Central effects of GLP-1: new opportunities for treatments of neurodegenerative diseases

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Abstract

The incretin hormone glucagon-like peptide 1 (GLP-1) has many effects in the body. It is best known for the 'incretin effect', facilitating insulin release from the pancreas under hyperglycaemic conditions. Building on this, GLP-1 mimetics have been developed as a treatment for type 2 diabetes. In the course of monitoring of patients, it has become apparent that GLP-1 mimetics have a range of other physiological effects in the body. In preclinical trials, a substantial body of evidence has been built that these mimetics have neuroprotective and anti-inflammatory effects. GLP-1 also has very similar growth-factor-like properties to insulin, which is presumably the underlying basis of the neuroprotective effects. In preclinical studies of Alzheimer's disease (AD), Parkinson's disease (PD), stroke and other neurodegenerative disorders, it has been shown that most GLP-1 mimetics cross the blood–brain barrier and show impressive neuroprotective effects in numerous studies. In animal models of AD, GLP-1 mimetics such as exendin-4, liraglutide and lixisenatide have shown protective effects in the CNS by reducing β-amyloid plaques, preventing loss of synapses and memory impairments, and reducing oxidative stress and the chronic inflammatory response in the brain. In animal models of PD, exendin-4 showed protection of dopaminergic neurons in the substantia nigra and prevention of dopamine loss in the basal ganglia while preserving motor control. These encouraging findings have spawned several clinical trials, some of which have shown encouraging initial results. Therefore, GLP-1 mimetics show great promise as a novel treatment for neurodegenerative conditions.

Key Words
- neurodegeneration
- Alzheimer's disease
- Parkinson's disease
- amyotrophic lateral sclerosis
- stroke
- ischaemia
- incretins
- multiple sclerosis
- glucagon-like peptide 1

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Introduction

The main hallmark of type 2 diabetes mellitus (T2DM) is insulin desensitisation. The discovery that the incretin hormone glucagon-like peptide 1 (GLP-1) facilitates insulin release during episodes of hyperglycaemia and has several additional properties to overcome insulin desensitisation made GLP-1 an ideal candidate as a treatment for diabetes (see Bayliss & Starling (1902) and reviews in this special issue). Several drugs have been developed and brought onto the market as treatments, and therefore, GLP-1 is primarily known in the context of diabetes. However, it has become apparent that GLP-1 has additional properties as well, which have not been researched to such a high degree as its properties in maintaining normoglycaemia.

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This paper is one of five papers that form part of a thematic review section on incretins. The Guest Editor for this section was Martin Haluzik, Charles University, Prague, Czech Republic.

Insulin desensitisation can occur in the brain

Recent research has shown that insulin desensitisation can also occur in the brain. In several patient database analyses, T2DM has been identified as a risk factor for Alzheimer's disease (AD) and Parkinson's disease (PD), indicating that insulin desensitisation in the periphery may be a factor in initiating or accelerating the development of neurodegenerative processes (Moroo *et al*. 1994, Aviles-Olmos *et al*. 2012). Several epidemiological studies found a correlation between T2DM and an increased risk of developing AD or other neurodegenerative disorders at a later stage in life (Luchsinger *et al*. 2004, Ristow 2004, Strachan 2005, Biessels *et al*. 2006, Haan 2006). One study by the Mayo clinic showed a clear correlation between T2DM and AD. In this study, 85% of AD patients had either T2DM or increased fasting glucose levels, compared with 42% in the age-matched non-demented control group (Leibson *et al*. 1997). In a different study, T2DM had been identified as a risk factor that doubled the chances of developing AD (Janson *et al*. 2004). In a longitudinal study, an oral glucose tolerance test showed an increased risk of developing AD in people with elevated 2-h postload glucose levels (Ohara *et al*. 2011). In general, reduced insulin sensitivity and efficacy is commonly observed in elderly people and contributes to the development of AD (Carro & Torres-Aleman 2004*b*, Hoyer 2004).

