Glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide analogues as novel treatments for Alzheimer’s and Parkinson’s disease

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Type 2 diabetes is a risk factor for developing chronic neurodegenerative disorders such as Alzheimer's disease (AD) or Parkinson's disease (PD). The underlying mechanism appears to be insulin desensitization in the brain. A range of glucagon-like peptide 1 (GLP-1) mimetics and glucose-dependent insulinotropic polypeptide (GIP) analogues initially designed to treat diabetes protected transgenic animals that model AD and PD. Other studies arrived at similar conclusions. In people with significantly elevated blood glucose levels, glucose intolerance in a oral glucose tolerance test study that followed up the health status of people over the chance of developing AD. In a longitudinal cohort T2DM had been identified as a risk factor that doubled the potential of developing disease-modifying treatments for AD and PD.

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Diabetes is a risk factor for neurodegenerative disorders

One of the established risk factors for the development of Alzheimer’s disease (AD) or Parkinson’s disease (PD) is type 2 diabetes mellitus (T2DM). In several patient database analyses, T2DM has been identified as a risk factor for PD, indicating that insulin desensitization in the periphery may be a factor in initiating or accelerating the development of neurodegenerative processes. In AD, several epidemiological studies found a correlation between T2DM and an increased risk of developing AD at a later stage in life. In one investigation, T2DM had been identified as a risk factor that doubled the chance of developing AD. In a longitudinal cohort study that followed up the health status of people over time, glucose intolerance in a oral glucose tolerance test correlated to an increased risk of developing AD in people with significantly elevated blood glucose levels. Other studies arrived at similar conclusions. In PD, T2DM has also been identified as a risk factor. In the basal ganglia, dopaminergic transmission failure, insulin desensitization and energy depletion had been associated with T2DM.

Insulin signalling desensitizes in the brain

A key mechanism that appears to link T2DM with neurodegenerative disorders is the loss of insulin signalling in the brain. A biochemical analysis of brain tissue of AD patients showed a clear profile of insulin desensitization, even in people who were not diabetic. Insulin receptor subunits and insulin receptor substrate 1 were found to be hyperphosphorylated, a biochemical profile also seen in diabetic patients in the peripheral tissue. Insulin desensitization was also observed in the key brain area such as the basal ganglia and substantia nigra. Energy utilization, mitochondrial function, insulin signalling and dopamine transmission were found to be compromised. It is interesting to note that these effects were also found in nondiabetic individuals. This demonstrates that insulin desensitization is not always dependent on glucose levels. However, patient data showed that a higher percentage of PD patients were diabetic or glucose intolerant compared with age-matched controls.

Insulin is a key growth factor

Insulin is an important growth factor that is essential for the homeostasis and cell growth and repair in neurons. Counterintuitively, glucose uptake in neurons is not insulin dependent, with the exception of large neurons that express the GLUT4 subtype. Hence, the brain had been commonly known as an ‘insulin insensitive’ organ. However, insulin and IGF-1 are important growth factors that activate cell growth, cell repair, gene expression, energy utilization and protein synthesis. This may explain why insulin desensitization in the brain increases the risk of developing neurodegenerative disorders such as AD and PD.
Treating Alzheimer’s disease patients with insulin
Just as insulin improves T2DM, treating AD patients with insulin shows improvements in cognition, attention, reducing levels of biomarkers for AD and normalizing brain energy utilization [32–35]. Insulin cannot be given to people who are not diabetic. Administration of insulin by means of nasal application wherein it enters the brain more directly can circumvent the problem of inducing hypoglycaemia. Nasal application of insulin improved attention and memory formation even in nondiabetic people [34,36,37]. A phase II clinical trial in AD patients showed improved cognition in patients with mild cognitive impairments (MCIs). It further improved the amyloid-1-40/1-42 ratio in the cerebrospinal fluid and increased brain activation as seen in 18F-fluorodeoxyglucose (18F-FDG)-PET scans, which measure brain activity and energy utilization, and showed improvement in mental tasks [38–40]. However, similar to patients with T2DM, insulin delivery appears to enhance brain insulin desensitization and worsen cognitive decline [40]. For a review, see Freiherr et al. [41] and Hölscher [42].

Type 2 diabetes mellitus drugs have neuroprotective properties
Drugs to treat T2DM and normalize insulin signalling are on the market. These are mimetics of the incretin hormone glucagon-like peptide 1 (GLP-1) [43,44]. GLP-1 is a growth factor of the glucagon family type and has properties similar to that of insulin [31]. These drugs do not affect blood glucose levels directly, and therefore are safe to be taken by people who are not diabetic [45]. The drugs are well received and have a good safety record [46].

