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Invited Review

Drugs developed for treatment of diabetes show protective effects in Alzheimer's and Parkinson's diseases

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Abstract: Type 2 diabetes has been identified as a risk factor for Alzheimer's disease (AD) and Parkinson's disease (PD). In the brains of patients with AD and PD, insulin signaling is impaired. This finding has motivated new research that showed good effects using drugs that initially had been developed to treat diabetes. Preclinical studies showed good neuroprotective effects applying insulin or long lasting analogues of incretin peptides. In transgenic animal models of AD or PD, analogues of the incretin GLP-1 prevented neurodegenerative processes and improved neuronal and synaptic functionality and reduced the symptoms of the diseases. Amyloid plaque load and synaptic loss as well as cognitive impairment had been prevented in transgenic AD mouse models, and dopaminergic loss of transmission and motor function has been reversed in animal models of PD. On the basis of these promising findings, several clinical trials are being conducted with the first encouraging clinical results already published. In several pilot studies in AD patients, the nasal application of insulin showed encouraging effects on cognition and biomarkers. A pilot study in PD patients testing a GLP-1 receptor agonist that is currently on the market as a treatment for type 2 diabetes (exendin-4, *Byetta*) also showed encouraging effects. Several other clinical trials are currently ongoing in AD patients, testing another GLP-1 analogue that is on the market (liraglutide, *Victoza*). Recently, a third GLP-1 receptor agonist has been brought to the market in Europe (Lixisenatide, *Lyxumia*), which also shows very promising neuroprotective effects. This review will summarise the range of these protective effects that those drugs have demonstrated. GLP-1 analogues show promise in providing novel treatments that may be protective or even regenerative in AD and PD, something that no current drug does.

Key words: diabetes; memory; Parkinson's disease; neurodegenerative; nerve growth factor; insulin; Alzheimer's disease; neurotoxicity

抗糖尿病药物有助于治疗阿尔茨海默病和帕金森病

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摘 要：2型糖尿病已被证实是阿尔茨海默病(Alzheimer's disease, AD)和帕金森病(Parkinson's disease, PD)的一个危险因素。已有报道表明，AD和PD患者脑内的胰岛素信号转导受到损害。这一发现使抗糖尿病药物的应用有了新的研究，并显示出良好效应。临床前期试验表明，胰岛素或长效肠促胰岛素肽(incretin peptide)类似物具有良好的神经保护作用。在AD和PD转基因模型动物中，胰高血糖素样肽1 (GLP-1，一种肠促胰岛素的类似物)阻止了神经退行性变进程，改善了神经元和突触的功能，并减轻了疾病的症状。在AD转基因小鼠模型中，GLP-1类似物阻止了淀粉样斑块的沉积、突触的丧失以及认知功能的损害；在PD动物模型中，GLP-1类似物改善了多巴胺能神经传递和运动功能。在此基础上，临床试验也在进行之中，并显示出令人鼓舞的结果。在AD患者中的初步研究表明，鼻腔给予胰岛素可改善患者的认知功能并减少脑内的AD标志物。对PD患者的初步研究也表明，目前已经上市用于治疗2型糖尿病的一种GLP-1受体激动剂(exendin-4, *Byetta*)对PD病人具有良好的疗效。另一种上市用于治疗糖尿病的GLP-1类似物(liraglutide, *Victoza*)也正在AD患者中进行临床测试。最近，第三种GLP-1受体激动剂(Lixisenatide, *Lyxumia*)已经在欧洲被批准上市，该药物也显示了良好的神经保护作用。本文将就以上抗糖尿病药物的神经保护作用进行归纳。可见，GLP-1类似物所显示的神经保护乃至神经再生作用为AD和PD提供了一种新的治疗手段，这些作用是当前其它药物所不具备的。

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1 Introduction

1.1 Diabetes is a risk factor for neurodegenerative diseases

The majority of Alzheimer's disease (AD) and Parkinson's disease (PD) cases are 'sporadic', which means that there is no clear genetic pathway that causes the onset of the disease. This makes it more difficult to identify which factors trigger the neurodegenerative processes that underlie these diseases. Analysing the effects of known risk factors therefore may be a useful guide to some of the underlying biochemical processes that initially may be responsible for initiating AD or PD. In several studies of patient data sets, type 2 diabetes mellitus (T2DM) has been identified as a risk factor for AD and PD, indicating that impairments in insulin signaling may be a factor in initiating or accelerating the development of neurodegenerative processes [1, 2]. 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 [3–7]. One study showed a correlation between T2DM and the development of AD at a later stage. In this study, 85% of AD patients had either T2DM or increased fasting glucose levels, compared to 42% in the age-matched non-demented control group [8]. In a different study it was found that T2DM doubled the likelihood of developing AD [9]. In a longitudinal study in Japan where people were tested for glucose intolerance in an oral glucose tolerance test, a clear correlation was found between glucose intolerance and the development of AD in people with elevated 2-hour post-load glucose levels [10].