Importantly, biochemical studies of brain tissue demonstrate that insulin signalling in the brain is desensitised in AD patients, and the brain tissue shows a very similar profile to that in diabetic people with respect to insulin signalling biomarkers of desensitisation in the periphery (Steen *et al*. 2005, Lester-Coll *et al*. 2006, Talbot *et al*. 2012). In an initial study, insulin receptor levels were found to be phosphorylated and expression levels down-regulated in the brains of patients with AD (Steen *et al*. 2005). In a histological study of AD brain tissue, IGF1 and insulin receptors were found to be internalised in neurons, and the second messengers insulin receptor substrate 1 (IRS1) and IRS2 were reduced in total levels but had increased levels of phospho- Ser^{312} (Moloney *et al*. 2010). Furthermore, in a recent study, it was found that in brain tissue of AD patients, IGF1 and insulin signalling was strongly desensitised. Phosphorylation of the insulin receptor β chain was reduced at positions IRβ $pY^{1150/1151}$ and IRβ pY^{960}, while the IRS1 was hyperphosphorylated at positions IRS1 pS^{616} and IRS1 pS^{636}, which deactivates IRS1 signalling, and IRS1 binding to phosphatidylinositol 3-kinase (PI3K) p85α was also much reduced. In addition, it was found in a AD brain tissue incubation study that treating brain tissue with insulin induced a reduced downstream second messenger activation (Talbot *et al*. 2012). The observed biochemical changes were very pronounced and also occurred in AD patients that were not diabetic. This type of CNS insulin signalling desensitisation is not dependent on glucose levels.

Initial studies of patients with PD found similar biochemical changes in insulin signalling in brain regions that are relevant to this disease. It was found that the levels of insulin receptor phosphorylation were increased in the basal ganglia and the substantia nigra (Moroo *et al*. 1994). Furthermore, increased IRS2 phosphorylation, a marker of IGF1 resistance, was found in the basal ganglia of the 6-hydroxydopamine lesion rat model of PD (Morris *et al*. 2008). Animal studies show similar changes. In a high-fat mouse model of T2DM, learning and memory and synaptic plasticity in the brain were impaired (Porter *et al*. 2010*b*). In a high-fat-diet rat model of early-stage T2DM, insulin resistance was observed while dopamine release was attenuated and dopamine clearance was diminished in the basal ganglia, indicating that dopaminergic signalling is compromised in T2DM (Morris *et al*. 2011).

This unexpected connection between T2DM and AD/PD opened up novel research avenues to investigate what the underlying mechanisms for this may be. Insulin is a hormone that has a range of functions in the body. Its general physiological profile is that of a growth factor (see Fig. 1). As a growth factor, insulin plays an important role in cell growth and survival. Neurons also carry insulin receptors, and activating these induces dendritic sprouting, neuronal stem cell activation and general cell growth, repair and neuroprotection (van Dam & Aleman 2004, Hoyer 2004, Stockhorst *et al*. 2004, Holscher 2005, Li & Hölscher 2007). In addition, insulin has potent neuroprotective effects against stressors (Carro & Torres-Aleman 2004*a*, Li & Hölscher 2007). Insulin enhances brain functions such as attention, memory formation and cognition in humans (Watson & Craft 2004, Zhao *et al*. 2004, Okereke *et al*. 2008, Reger *et al*. 2008*a*). When administered by nasal application where it enters the brain more directly, insulin improved attention and memory formation (Craft 2007, Reger *et al*. 2008*a*,*b*). Importantly, a phase II clinical trial showed that nasal application of insulin improved cognition in patients with mild cognitive impairments (MCI), considered to be the early phase of AD. It further improved the amyloid1–40:1–42 ratio in cerebrospinal fluid (CSF), increased the cortical activation as seen in fluorodeoxyglucose–positron emission tomography scans and also showed improvement in mental tasks (Craft 2010). Several follow-up clinical

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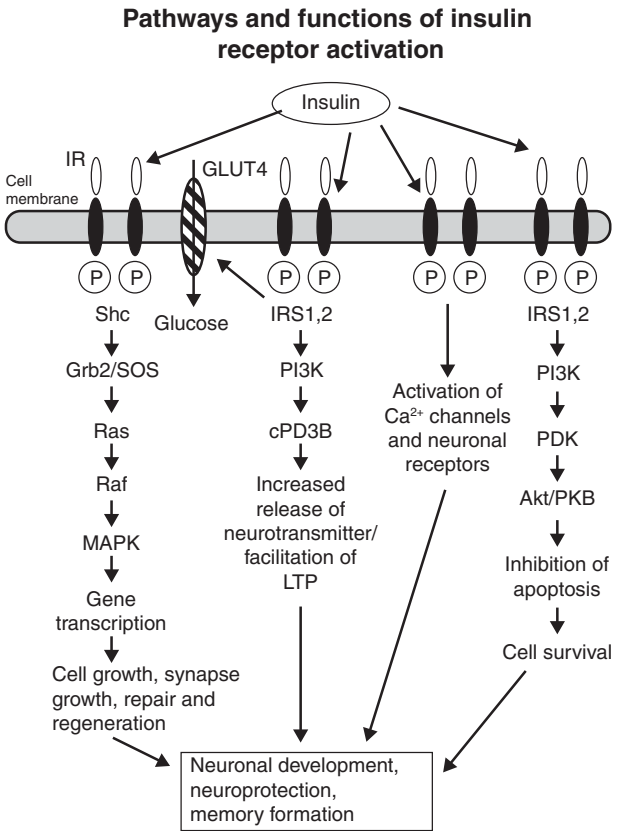

