Glucagon-Like Peptide 1, Neuroprotection and Neurodegenerative Disorders

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Editorial

Glucagon-Like Peptide 1 (GLP-1) is a hormone belonging to the family of incretins whose peripheral insulinoergic effects in maintaining glucose homeostasis in response to food ingestion have long been known [1]. GLP-1 (7-36), the most common and biologically active form, is a 30 amino acid peptide formed by post-translational cleavage of the pro-glucagon gene, it shows 50% homology to glucagon and it is mainly produced by enteroendocrine L-cells, which secrete it into the bloodstream. Although GLP-1 is blood brain barrier permeable, it is also synthesized in the brain and, in particular, in neurons of the nucleus tractus solitarius and of the intermediate reticular nucleus, which innervate the cerebral cortex, the hypothalamus, the amygdala, the hippocampal region and the paraventricular nucleus of the thalamus [2-5].

In the periphery, GLP-1 has a rather short half-life, being rapidly inactivated to GLP-1(9-36) amide by dipeptidyl peptidase IV (DPP-IV) [6,7] an enzyme which is present in peripheral tissues, in body fluids (i.e., blood plasma and cerebrospinal fluid) and seems to localize also in the brain [8-10].

GLP-1 acts by activating a classic 7TM-G-protein coupled receptor named GLP-1R that, in the functional studies carried out so far, has been shown to stimulate adenylyl cyclase via the α subunit of the Gs protein, thus increasing intracellular cAMP levels and triggering a cascade of downstream events, such as activation of PKA, Epac2, PKC, MAPK and PI-3K pathways. However, it has been reported that GLP-1R can also couple to other G-protein α-subunits (i.e., Gq, o, i), although the functional meaning of this molecular promiscuity is not fully understood [11].

A milestone in the understanding of the physiological roles of the GLP-1/GLP-1R system was the isolation and characterization of the DPP-IV resistant, BBB permeable GLP-1R selective agonist exendin-4 and the selective antagonist exendin-(9-39) that permitted, in addition to in vitro experiments, to initiate various in vivo studies [12,13]. After exendin-4, liraglutide and lixisenatide have been produced as other GLP-1R agonists, whereas sitagliptin, saxagliptin and vildagliptin have been developed as selective DPP-IV inhibitors able to increase endogenous GLP-1 levels.

Although the interest for the GLP-1/GLP-1R system began in the field of diabetes treatment, it was soon clear that this hormone could also have important functions in the central nervous system.

The first evidence for a central physiological role of GLP-1, dates back to 1996 when it was shown that its intracerebroventricular (icv) administration, potently inhibited feeding in rats [14]. However, it was only six years later that the neuroprotective role GLP-1 and exendin-4 was demonstrated for the first time [15]. In that study, activation of GLP-1Rs was able to completely protect cultured rat hippocampal neurons from apoptotic death caused by glutamate excitotoxicity and to greatly reduce the in vivo ibotenic acid-induced depletion of choline acetyltransferase in the basal forebrain, leading the authors to hypothesise that “…such peptides may have potential for halting or reversing neurodegenerative processes in CNS disorders, such as Alzheimer's disease…”

Since then, a large body of evidence has accumulated indicating that the activation of GLP-1Rs could represent a novel and effective disease modifying therapeutic strategy for treating neurodegenerative disorders.

Indeed, both in vitro and in vivo studies using validated animal models of Alzheimer’s (AD) and Parkinson’s (PD) diseases, Huntington’s chorea, amyotrophic lateral sclerosis and stroke have undoubtedly demonstrated the protective properties of GLP-1R agonists using both anatomo-pathological and behavioural analysis [16-18].

Significant neuroprotection has been reported also for the DPP-4 inhibitors sitagliptin and saxagliptin in PD and AD animal models, as well as in models of cerebral ischemia [19-21]. However, administration of sitagliptin to type 2 diabetic rats has been found to aggravate γ-tau phosphorylation in the hippocampus, thus highlighting the need of further studies before considering its use in AD [22].