Recently, histological and biochemical analysis of brain tissue taken from AD patients showed that insulin signaling in the brain is desensitised in most patients, even if they did not have diabetes [11–13]. In a histological study of AD brain tissue, insulin-like growth factors-1 (IGF-1) and insulin receptors were found to be internalised in neurons, and the second messengers insulin receptor substrate 1 (IRS1) and 2 (IRS2) associated with insulin and IGF-1 signaling were inactivated and showed increased levels of IRSphospho^{Ser312} [14]. In a separate study it was found that in brain tissue of AD patients, IGF-1 and insulin signaling was strongly desensitised. Phosphorylation of the insulin receptor β chain that activated insulin signaling 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 signaling [15]. The observed biochemical changes were substantial, demonstrating almost complete loss of signaling, and suggest that the reduction in signaling of these growth factors may play a role in the initiation of AD.

In similar studies of brain tissue taken from patients with PD, similar biochemical changes in insulin signaling were found. It was shown that the levels of insulin receptor phosphorylation which deactivates insulin signaling were increased in the basal ganglia and the substantia nigra, brain regions that are affected in PD [1]. In addition, increased IRS2 phosphorylation, a marker of IGF-1 resistance, was found in the basal ganglia of an animal model of PD [16]. Other preclinical studies report similar changes. Feeding rats a high fat diet made them insulin resistant and more vulnerable to damage by 6-hydroxy dopamine (6-OHDA) treatment. The PD like symptoms that are induced by the 6-OHDA treatment were much enhanced in the high fat diet group. Motor activity was affected and dopamine depletion in the basal ganglia and substantia nigra was much enhanced [17]. In a high fat diet mouse model of T2DM, learning and memory and synaptic plasticity in the hippocampus was impaired [18]. In a high-fat diet rodent model of T2DM, insulin resistance was measured in the basal ganglia, while dopamine release was attenuated and dopamine clearance was reduced, suggesting that dopaminergic signaling is compromised in T2DM [19].

This correlation between T2DM and AD or PD offers new research strategies to investigate what the underlying biochemical mechanisms for the development of these neurodegenerative disorders may be. Insulin has a number of physiological roles to play, including that of a growth factor (GF), see Fig. 1. Neurons express insulin receptors, and the physiological effects of insulin include dendritic sprouting, neuronal stem cell activation, cell growth, repair and neuroprotection from stressors [20–23]. Insulin facilitates attention, memory formation and cognition in humans [24–27]. As insulin cannot be given to non-diabetic people, the route of nasal application was chosen for clinical trials. Using