Figure 1
Insulin signalling in neurons. The insulin receptor (IR) is expressed on neurons and activates growth factor-type cell signalling pathways. The IR plays an important role in neuronal growth, synaptic development and control of neurotransmitter release at the synapse. Its role in glucose uptake is limited in neurons, as the insulin-dependent GLUT-4 glucose uptake transporter is only expressed in a sub-population of large excitatory neurons (Benomar *et al*. 2006, Grillo *et al*. 2009). Insulin binds to the α-subunit of the receptor. This activates the tyrosine kinase phosphorylation of the β-subunit. This activates second messenger pathways. (1) Activation of the insulin receptor MAP kinase pathway activates growth-related gene expression required for the control of cell metabolism and energy homeostasis, cell growth, synapse growth and for cell repair and maintenance (Hoyer 1997, Biessels *et al*. 2006). (2) Insulin also modulates synaptic neurotransmission and primes synapses for induction of long-term potentiation of synaptic transmission (LTP; Biessels *et al*. 2004). This pathway most probably involves binding of IRS1 to activate the phosphatidylinositol 3-kinase (PI3K; Zhao *et al*. 2000). This may prime the synapse for increased neurotransmitter vesicle release (de la Monte & Wands 2006). Modulation of neurotransmission may be the basis for memory formation and information processing in the CNS (Hölscher 1999).

studies have started (e.g. http://clinicaltrials.gov/ct2/show/NCT01767909?term=insulin+AND+Alzheimer&rank=1). For a review, see Freiherr *et al*. (2013).

One possibility for the development of neurodegenerative disorders is an impairment in signalling by growth factors such as insulin and IGF1. The desensitisation would reduce vital gene expression for cell repair and growth and could put neurons at an increased risk over time if additional stressors occur (Holscher 2011). Neurons do not divide and cannot be replaced, and most of them live for the duration of a person's lifetime. The amount of actual neurogenesis is far too insufficient to compensate for the loss. This means neurons are exposed to stressors over a long time frame, and damage may accumulate over decades and will finally result in synaptic loss and neuronal dysfunction and ultimately, neuronal death (Holscher 2011).

GLP-1 mimetics have neuroprotective properties

AS T2DM had been identified as a risk factor for AD, the concept developed that drugs that can treat T2DM successfully may also have neuroprotective properties. In diabetes, a range of drugs is on the market or under development, which could be tested for potential neuroprotective properties. As described in this special issue, use of mimetics of the incretin GLP-1 is a successful strategy to treat T2DM (Holst 2004, Drucker & Nauck 2006, Campbell & Drucker 2013). Not only have a range of effective and long-lasting mimetics been developed and tested, three of these have received approval as treatments for T2DM (Madsbad *et al*. 2011, Elkinson & Keating 2013). In the brain, GLP-1 receptors are expressed by neurons, in particular on pyramidal neurons in the hippocampus and neocortex, and Purkinje cells in the cerebellum (During *et al*. 2003, Perry *et al*. 2007, Hamilton & Holscher 2009). Glia cells were not found to express this receptor but induced expression when activated in an inflammatory response (Iwai *et al*. 2006). In initial studies of synaptic plasticity in the hippocampus, we found that novel GLP-1 analogues such as Val8GLP-1, liraglutide or exendin-4, which are dipeptidyl peptidase 4 protease-resistant and have a much enhanced biological half-life in the body (Holst 2004), have profound effects on memory formation and on synaptic plasticity in the brain (Holscher 2010). In addition, GLP-1 mimetics can protect synapses from the detrimental effects that β-amyloid has on synaptic plasticity in the hippocampus (Gault & Holscher 2008). Most of these novel mimetics can cross the blood–brain barrier (Kastin *et al*. 2002, Kastin & Akerstrom 2003, McClean *et al*. 2011, Hunter & Holscher 2012, McGovern *et al*. 2012), a property that is of vital importance if they are to be used to treat neurodegenerative disorders of the CNS.

