels without the risk of hypoglycaemia in critically ill patients, thereby minimising the occurrence of treatment-related morbidity [97].

By further elucidating the molecular mechanisms responsible for the beneficial effects of GLP-1R activation in the brain, it may be possible to harness the neuroprotective properties of GLP-1 for the targeted treatment of ischaemic stroke and neurodegenerative disease. Moreover, clinical trials are currently underway where GLP-1 analogues are being utilised as anti-obesity therapies, due to their potent effects on satiety and food intake [98-101]. As such, GLP-1 could soon be added to our armamentarium as a therapeutic target above and beyond its usefulness as a glucose-regulating agent in type 2 diabetes.

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