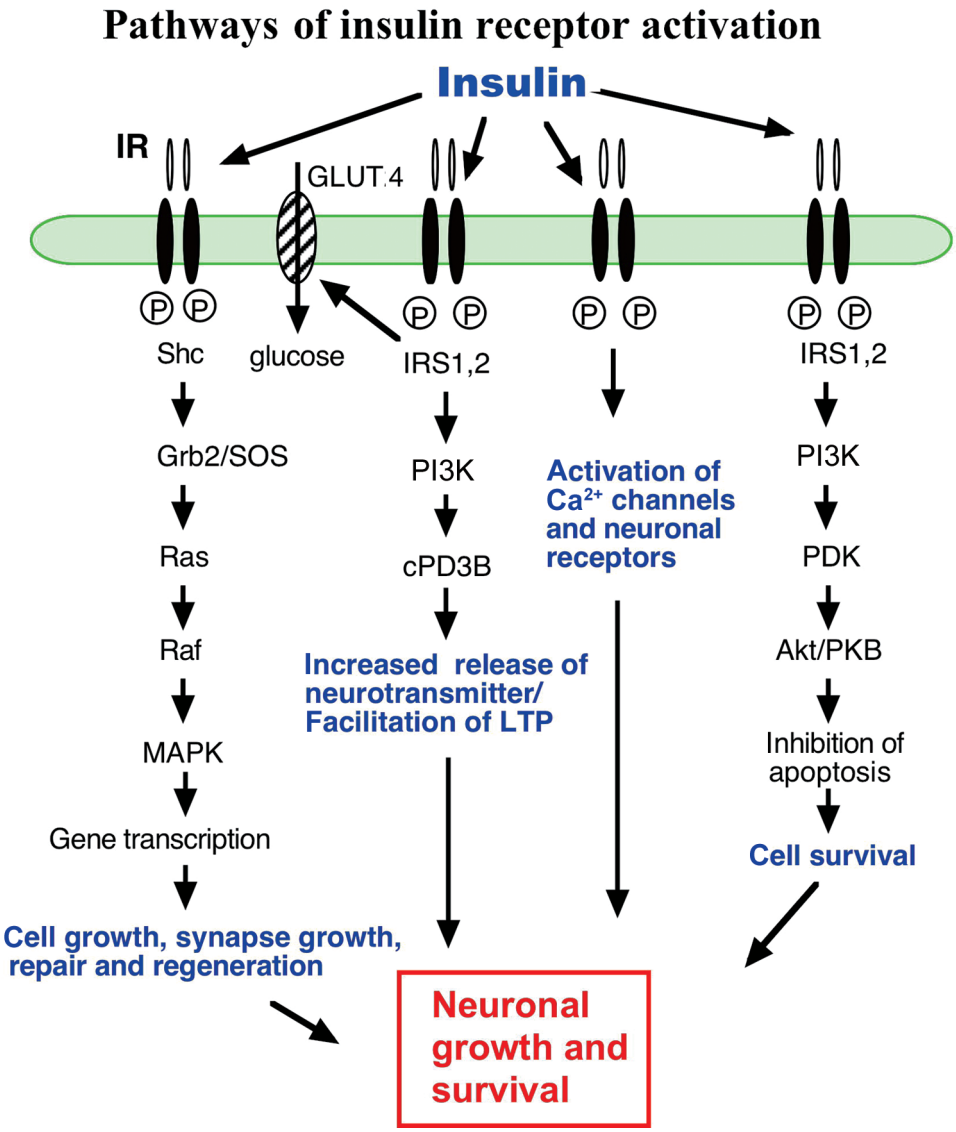

Fig. 1. An overview of some of the roles and functions of insulin receptors in neurons. Insulin signaling plays important roles in neuronal growth, synaptic development, and direct control of neurotransmitter release. Insulin binds to the α-subunit of the receptor. This activates the tyrosine kinase phosphorylation of the β-subunit. Then, several second messenger pathways can be activated: (1) Activation of the insulin receptor-Shc-MAP kinase pathway activates gene expression. These code for proteins that are required for cell growth, synapse growth, and for cell repair and maintenance [7, 108]. (2) Insulin receptor activation has a direct effect on neurotransmission, and primes synapses for induction of long-term potentiation of neuronal transmission (LTP) [109]. This pathway most likely involves binding of insulin receptor substrate-1 (IRS1) and insulin receptor substrate-2 (IRS2) to phosphatidylinositol 3-kinase (PI3K). Then, the cyclic nucleotide phosphodiesterase 3B (cPD3B) is activated [110]. This would prime the synapse for increased neurotransmitter vesicle release [111]. Modulation of neurotransmission will influence memory formation, information processing, and cognitive processes [112]. (3) Insulin receptors furthermore modulate neurotransmission directly by altering glutamatergic and GABAergic receptor activity. NMDA glutamate receptors can be phosphorylated to increase the opening of the associated Ca^{2+} channel [113]. IR activation also affects GABA transmission by recruiting functional GABA receptors to the postsynaptic site [114]. (4) As a growth factor, insulin also suppresses the induction of apoptosis. This pathway involves stimulation of PI3K binding to IRS-1 and -2, activation of PI3K, PDK, and protein kinase B (Akt/PKB), which suppresses the induction of apoptosis and thereby protects neurons [110, 115, 116]. Akt/PKB, protein kinase B complex; cPD3B, cyclic phosphodiesterase 3 beta; Grb2/SOS, Growth factor receptor binding protein 2/son of sevenless protein; IRS, insulin receptor substrates that get phosphorylated after activation; MAPK, mitogen activated protein kinase; PDK, phosphatidylinosite dependent kinase; PI3K, phosphatidylinositol 3 kinase; Raf, regulation of alpha-fetoprotein; Ras, rat sarcoma virus peptide; Shc, Src homology collagen peptide. Modified from Hölscher and Li, *Neurobiol Aging*, 2010[117].

this technique, insulin enters the brain more directly via the nasal epithelia with little effect on peripheral glucose levels. In such tests, insulin improved attention and memory formation in humans [26, 28, 29]. In a pilot study, nasal application of insulin improved cognition in patients with mild cognitive impairments (MCI), which is the early developmental phase of AD. It further improved the amyloid1-40/1-42 ratio in the cerebrospinal-fluid (CSF), increased cortical activation as seen in FDG-PET scans, and showed improvements in cognitive tasks [30]. In a follow up phase II study, a randomized, double-blind, placebo-controlled clinical trial of 104 patients with either MCI (n = 64) or mild to moderate AD (n = 40) had been conducted. Patients received either placebo (n = 30), 20 IU of insulin (n = 36), or 40 IU of insulin (n = 38) via nasal application for 4 months. Primary measures consisted of delayed story recall score and the Dementia Severity Rating Scale score, and secondary measures included cognitive tests. CSF samples were taken and ^{18}FDG-PET imaging was conducted in a subset of patients. Treatment with 20 IU of insulin improved memory, and both doses of insulin (20 and 40 IU) preserved the ability to conduct day-to-day activities, as rated by caregivers. Both insulin doses also preserved general cognition for younger participants and functional abilities as assessed by the ADCS-ADL scale. AD biomarkers in CSF samples did not change for insulin-treated participants overall, but changes in memory and function were correlated with changes in the Abeta42 level and in the tau-to-Abeta42 ratio. The placebo group showed decreased ^{18}FDG-PET levels in key brain regions, and insulin treatment reduced this development. It is of interest to note that the memory improvements were still present two months after drug treatment, suggesting that neuronal functional recovery had taken place [31]. For a review, see references [23, 32]. These studies testing the effects of insulin treatment in AD patients clearly demonstrate that enhancing insulin signaling does indeed improve cognition and key AD biomarkers.