GLP-1 is a growth factor, and the neuroprotective effects are most probably due to classic growth factor effects such as increased expression of genes that are

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linked to cell growth and repair and replacement, increase of cell metabolism, inhibition of apoptosis and reduction of inflammatory responses (see Fig. 2 for details on the underlying molecular mechanisms). Other growth factors have shown similar neuroprotective properties (Bradbury 2005, Kuipers & Bramham 2006). However, most neuroprotective growth factors such as nerve growth factor and brain-derived neurotrophic factor do not cross the blood–brain barrier and therefore have no protective effect in the CNS when injected peripherally (Holscher 2011).

GLP-1 mimetics have anti-inflammatory properties

Progressive neurodegenerative diseases as well as stroke induce a chronic inflammatory response in the brain. This secondary downstream process causes further neurodegenerative effects via the activation of immune cells such as microglia in the brain. These cells release pro-inflammatory cytokines and free radicals such as nitric oxide (NO), which is neurotoxic (Ayasolla *et al*. 2004). The degenerative effects of chronic inflammation in the brain are extensive (Arnon & Aharoni 2009), and intense research into anti-inflammatory drugs for such conditions is currently ongoing (Aisen 2002, Cole *et al*. 2004, Griffin 2008, Lee *et al*. 2010).

It is therefore of great interest to note that GLP-1 mimetics are not only neuroprotective but also have anti-inflammatory properties. One study demonstrated that both activated microglia and activated astrocytes, which take part in the immune/inflammatory response, induce GLP-1 receptor expression. GLP-1 treatment prevents an endotoxin (lipopolysaccharide (LPS))-induced release of the cytokine IL1β by these cells (Iwai *et al*. 2006). IL1β is pro-inflammatory and reduces neuronal transmission while increasing apoptosis-related signalling. Furthermore, exendin-4 can reduce monocyte adhesion to aortic endothelium in an inflammatory response in atherosclerosis and also prevents LPS-induced cytokine and chemokine release in both human and mouse monocytes (Arakawa *et al*. 2010) and an increase in microvascular permeability (Dozier *et al*. 2009). LPS activates a systemic inflammatory response, as bacterial walls contain molecules of this class. In our study of chronic treatment, the amyloid precursor protein (APP)/presenilin-1 (PS1) mouse model of AD with liraglutide injected i.p., the numbers of activated microglia in the brain was much reduced (McClean *et al*. 2011). As this effect may be due to the reduction of amyloid plaque, we followed up this study with a second study that measured the effects of liraglutide on inflammation only. X-ray exposure is known to induce an inflammatory response. We found that the main pro-inflammatory cytokines and NO syntheses in the brains of X-ray-exposed mice (6 Gray) after 30 days of i.p. once-daily injections of liraglutide was significantly reduced (Parsarathy & Holscher 2011).

These data indicate that GLP-1 mimetics may be useful in treating the chronic inflammatory response seen in neurodegenerative disorders.

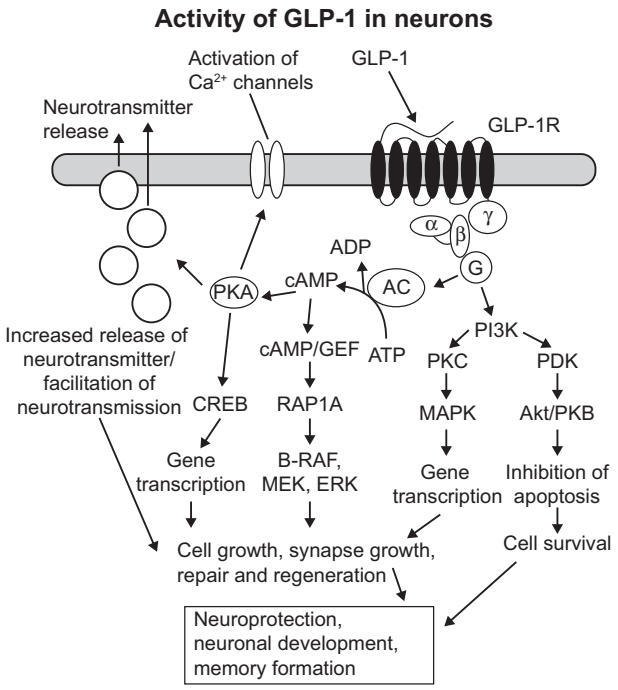

Figure 2
Overview of the main pathways induced by GLP-1 in neurons. The GLP-1 receptor is a member of a different classes of receptors compared with the IR. Activation of the GLP-1R activates an adenylyl cyclase and increases cAMP levels. This activates PKA and other downstream kinases that are related to growth factor signalling. This may be the reason why GLP-1 mimetics can compensate for insulin desensitisation in diabetics and in AD. For more details, see Holscher (2010) and Holscher & Li (2010).