Several of these drugs can cross the blood–brain barrier, which demonstrates that there is a transporter for GLP-1, similar to other growth factors such as insulin or leptin [25,47–51].

There has been some discussion on whether glucagon-like peptide 1 receptors (GLP-1Rs) are expressed in neurons. A study that analysed RNA expression of the GLP-1R has demonstrated a wide distribution of GLP-1Rs in the brain, including the cortex, hippocampus and the substantia nigra – key brain areas in AD and PD disease development [52]. Several antibody-based histological investigations of GLP-1R expression in the brain have been conducted since [53–59]. However, one study has demonstrated that these antibodies may not be selective for the receptor followed [60], and a recent analysis of GLP-1R expression in the brain using a transgenic green fluorescent protein expression reporter mouse strain showed a significant expression of GLP-1Rs in the cortex, hippocampus area CA3, in the dentate gyrus and in others [61], putting the discussion to rest once and for all.

Glucagon-like peptide 1 mimetics show effects in animal models of Alzheimer’s disease
In several transgenic mouse models of AD, which express the human Swedish mutated form of the amyloid precursor protein and a mutated human form of presenilin-1, both mutations that lead to AD in humans, GLP-1 mimetics were neuroprotective. Liraglutide (Victoza) is in the market as a treatment for T2DM [62]. Once-daily injections for 8 weeks reduced key parameters such as memory loss, synapse loss, reduced synaptic transmission, chronic inflammation in the brain and amyloid plaque load in the brain [63]. The same treatment in aged transgenic mice with advanced amyloidosis still showed some protective effects, suggesting that treatment at later disease stages may still have benefits [64]. When treated from an early age onward, the drug did prevent disease progression and has the potential to be used as a prophylactic [65]. The GLP-1 mimetic lixisenatide (Lyxumia) also had similar neuroprotective effects as those of liraglutide [66]. Liraglutide had clear protective effects in a mouse model of tau phosphorylation and tangle formation, a key biomarker for AD. In the human P301L-mutated tau-expressing mouse, a model of frontotemporal lobe dementia and amyotrophic lateral sclerosis, liraglutide reduced the amount of tangles and hyperphosphorylated tau [67]. In the accelerated senescence SAMP8 mouse model, liraglutide also showed good protective effects on memory formation and neuronal loss [68]. The GLP-1 mimetic exenatide (Byetta and Bydureon) also showed good effects in a triple transgenic mouse model of AD [69].

Exendin-4 showed neuroprotective effects in other animal models of neurodegeneration as well [70–73]. GLP-1 mimetics furthermore improve neuronal progenitor cell proliferation and neurogenesis in the mouse brain. In mouse models of AD and of diabetes, GLP-1 analogues can increase or normalize neuronal progenitor cell proliferation in the central nervous system [50,57,63,69,74–76]. Testing analogues of the sister incretin glucose-dependent insulinotropic polypeptide (GIP) also showed significant effects in the amyloid precursor protein/presenilin-1 mouse model of AD [77–79].

Glucagon-like peptide 1 mimetics show effects in animal models of Parkinson’s disease
Exendin-4 has shown good neuroprotective effects in several mouse models of PD. In the 6-hydroxydopamine (6-OHDA) model of PD in which dopaminergic neurons are eliminated by 6-OHDA, the animals were treated for 3 weeks and showed functional recovery. In the substantia nigra, dopaminergic neurons were partly protected from the toxic effects of 6-OHDA [80].

This result was confirmed in a second study, which also used the 6-OHDA lesion technique and a second
technique, the lipopolysaccharide-induced substantia nigra lesion. Exendin-4 reduced the lesions induced by the toxins. The levels of dopamine measured in the basal ganglia were also increased. The numbers of neurons in the substantia nigra were also higher than that in the lesion only group [81]. In a third study, exendin-4 protected dopaminergic neurons and rescued motor function in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesion mouse model of PD [59].

On comparing the more effective GLP-1 mimetics liraglutide and lixisenatide with exendin-4, it was found that both liraglutide and lixisenatide demonstrated good protective effects, whereas exendin-4 showed only minor protection in the MPTP mouse model of PD. Motor activity was partly rescued and dopaminergic neurons were protected in the substantia nigra. Expression of the dopamine biomarker tyrosine hydroxylase was also rescued in the liraglutide and lixisenatide treated mice. Proapoptotic cell signalling was reduced, whereas growth factor signalling was enhanced by both drugs [82]. When testing the sister incretin GIP in the MPTP mouse model, it was found that the long-lasting protease-resistant analogue D-Ala2-GIP-glu-PAL showed good protective effects. Motor activity was partly rescued, and the number of dopaminergic neurons in the substantia nigra was increased. Synapse numbers were increased, and the cAMP/PKA/CREB growth factor second messenger pathway was shown to be activated by D-Ala2-GIP-glu-PAL [83].