1.2 GLP-1 mimetics developed to treat T2DM have neuroprotective properties

Using insulin to treat non-diabetic patients is not without risks, and the continued use of insulin may accelerate insulin desensitisation in the brain. Therefore, alternative strategies to normalise insulin or GF signaling may be employed, such as using drugs that have been developed to treat T2DM. In diabetes, a range of drugs are on the market or under development which could be tested for potential neuroprotective properties. Extensive research in diabetes has shown that mimetics of the incretin glucose-dependent polypeptide-1 (GLP-1) are a successful strategy to treat T2DM [33–35]. Importantly, 3 of these drugs are approved as treatments for T2DM, exendin-4, liraglutide and lixisenatide [36, 37]. The drugs are well received and only show small side effects such as initial nausea that dissipates after a few weeks. Importantly, the drugs do not directly affect blood sugar levels and can be given to people without diabetes [38, 39].

GLP-1 receptors are expressed in the brain, mainly on large neurons such as pyramidal neurons in the cortex or hippicampus, and Purkinje neurons in the cerebellum [40–42]. Glia cells do not express GLP-1 receptors unless they are activated in an inflammation response [42]. GLP-1 mimetics can protect cultured neurons from stressors, reduce apoptosis and enhance cell division [43, 44]. They also protect synapses from the detrimental effects that beta-amyloid has on synaptic plasticity in the hippocampus [45, 46]. Furthermore, these drugs can cross the blood brain barrier [47–52], a property that is of central importance in order to be effective in treating neurodegenerative disorders of the CNS.

GLP-1 just like insulin and IGF-1 activates second messenger signaling pathways that are commonly linked to growth factor signaling [53, 54]. GLP-1 activates classic GF second messenger cascades in neurons [44]. Figure 2 shows a summary of these findings.

1.2.1 AD

Testing GLP-1 mimetics in transgenic animal models of AD demonstrated clear neuroprotective effects. In the APP/PS1 transgenic mouse model of AD, which expresses the human Swedish mutated form of amyloid precursor protein (APP) and a mutated human form of presenilin-1 (PS-1), chronic ip. injection of the GLP-1 analogue Val(8)GLP-1 prevented the impairment in synaptic transmission that is observed in this AD mouse model [55]. In a study that tested the effects of induced diabetes on AD biomarkers in a triple-tg mouse model of AD, the GLP-1 mimetic exendin-4 showed effects in reducing key biomarkers [56]. The GLP-1 receptor agonist lixisenatide that recently has been released onto the market in Europe as a treatment for T2DM (*Lyxumia*) [37] also shows promising effects. The drug can cross the blood-brain barrier (BBB) and activate GLP-1 recep-