Alzheimer's disease

In preclinical studies of established animal models of AD, neuroprotective effects were observed. In the APP/PS1 transgenic mouse model of AD, which expresses the human Swedish mutated form of APP and a mutated human form of PS-1, both mutations which lead to AD, it was found that chronic i.p. injection of the GLP-1 mimetic Val(8)GLP-1 blocked synaptic degradation that is observed in this AD mouse model and rescued synaptic plasticity in the hippocampus (Gengler *et al*. 2012). In rats that received i.c.v. injections of β-amyloid, a protein that

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accumulates in the brains of AD patients, it was found that Val(8)GLP-1 prevented the blocking of synaptic plasticity in the brain and prevented the impairment of spatial learning (Wang *et al*. 2010). In a separate study, the GLP-1 mimetic liraglutide also protected synapses from the detrimental effects of β-amyloid and rescued memory formation (McClean *et al*. 2011, Han *et al*. 2013). Liraglutide (Victoza) is on the market as a treatment for T2DM (Courreges *et al*. 2008). When tested in the APP/PS1 mouse model of AD, once-daily injections i.p. had clear neuroprotective effects. Liraglutide prevented the memory impairment that is usually observed in ageing APP/PS1 mice, protected the synapses in the hippocampus from degradation and furthermore protected synaptic plasticity. The β amyloid plaque load and the total amount of β-amyloid in the brain were much reduced. This is an important biomarker for AD, and a reduction in amyloid levels is an important beneficial property. Furthermore, the chronic inflammatory response that is found in the brains of the AD mouse model was also much reduced (McClean *et al*. 2011). Exendin-4 has also been shown to reduce endogenous levels of β-amyloid in the mouse brain (Perry *et al*. 2003). This drug is also on the market as a treatment for T2DM under the name Byeatta. Exendin-4 has a range of neuroprotective properties in transgenic mouse models of AD (Li *et al*. 2010) and cell culture studies (Perry & Greig 2005). GLP-1 mimetics have also been shown to induce neurite outgrowth and to protect against excitotoxic cell death in cell cultures (Perry *et al*. 2002, 2007). Furthermore, mice that overexpressed GLP-1 receptors in the hippocampus showed increased neurite growth and improved learning (During *et al*. 2003). GLP-1 mimetics, exendin-4 as well as liraglutide and lixisenatide, also normalise neuronal progenitor cell proliferation and neurogenesis. It has been demonstrated in several studies in mouse models of AD and of diabetes or in wild-type mice that incretin analogues can increase or normalise neuronal progenitor cell proliferation in the CNS (During *et al*. 2003, Li *et al*. 2010, Porter *et al*. 2010*a*,*b*, Hamilton *et al*. 2011, McClean *et al*. 2011, Hunter & Holscher 2012).

In conclusion, GLP-1 mimetics show an impressive range of protective effects on synaptogenesis, neurogenesis, cell repair and the reduction of the chronic inflammatory response and most importantly reduce the levels of amyloid plaques in the brain. These findings indicate that these drugs may be used as novel treatments for AD (Azzouz *et al*. 2004, Bradbury 2005, Cotman *et al*. 2007, Gregory-Evans *et al*. 2009, Holscher 2011).