As for the possible mechanisms through which GLP-1Rs trigger neuroprotection, several studies have revealed that these receptors are capable of stimulating neurite outgrowth, promoting adult neurogenesis with cell proliferation and survival, interrupting apoptotic processes, and reducing neuroinflammation. In addition, they have beneficial effects for mitochondrial functions by means of different molecular mechanisms, including the stabilisation of the outer membrane through activation of the PI3K/AKT pathway, thus preventing the initiation of the apoptotic intrinsic pathway [17,18]. Indeed, mitochondria dysfunctions represent a common feature of different neurodegenerative disorders.

It is also worth noting that GLP-1 and GLP-1R have important effects also on learning and memory formation both under physiological and pathological conditions. In fact, in rodents, icv administration of GLP-1 or GLP-1R overexpression resulted in the enhancement of learning and memory, whereas GLP-1R knock-out caused significant deficits in cognitive processes [23,24]. The pro-ammnec effects of

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GLP-1R agonists are associated with the facilitation of hippocampal long term potentiation (LTP), the electrophysiological substrate of memory, as measured both in vitro and in vivo [25,26]. Accordingly, this synaptic plasticity phenomenon is impaired in GLP-1R knock-out mice [24]. Moreover, administration of GLP-1, GLP-1 agonists or DPP-IV inhibitors rescues LTP and the memory impairment caused by exogenous or endogenous β-amyloid, the self-agonizing peptide that accumulates AD brains [21,25-36].

Such overwhelming evidence has led to clinical trials in which GLP-1 mimetic have been tested for their efficacy in neurodegenerative disorders such as PD and AD.

In the first case, a single-blind proof of concept evaluated the progression of motor and nonmotor symptoms in a small group of PD patients treated with exenatide (exendin-4) administered subcutaneously for 12 months and found clinically relevant ameliorations both in motor and cognitive performances, evaluated by MDS-UPDRS (Movement Disorder Society Unified Parkinson’s Disease Rating Scale) and Mattis DRS-2 (Dementia Rating Scale 2) at the end of the therapy and after two months of washout [31]. Most interestingly, the improvement persisted 12 months after the trial, with exenatide-treated patients showing a 5.6 and 5.3 point advantage on the MDS-UPDRS part 3 and on the Mattis DRS-2, respectively [32]. These encouraging results have fuelled a larger, randomized, double-blind, placebo-controlled phase II trial that is investigating the efficacy of a once weekly treatment with exenatide for 48 weeks in patients with moderate PD (NCT01971242).

As for AD, the efficacy of a six-month treatment with liraglutide has been evaluated in a small, randomized, double-blind, placebo-controlled trial on a total of 38 patients (18 liraglutide treated vs 20 placebo) [33]. The primary outcome was the change in brain β-amyloid deposit assessed by PIB (Pittsburgh compound B) PET scan, whereas secondary outcomes were changes in CMB (Cerebral Metabolic Rate of glucose consumption) measured by FDG (Fluoro Deoxy Glucose) PET scan and changes in cognition assessed by the WMS-IV (Wechsler Memory Scale IV). The results show that CMB was significantly declined in placebo controls but not in liraglutide-treated patients. Actually, the values were increased in this group, although insignificantly. However, β-amyloid load and cognitive scores were not different between the two groups. At the moment, there are two ongoing randomized, double blind, phase II trials: a pilot study that will evaluate safety, tolerability and efficacy of exenatide on MCI (Mild Cognitive Impairment) and early AD (NCT01255163) with an estimated enrolment of 100 patients, and a safety/efficacy study of liraglutide on mild AD with an estimated enrolment of 206 patients (NCT01843075).

In conclusion, pre-clinical and clinical studies point to stimulation of GLP-1 receptors as a novel and promising neuroprotective pharmacological intervention to treat different neurodegenerative disorders with the hope of slowing their progression. Will these promises become reality?

References