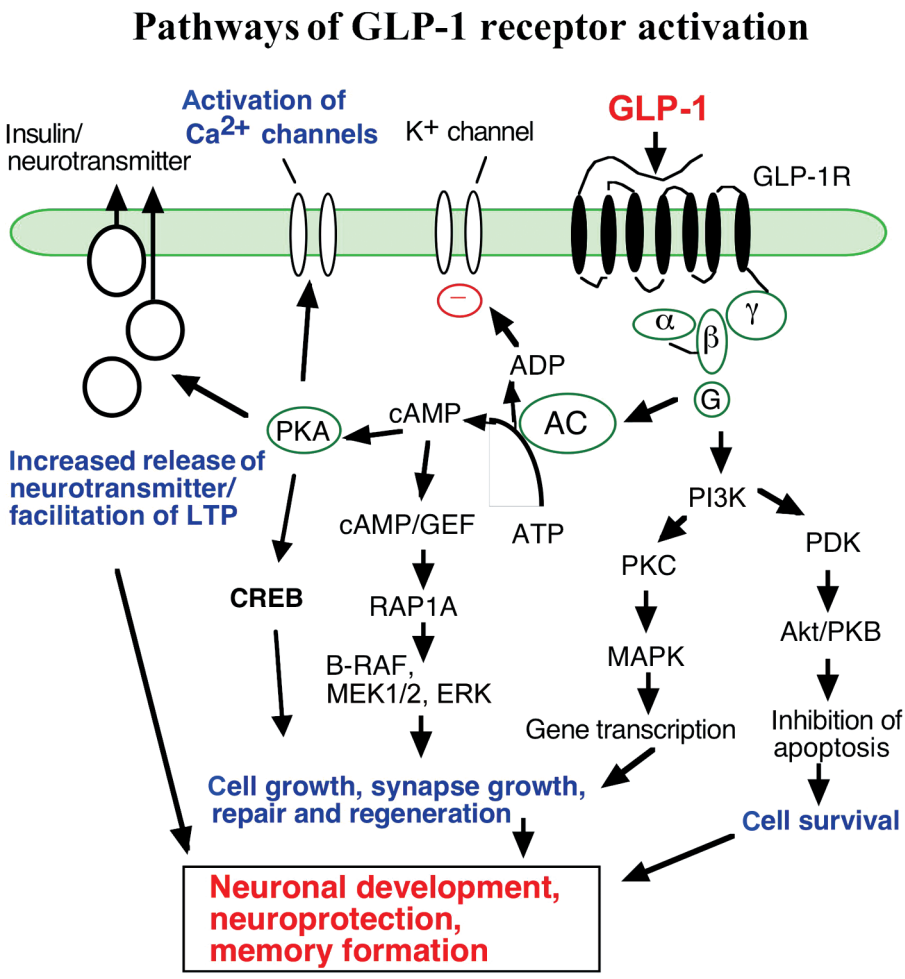

Fig. 2. Growth-factor related cell signaling activated by GLP-1 receptors in neurons. Diagrammatic representation of the neuroprotective effects of the long lasting GLP-1 analogue Liraglutide, mediated by PKB/Akt and MAPK/ERK pathways. Liraglutide stimulates GLP-1R resulting in an increase in the cAMP further leading to intracellular events such as cell survival, inhibition of apoptosis, activation of Ca^{2+} channels, cell growth, repair and regeneration and regulation of translation/transcription in response to stress. GLP-1R, GLP-1 receptor; PKA, protein kinase A; PI3K, phosphoinositide 3 kinase; PKB, protein kinase B; AC, adenylate cylase; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; CREB, cyclic AMP response element binding protein; MEK1/2, MAPK or Erk kinases; RAP1A, ras associate protein 1A; B-RAF, rapidly accelerated fibrosarcoma protein B; Ca^{2+}, calcium ions. For details see Sharma *et al* [44]. Modified from Hölscher and Li, *Neurobiol Aging*, 2010 [117].

tors in the brain and increase stem cell proliferation [51]. A recent study at the Shanxi Medical University at Taiyuan found that lixisenatide protects from the effects of beta-amyloid on learning and memory and synaptic plasticity in the hippocampus in rats [57] (see Fig. 3). The GLP-1 analogue liraglutide also reduced AD biomarkers in tg mice and protected synapses from the detrimental effects of beta-amyloid, and furthermore rescued memory formation [50, 52, 58], see Fig. 4. Liraglutide is on the market as a treatment for T2DM [59]. When tested in the APP/PS1 mouse model of AD, once-daily injections of liraglutide ip. for 8 weeks prevented the memory impairment that is usually observed in 9-month old APP/PS1 mice, protected the synapses in the hippocampus from degradation, and furthermore protected synaptic plasticity. Importantly, the beta amyloid plaque load and the total amount of beta-amyloid in the brain were much reduced. Also, the chronic inflammation response that is found in AD was also much reduced [50]. This result found in tg mice that started to develop the AD related symptoms indicates that the drug may be helpful in preventing disease pro-