Parkinson's disease

There are several preclinical studies that have demonstrated neuroprotective effects of exendin-4 in animal models of PD. The protective effects of exendin-4 on neural stem/progenitor cells in the subventricular zone in the rat brain and the beneficial effects in an animal model of PD as well as in cell culture had been tested (Bertilsson *et al*. 2008). Exendin-4 increased the number of neural stem/progenitor cells in cell culture experiments. Furthermore, in an *in vivo* experiment, i.p. injection of exendin-4 enhanced the numbers of BrdU-positive progenitor cells in the subventricular zone. Neuronal precursor cell counts were also increased, suggesting that new neurons form that may compensate for the loss of dopaminergic neurons in the substantia nigra (Bertilsson *et al*. 2008). Exendin-4 was injected i.p. to test its effect in the 6-hydroxy-dopamine (6-OHDA) PD animal model which demonstrates neuronal loss in the substantia nigra. Five weeks after unilateral 6-OHDA lesion, the rats received i.p. injections of extendin-4 for 3 weeks. In a functional test of the dopaminergic system, amphetamine was injected, which that enhances dopamine release in the basal ganglia. A reduction of rotations in the movement of the exendin-4 group demonstrated a reduced functional impairment in this group. The expression of dopamine-synthesis-related enzymes was also elevated in the drug group. This result demonstrates that exendin-4 has cellular and functional beneficial properties in protecting rodents from the loss of dopaminergic neurons and transmission induced by 6-OHDA (Bertilsson *et al*. 2008). This was confirmed in a second study that employed the 6-OHDA and the LPS-induced substantia nigra injection lesion model of PD, which were used to test the effects of exendin-4. Seven days after inducing the pharmacological lesions, exendin-4 was injected i.p. After 7 days of treatment, amphetamine-induced circling behaviour was reduced in the exendin-4 groups. The levels of dopamine measured in the basal ganglia were also increased. Histological markers also confirmed that dopamine production was increased compared with the lesion-only groups (Harkavyi *et al*. 2008). An additional study tested exendin-4 in cultured dopaminergic rat neurons. These cells are vulnerable to 6-OHDA exposure. Exendin-4 protected the neurons taken from wild-type mice, but not those taken from GLP-1-receptor-knockout mice. In an *in vivo* study, exendin-4 protected dopaminergic neurons and rescued motor function in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine lesion mouse model of PD (Li *et al*. 2009).

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Patient data analyses also confirmed that a higher percentage of PD patients were diabetic or had elevated levels of glucose compared with age-matched control subjects. It was found that 8–30% of PD patients are diabetic, a significantly higher percentage compared with age-matched controls (Pressley *et al.* 2003, Aviles-Olmos *et al.* 2012). Based on the encouraging preclinical studies, a clinical trial testing exendin-4 in PD patients has been conducted (see below).

Amyotrophic lateral sclerosis

A different progressive neurodegenerative disorder that may be treated with GLP-1 mimetics is amyotrophic lateral sclerosis (ALS). The dominant symptom is increased motor neuron degeneration in the cortex, the brain stem and spinal cord. As a consequence, patients with ALS show fast developing paralysis and muscle wasting and die within 3–5 years after diagnosis, mainly due to respiratory failure (Kunst 2004).

In order to test the effects of exendin-4 in this disease, the drug was tested in NSC-19 neuroblastoma cells and a mouse model of ALS (SOD1 G93A mutant mice). It was found that exendin-4 protected NSC-19 cells and elevated the biomarker for acetylcholine neurotransmission, choline acetyltransferase (ChAT) activity and also protected cells from hydrogen peroxide-induced stress. The SOD1 mutant mice were treated with exendin-4 from 6 weeks of age onwards until the final stage of disease progression. The drug-treated SOD1 mice had near normal motor activity. In histological analyses, extending 4-treated mice had a reduced rate of degeneration of motor neurons in the spinal cord. In immunohistochemical analyses, motor neuron markers such as ChAT were normalised (Li *et al.* 2012). In a different approach, injection of cells that release GLP-1 into the brains of SOD1 mice, their survival was significantly extended and motor impairment and weight loss were much delayed. In motor activity analysis, an improvement of function was also observed. The chronic inflammatory response in the CNS was also reduced (Knippenberg *et al.* 2012). These neuroprotective effects of the GLP-1 mimetic exendin-4 support the concept that GLP-1 signalling is neuroprotective and may be a treatment strategy for ALS.

Peripheral neuropathy

Peripheral neuropathy is a degeneration of the neurons of the peripheral nervous system and can be induced by a range of causes. In chronic T2DM, peripheral neuropathy is often observed. To test the potential neuroprotective effect of exendin-4, the drug was tested in the diabetic polyneuropathy that is found in the streptozotocin (STZ) animal model of diabetes. STZ is toxic to β cells in the pancreas and reduces insulin production. The effects of GLP-1 (7–37) or exendin-4 were tested in cultured dorsal ganglion neurons from the peripheral nervous system. Both drugs accelerated the neurite outgrowth of cultured ganglion neurons. In the STZ-induced diabetes mouse model, exendin-4 was injected i.p. for 4 weeks. When testing the motor and sensory nerve conduction velocity of peripheral nerves, both GLP-1 (7–37) and exendin-4 protected the conduction of neurons. In behavioural tests, pain perceptions and motor and sensory neuronal conduction were improved by exendin-4. In histological studies, the skin nerve fibre densities were also normalised by exendin-4 (Himeno *et al.* 2011). Exendin-4 has been tested in a different model of peripheral neuropathy that was induced by vitamin B6 overdose. In anatomical studies, axon sizes were normalised by GLP-1. In motor tasks, the rats were partially protected from the effects of high B6 doses (Perry *et al.* 2007). Again, GLP-1 signalling has neuroprotective effects on peripheral neuropathy and may be of use in treating patients with such conditions.