New dual GLP-1 and GIP receptor agonists have been developed to treat T2DM. Some have already been tested in clinical trials and show superior performance compared with liraglutide [84]. When testing a novel dual agonist in the MPTP mouse model of PD, it was found that it rescued motor activity, synapse numbers, and numbers of dopaminergic neurons in the substantia nigra and reduced chronic inflammation (Fig. 1). Interestingly, the expression of the neuroprotective growth factor brain-derived neurotrophic factor was enhanced, which can explain some of the neuroprotective effects observed [85, 86]. Brain-derived neurotrophic factor has clear protective effects on synaptic activity [87,88].

**Clinical trials**

The results obtained in the preclinical studies show an impressive range of neuroprotective effects of GLP-1 and GIP mimetics. As several GLP-1 mimetics are already on the market as treatments for T2DM with a better safety profile, clinical trials have started investigating the neuroprotective effects of exendin-4 or liraglutide in PD or AD patients.

**Parkinson’s disease**

A clinical pilot trial of exendin-4 in PD patients has been completed (clinical trials identifier: NCT01174810). This ‘proof of concept’ study tested the effects of exendin-4 in a randomized, open label trial in 45 patients. The drug was administered over 12 months, followed by a 2-month washout period. In a single-blinded rating of motor activity, clear improvements were found, and cognitive measures were improved in the drug group compared with controls. Exendin-4-treated patients had a mean improvement of 2.7 points at 12 months on the Movement Disorder Society unified Parkinson’s disease rating, compared with a mean decline of 2.2 points in controls ($P = 0.037$). Importantly, the drug group showed a clear improvement in the Mattis dementia rating scale 2 cognitive score, suggesting that exendin-4 has beneficial effects on cognition and memory [89]. The group was retested 12 months after the trial was completed, and the clear differences between groups in motor performance and cognitive scores had not changed [90]. This suggests that the difference between groups is not due to a placebo effect, as 12 months is too long a period for such subjective effects to last.

A phase II trial testing the once-weekly formulation of exendin-4 (Bydureon) has been completed (NCT01971242). The results will be reported shortly and initial observations suggest a good outcome.

A phase II trial testing liraglutide in PD patients is under preparation and will start in July 2016, testing 100 patients in a double-blind, placebo-controlled design.

**Alzheimer’s disease**

A randomized, double-blind clinical trial to assess the safety and efficacy of exendin-4 treatment in 230 MCI patients (early phase AD) is ongoing at the National Institutes of health/National Institute of Aging in the USA. This trial is being carried out to test the effects of exendin-4 on key parameters such as performance in the Clinical Dementia Rating scale sum-of-boxes, the Alzheimer’s Disease Assessment Scale cognitive sub-scale, behavioural and cognitive performance measures, changes in structural and functional MRI brain imaging, and hormonal and metabolic changes in cerebrospinal fluid and plasma AD biomarkers (ClinicalTrials.gov identifier: NCT01255163).

A small-scale trial with 34 patients has been completed in Denmark at the University of Aarhus. This double-blind, randomized trial investigated the effects of liraglutide versus placebo on MCI patients, using $^{18}$F-FDG-PET imaging to estimate cortical activity and Pittsburgh Compound-B (PIB) PIB-PET imaging to measure plaque load [91]. Excitingly, there was a clear effect on brain $^{18}$F-FDG-PET activity. $^{18}$F-FDG is a modified glucose molecule, and the uptake correlates well with brain activity, synaptic activity and disease progression [92]. Although the placebo group showed the expected reduction (≤20%) in the $^{18}$F-FDG-PET signal, the drug group showed no reduction at all and even demonstrated improved signalling in some brain areas (NCT01469351) [93].
A second larger scale phase II clinical trial with liraglutide in 206 MCI patients is ongoing in the UK. The trial has a randomized, placebo-controlled, double-blind design and will analyse 18F-FDG-PET brain activity, PET inflammation markers (microglia activation), MRI brain scan changes, cerebrospinal fluid samples for inflammation markers and amyloid/tau levels and cognitive tests such as the Alzheimer’s Disease Assessment Scale Exec score. Patient recruitment is currently ongoing (NCT01843075).

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Conflicts of interest
The author is a named inventor on several patents that cover the use of GLP-1 or GIP analogues to treat Alzheimer’s or Parkinson’s disease. The patents are owned by Ulster and Lancaster Universities.

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