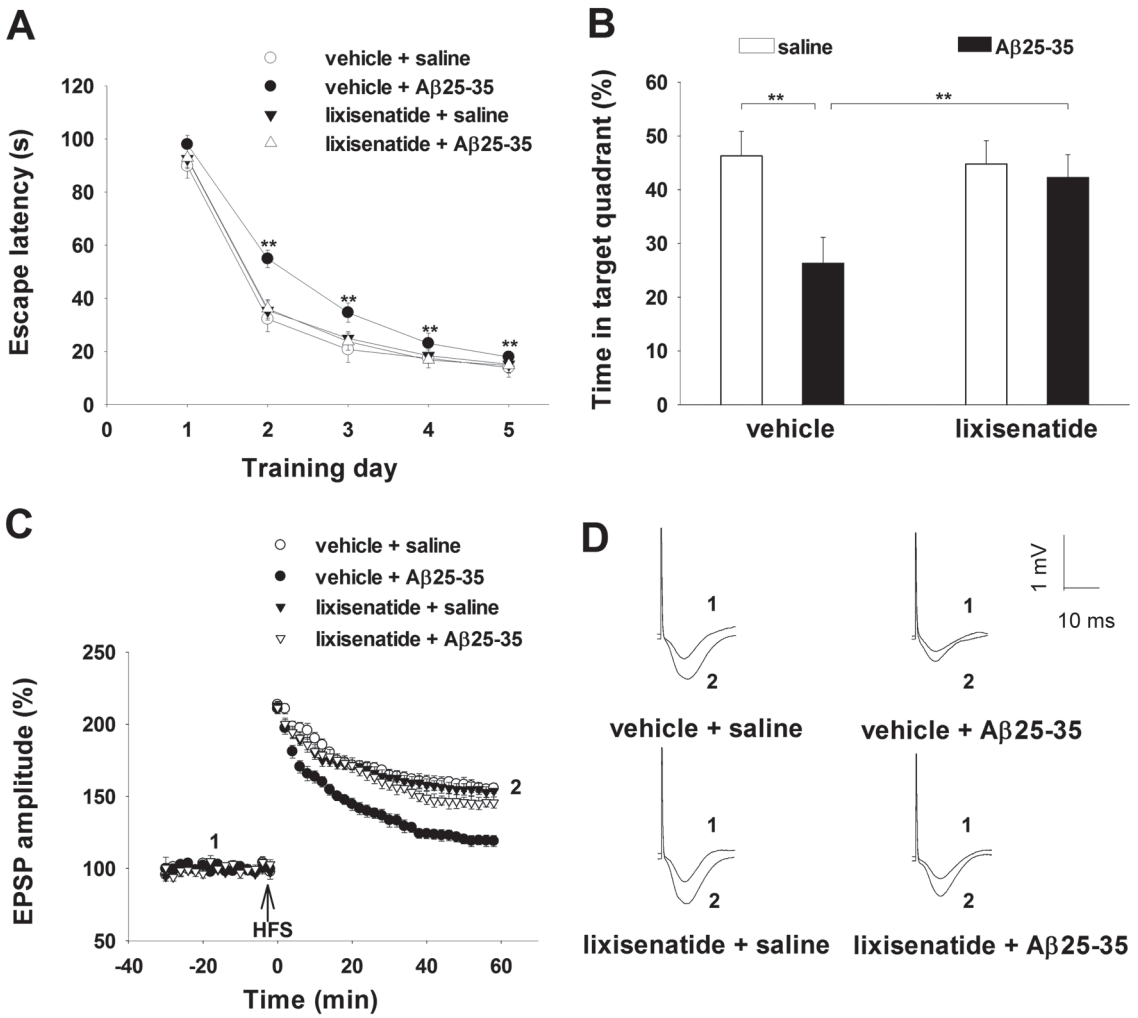

Fig. 3. Lixisenatide treatment reverses Aβ25-35-induced impairments of memory formation and of hippocampal LTP in rats. *A*: Time needed to find the hidden platform in a water maze task. A significant increase in the escape latency can be found in the Aβ25-35 group compared to the control ($n = 10$, $P < 0.001$), while lixisenatide treatment reversed this increase induced by Aβ25-35 ($n = 10$, $P < 0.001$). *B*: Probe test: swim time of rats in the target quadrant, with a significant decrease in the time in Aβ25-35 rats compared to the control group ($n = 10$, $P < 0.001$), and a significant reversal in lixisenatide treated group ($n = 10$, $P < 0.001$). *C*: Aβ25-35 injection produced a significant decrease in the magnitude of LTP in vehicle-treated rats ($n = 6$, $P < 0.001$), but this decrease was prevented by lixisenatide treatment ($n = 6$, $P < 0.001$). *D*: Typical fEPSP traces from the four groups at the time points indicated in the graph *C*. $^{**}P < 0.001$. Reprinted from Cai *et al*., *Neuroscience*, 2014 [57].

gression in MCI patients. When testing liraglutide in 14-month old APP/PS1 mice in which the disease progression had been advanced, the drug was still able to reduce synapse loss, suggesting that new synapses had sprouted, reverse memory loss, and reduce amyloid plaque load and chronic inflammation to some degree (Fig. 2) [52]. This encouraging result suggests that the drug may still be helpful even in more advanced cases of AD. Exendin-4 also has been shown to reduce endogenous levels of beta-amyloid in the mouse brain [60]. Exendin-4 has a range of neuroprotective properties in transgenic mouse models of AD [56] and cell culture studies [61]. GLP-1 mimetics also have been shown to induce neurite outgrowth and to protect against excitotoxic cell death in cell cultures [43, 44, 62]. GLP-1 receptor activation also normalises neuronal progenitor cell proliferation and neurogenesis in the dentate gyrus. The GLP-1 receptor agonists exendin-4, Val8-GLP-1, liraglutide and the novel agonist lixisenatide that is on the market as a treatment for type 2 diabetes showed these effects in cell culture studies, in mouse models of AD and of diabetes or wild-type mice in the CNS [18, 50, 51, 56, 63–65].