Ischaemia and stroke

The anti-inflammatory properties and the neuroprotective effects of GLP-1 mimetics indicate that these drugs may be useful in treating stroke victims. Exendin-4 showed good neuroprotection in a transient middle cerebral artery occlusion stroke model in rats. It was found that exendin-4 reduced the brain area that degenerated after the stroke had been induced. In a functional score of motor activity, the drug-treated group performed better (Li *et al.* 2009). In a transient cerebral ischaemia model in gerbils, the effect of exendin-4 treatment was measured for the hippocampal CA1 region. It was found that GLP-1 receptor expression was increased after 1 day, and GLP-1R immunoreactivity was found not only in pyramidal neurons but also in astrocytes and GABAergic interneurons. Exendin-4 reversed the ischaemia-induced hyperactivity, reduced neuronal loss and also reduced microglial inflammatory activation in a dose-dependent manner (Lee *et al.* 2011). A further study tested the neuroprotective effect of exendin-4 injected i.v. after a 60-min focal cerebral ischaemia induction. The drug reduced infarct volume and protected the mice from motor impairment. It also reduced oxidative stress, induction of an inflammatory response and neuronal death after reperfusion (Teramoto *et al.* 2011). In a neuronal

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cell culture study, exendin-4 showed good neuroprotection under hypoxic conditions. This process was dependent on PKA the kinase that is activated by the GLP-1 receptor via adenylyl cyclase activation (Wang *et al*. 2012).

Taken together, these preclinical studies demonstrate good efficiency of GLP-1 signalling in protecting neurons from stressors and in reducing the inflammatory response in stroke and ischaemia. GLP-1 mimetics therefore show promise in preventing some of the secondary damage that occurs after a stroke or an ischaemic insult.

Multiple sclerosis

Considering that GLP-1 mimetics have anti-inflammatory properties and also protect synapses from stressors, it appears that these drugs may have beneficial effects in multiple sclerosis. The main hallmarks of this disease are continuous or intermittent inflammatory responses that seem to be directed against the myelin sheath that insulates larger axons. A strong inflammatory response that causes the loss of myelin sheaths slows axonal signal conduction and also results in loss of synapses and finally neuronal loss and impairment of motor control (Arnon & Aharoni 2009, Rossi *et al*. 2012). At present, no scientific publications are available on the effects of GLP-1 mimetics in animal models of multiple sclerosis. However, a patent is available that reports the effects of exendin-4 in mouse models of multiple sclerosis ('GLP-1 receptor agonists for treating autoimmune disorders' (WO 2011/024110A2) by the companies Pfizer and Rinat).

In this patent, the experimental results of the effects of exendin-4 and GLP-1 in several mouse models of multiple sclerosis are reported. One mouse model named Experimental Autoimmune Encephalomyelitis (EAE) involves the active immunisation of mice with membrane components of myelin such as the myelin basic protein, proteolipid protein and myelin oligodendrocyte glycoprotein. This induces an autoimmune response and develop ascending paralysis. The development of this autoimmune response can be acute or chronic, depending on the mouse strain and the myelin proteins used in the immunisation. Further hallmarks of EAE are a strong inflammatory response, mainly induced lymphocytes and macrophages that infiltrate the brain, followed by demyelination in the CNS (Arnon & Aharoni 2009, Aharoni *et al*. 2011, Rossi *et al*. 2012).

The experimental studies analysed spinal cord sections for infiltrating cells, T cells, monocytes and microglia. The level of demyelinisation was also assessed. Cytokine levels of Il-17 and interferon-γ were measured. The motor activity of the mice was also scored, and survival times were quantified. The motor impairment in the mice was reduced by exendin-4, and life expectancy was increased. The main inflammatory responses, such as T-cell proliferation and activation, as well as the inflammatory cell invasion into the CNS were much reduced, as was the level of demyelinisation. In addition, the cytokine release in the spleen was reduced.