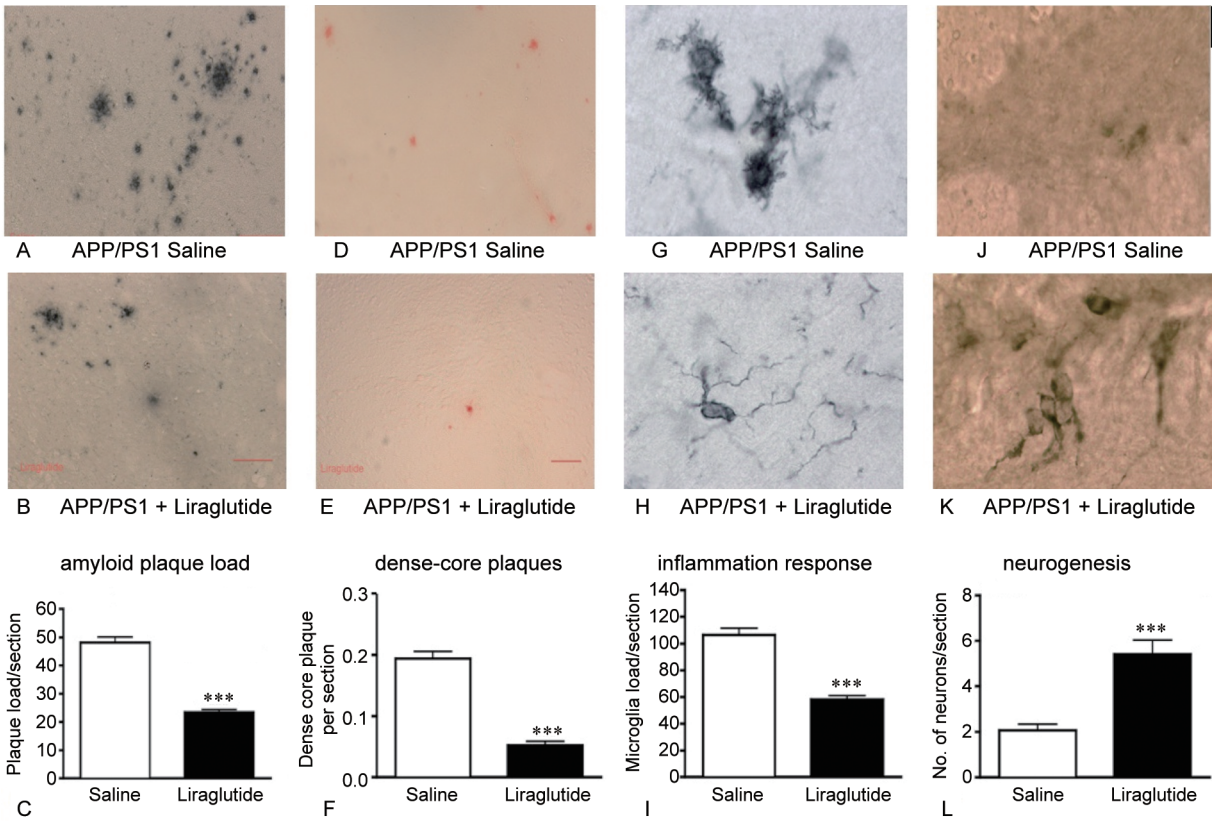

Fig. 4. Histological hallmarks of AD are improved with liraglutide. Histological analysis of the liraglutide-injected APP/PS1 mice showed a reduction in the number of plaques in the cortex and hippocampus of liraglutide-treated APP/PS1 mice was halved (*A*, *B*, *C*). The number of Congo-red positive dense core plaques was reduced to 25% (*D*, *E*, *F*). The inflammatory response, as shown by activated glia (IBA-1 antibody stain to identify activated microglia), was also halved (*G*, *H*, *I*). Mice treated with liraglutide also had a significant increase in neurogenesis (Doublecortin positive cells to identify young neurons) compared with saline treated animals (*J*, *K*, *L*). Sample micrographs show saline-treated on top, liraglutide below, and overall quantification at bottom. $^{***}P < 0.001$, (student's *t*-test, $n = 6$). Modified from McClean *et al*., *J Neurosci*, 2011 [50].

Based on these very promising preclinical results, clinical trials in AD patients have been started.

A randomized, 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 NIH/NIA in the USA. This trial will take 3 years, with exendin-4 given. The outcomes are performance in the Clinical Dementia Rating (CDR) scale, the Alzheimer's Disease Assessment scale-cognitive sub-scale (ADAS-cog), behavioral and cognitive performance measures, observed changes in structural and functional MRI and MRS brain scans, hormonal and metabolic changes and changes in CSF and plasma AD biomarkers. See http://clinicaltrials.gov/ct2/show/NCT01255163?term=exendin-4+AND+alzheimer&rank=1.

A second, larger scale phase II clinical trial with liraglutide in 206 MCI patients has started. The trial is randomised and placebo controlled and double blind in design, and will analyse FDG-PET signal changes in neuronal metabolism and cortical activation in the CNS, inflammation markers (microglia activation) using a novel PET imaging marker, changes in CSF samples for inflammation markers and amyloid/tau levels, and the change in the ADAS Exec scores. Drug or placebo will go for 12 months, with a drug dose of 1.8 mg subcut. per day in the drug group. See http://clinicaltrials.gov/ct2/show/NCT01843075?term=liraglutide+and+alzheimer&rank=1.

1.2.2 PD

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 [66]. Exendin-4 increased the number of neural stem/progenitor cells in cell culture experiments. Furthermore, in an *in vivo* experiment, ip. injection of exendin-4 enhanced the numbers of BrdU positive progenitor cells in the subventriclar 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 [66]. Exendin-4 was injected ip. to test its effect in the 6-OHDA PD animal model which demonstrates neuronal loss in the substantia nigra. Five weeks after unilateral 6-OHDA lesion, the rats were injected ip. for 3 weeks with exendin-4. In a functional test of the dopaminergic system, amphetamine was injected 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 enzymes that are linked to dopamine synthesis 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 neuronal transmission induced by 6-OHDA [66]. This was confirmed in a second study which employed the 6-OHDA and the lipopolysaccaride (LPS) induced substantia nigra injection lesion model of PD to test the effects of exendin-4. Seven days after inducing the pharmacological lesions, exendin-4 was injected ip. 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 to the lesion-only groups [67]. 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 (MPTP) lesion mouse model of PD [49].

The evaluation of large patient data sets also confirmed that a higher percentage of PD patients were diabetic or glucose compared to age matched control subjects. It was found that 8%–30% of PD patients were diabetic, showing a significantly higher percentage compared to age matched non PD controls [2, 68].