These preclinical results are encouraging and indicate that GLP-1 mimetics may have beneficial effects in patients with multiple sclerosis. It is important to note, however, that the scientific results presented in the patent have not been peer reviewed.

Clinical trials

The preclinical studies listed above show an impressive range of neuroprotective and anti-inflammatory effects of GLP-1 mimetics. Furthermore, since three GLP-1 mimetics are already on the market as treatments for T2DM with a good safety profile in chronic use, several clinical trials have started that investigate the neuroprotective effects of exendin-4 or liraglutide in PD or AD patients. GLP-1 analogues have low-to-absent potential for inducing hypoglycaemia, as this propriety makes them potentially suitable as safe treatments for non-hyperglycaemic conditions such as neurological disorders.

Parkinson's disease

Recently, a clinical trial of exendin-4 in PD patients has been completed. This proof of concept study tested the effects of exendin-4 in a randomised open-label trial in 45 patients. The drug was given for 12 months followed by a 2-month washout period. The drug group was compared with a matched group that did not receive an injection. It was found that exendin-4 was well tolerated, although weight loss was common. In a single-blinded rating of the drug group, clinically relevant improvements in PD across motor and cognitive measures were compared with those in the control group. Exenatide-treated patients had a mean improvement at 12 months on the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) of 2.7 points, compared with mean decline of 2.2 points in control patients ($P=0.037$). Most interestingly, exendin-4 showed a clear improvement in the Mattis dementia rating scale 2 (DRS-2) cognitive score, suggesting that exendin-4 has beneficial effects in the CNS on cognition and memory (Aviles-Olmos *et al*. 2013).

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Alzheimer's disease

A randomised, double-blind clinical trial to assess the safety and efficacy of exendin-4 treatment in 230 MCI patients/early phase AD is currently ongoing at the National Institutes of Health (NIH)/National Institute on Aging (NIA) in the USA. This trial will take 3 years, with exendin-4 given. The outcomes are performance in the Clinical Dementia Rating scale sum-of-boxes, Alzheimer's Disease Assessment scale – cognitive sub-scale, behavioural and cognitive performance measures, changes on structural and functional MRI and MRS, hormonal and metabolic changes and changes in cerebrospinal fluid and plasma AD biomarkers (http://clinicaltrials.gov/ct2/show/NCT01255163?term=exendin-4+AND+alzheimer&rank=1).

A small-scale trial with 34 patients has been completed in Denmark at the University of Aarhus, but the results have not been published yet. This double-blind, randomised trial tests the effects of liraglutide vs placebo on MCI patients, using FDG–PET imaging to estimate glucose uptake in neurons and Pittsburgh compound B-PET imaging to measure plaque load, cognitive tests were also scheduled, see Egefjord *et al*. (2012) for details of the study design. A caveat regarding this study is that it is underpowered to produce meaningful results. (ClinicalTrials.gov Identifier: NCT01469351).

A second large-scale phase II clinical trial with liraglutide in 206 MCI patients has started. This trial is being conducted by Imperial College London. The trial has a randomised and placebo-controlled double-blind design and will analyse FDG–PET signal changes in neuronal metabolism and cortical activation, inflammation markers (microglia activation) in PET imaging, will take CSF samples for inflammation markers and amyloid/tau levels and the change in *z*-scores for the Alzheimer's Disease Assessment Scale Executive (ADAS Exec), and MRI changes. It will take 12 months, with a drug dose of 1.8 mg subcutaneously per day in the drug group or placebo injection (http://clinicaltrials.gov/ct2/show/NCT01843075?term=liraglutide+and+alzheimer&rank=1).

Conclusions

The preclinical experimental results demonstrate a wide range of important neuroprotective properties in engaging the therapeutic targets associated with neurodegenerative disease, such as impaired memory, synapse loss and impaired neuronal communication/synaptic plasticity, β-amyloid plaque formation (AD), motor function impairment, dopaminergic neuronal loss and dopaminergic loss in the basal ganglia (PD), chronic inflammation and reduced neuronal regeneration and neurogenesis (stroke MS, ALS). As GLP-1 mimetics are already on the market to treat T2DM and are well tolerated (Nauck 2011) and show a range of additional benefits (Ussher & Drucker 2012), and clinical trials in patients with PD or AD testing the effects of exendin-4 or liraglutide have been started, GLP-1R activation shows great promise of being helpful in treating a range of neurodegenerative disorders (Holscher 2010).

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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