Based on the encouraging preclinical studies, a clinical trial testing exendin-4 in PD patients has been conducted. This pilot 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 wash-out period. The drug group was compared to 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, clinically relevant improvements in PD across motor and cognitive measures were observed when compared with the control group. Exendin-4 treated patients had a mean improvement at 12 months on the 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 DRS-2 cognitive score, suggesting that the drug has beneficial effects on cognition and memory [69]. A follow-up study showed that the beneficial drug effects were still visible one year after the clinical trial [70]. This result greatly supports the hypothesis that GLP-1 receptor agonists may be a novel effective treatment for PD as well. A larger clinical trial using a double blind placebo controlled design is planned.

1.3 Other growth factors show neuroprotective effects

Incretins such as GLP-1 and the sister incretin glucagon-like polypeptide (GIP) [71–73] show an array of impressive protective effects. This is due to the fact that they are growth factors and activate a range of processes, from synaptic transmission to gene expression [53]. The observation that growth factors have neuroprotective effects in neurodegenerative models is not entirely new. The effects that insulin or incretins have on memory formation and the protection of synapses from the detrimental effects of beta amyloid are very similar to the neuroprotective effects of other growth factors. For example, brain derived neurotrophic factor (BDNF) has been shown to protect synapses in mouse models of AD. Injecting BDNF icv. improved cognition, prevented impairments of LTP and led to an enhancement of hippocampal synaptic density [74]. Increasing BDNF production in the brain by gene delivery vectors also has protective effects on synapses. Increase of BDNF levels, when administered after disease onset, reverses synapse loss, improves synaptic plasticity and restores learning abilities of a mouse model of AD [75, 76]. It is of interest to note that the effects of BDNF are therefore very similar to those of GLP-1 and insulin. This documents that growth factors have common modes of

action (see below). There is, however, one important difference: BDNF does not cross the BBB. BDNF therefore will not be effective in protecting neurons in the CNS. To get around this, a gene delivery system to the brain has to be developed, or BDNF has to be injected directly into the brain [77, 78]. This clearly limits the use of BDNF as a treatment for AD.

Another growth factor that is under investigation as a treatment for neurodegenerative disorders is nerve growth factor (NGF). Preclinical studies showed that NGF was found to protect synapses, LTP, and learning abilities in AD mouse models or in nonprimate monkeys without affecting amyloid plaque load, similar to BDNF [79–81]. However, NGF does not cross the BBB either, which makes it difficult to utilise it as a treatment for CNS disorders. Again, gene delivery systems are being developed to be able to use NGF as a treatment of CNS disorders. However, attempts to insert the NGF gene into cells in the CNS and to increase the amount of NGF production in the CNS have not been successful so far [78, 80, 82, 83]. Currently, clinical tests of gene delivery via a viral vector when injected in the brains of patients are ongoing [84]. Another clinical trial investigates the effects of the implantation of NGF-expressing cells into the basal brain (nucleus basalis) of patients with AD, with the aim that the degeneration of cholinergic neurons in AD can be prevented [85].

There is a range of additional growth factors that have similar protective effects on neurons, eg. insulin-like growth factor 1 (IGF-1) [86, 87], vascular endothelial growth factor (VEGF) [88–90], or glial cell line-derived growth factor (GDNF)[91]. In preclinical studies, these growth factors have shown promising results in protecting neurons from the effects of amyloid aggregation, they promote cell repair and protect synapses and cognitive performance. As most growth factors, they do not readily cross the BBB. In order to deal with this, delivery systems are under development in order to be able to deliver these growth factors into the brain, which is not a trivial problem to solve[88, 89, 91–94].

2 Mechanisms of action: neuroprotective activities of growth factors

Growth factors such as NGF, BDNF, insulin or GLP-1 activate second messenger signaling pathways that activate key kinases such as MAPKII and Erk1/2[53,83,95]. Figure 1 and 2 show the signaling pathways that are involved here. Studies show that the activation of these kinases is neuroprotective [77, 96–100]. Furthermore, growth factor signaling activates gene expression for cell repair and cell growth which can repair neurons and protect them from oxidative stress. One of the key effects that growth factor seem to have is to protect synapses, keep them functional even in the presence of stressors such as amyloid and chronic inflammation, and to enhance synapse growth [50, 101, 102].

3 Future developments

GLP-1 analogues are being optimised for improved control of diabetes. Once-weakly versions have been developed [103], and the first one is on the market (Bydureon), a slow release depot injection of exendin-4. Drug development for diabetes has produced a range of new analogues, including long-lasting analogues of other incretin hormones such as glucose dependent insulinotropic polypeptide (GIP) [72], oxyntomodulin, CCK [104], and novel dual-agonistic peptides that are currently tested in diabetes [105]. The ongoing research in improved analogues and novel drug treatments for diabetes offers a promising research area to test such drugs in models of neurodegeneration. The results of ongoing clinical trials in AD and PD patients will inform us in more detail of the effectiveness of these drugs.

4 Conclusion

In conclusion, nasal insulin delivery as well as GLP-1 mimetics show an impressive range of protective effects on synaptogenesis, neurogenesis, cell repair, and the reduction of the chronic inflammation response, and reduce the levels of amyloid plaques in the brain in AD and a normalisation of dopamine production and functionality in PD in preclinical studies. Furthermore, first clinical trials testing insulin or exendin-4 showed promising first results. These findings suggests that these drugs may be used as a novel treatment for AD or PD [69, 82, 88, 92, 106, 107].

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