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Protective Roles of the Incretin Hormones Glucagon-Like Peptide-1 and Glucose-Dependent Insolinotropic Polypeptide Hormones in Neurodegeneration

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1. Introduction

Alzheimer's disease is a sporadic disease with very few risk gene links associated with it. Therefore, it is very difficult to assess what the underlying causes of this diseases are, and what the initial triggering mechanisms may be. As the disease can only be diagnosed when it has already developed, very little is known what those early phase processes are that initiate the sequence of events that evenutally lead to neurodegeneration. Another approach to investigate the contributing factors is the correlation with other conditions that increase the risk of developing AD. Several such risk factors have been identified, and interestingly, type 2 diabetes is one of these. In type 2 diabetes mellitus (T2DM), insulin is no longer able to reduce the levels of blood sugar after a meal. In fact, ensulin levels may even be increased as an attempt by the body to overcome the reduced effectiveness of insulin in the periphery, which may be caused by insulin receptor desensitisation. Due to the change of lifelstyle in the industrialised nations, an unhealthy diet in combination with lack of exercise, levels of T2DM are on the rise. This may increase the rate of AD cases in the future. A lot of research is currently conducted in developing novel treatments of T2DM (Dailey 2008, Frias & Edelman 2007, Pi-Sunyer 2008, Scheen 2008). Since insulin effectiveness is reduced in diabetes, research into other signalling pathways that support insulin actions or that reduce blood glucose independently is ongoing. One of these strategies focus on the use of the incretins, a class of peptide hormones that helps to normalise insulin signaling and also improves blood sugar levels. Incretins increase the release of insulin during high blood sugar levels, the so-called 'incretin effect'. They have little effect on normal blood sugar levels and therefore are suitable for treating non-diabetics. In addition, incretins have a range of other effects that help regulate physiological lipid and glucose levels, eg. they increase the uptake of lipids and glucose in cells that express the receptor (Baggio & Drucker 2007, Drucker & Nauck 2006, D. E. Green 2007).

T2DM has been identified as a risk factor for AD, indicating that insulin signaling impairment may be a factor in initiating or accelerating the development of AD. Epidemiological studies found a clear correlation between T2DM and the risk of developing AD or other neurodegenerative disorders at a later stage (Haan 2006, Luchsinger, Tang, Shea, & Mayeux 2004, Ristow 2004, Strachan 2005). For example, a study of patient databases of the Mayo clinic showed a clear correlation between T2DM and AD. In this study, 85% of AD patients also had T2DM or

increased fasting glucose levels, compared to only 42% in the control group. T2DM was clearly identified as a risk factor that doubled the chance of developing AD (Janson et al. 2004). Reduced insulin sensitivity and efficacy is also observed in the majority of elderly people and contributes to the development of AD (Carro & Torres-Aleman 2004, Hoyer 2004). It was also shown that insulin receptors in the brain are desensitised in AD patients, which has been named 'type 3 diabetes' (Lester-Coll et al. 2006, Steen et al. 2005). A recent study reported that insulin receptor levels are downregulated in the brains of patients with AD. Insulin receptors were found to be internalised in neurons, and the second messengers IRS1 and IRS2 were reduced in total levels but had increased levels of inactivated phospho^{Ser312} (Moloney et al. 2010). This unexpected connection between T2DM and AD 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). Insulin is crucial for 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 (Holscher 2005, Hoyer 2004, L. Li & Hölscher 2007, Stockhorst, de Fries, Steingrueber, & Scherbaum 2004, van Dam & Aleman 2004). Furthermore, insulin has potent neuroprotective factors, and also regulates GSK3ß, the main kinase that phosphorylates Tau, which is the major component of neurofibrillary tangles found in the brains of AD (Carro & Torres 2004, L. Li & Hölscher 2007). Insulin also improves brain activity such as attention, memory formation and cognition in humans (Okereke et al. 2008, Reger, Watson, Green, Baker et al. 2008, Watson & Craft 2004, W. Q. Zhao, Chen, Quon, & Alkon 2004). Nasal application of insulin, an application route where it enters the brain more directly, had clear effects on attention and memory formation (S. Craft 2007, Reger, Watson, Green, Baker et al. 2008, Reger, Watson, Green, Wilkinson et al. 2008). A recent phase II clinical trial showed that nasal application of insulin improves memory in patients with mild cognitive impairments and early AD patients, improves the CSF amyloid1-40/1-42 ratio, showed enhancement of cortical activation in PET scans, and also showed improvement in cognitive tasks (S Craft 2010).

In animal models, a decrease in insulin receptor signalling produces cognitive impairments and a reduction in hippocampal synaptic neurotransmission and synaptic plasticity, a mechanism that may be linked to memory formation (Biessels, De Leeuw, Lindeboom, Barkhof, & Scheltens 2006, C. Hölscher 2001, Trudeau, Gagnon, & Massicotte 2004). Diabetic mice show clear imprairments in spatial learning and synaptic plasticity (LTP) in the hippocampus. Treatment with incretins effectively prevented   or reversed these impairments (V. A. Gault, Porter, Flatt, & Holscher 2010, Porter, Kerr, Flatt, Holscher, & Gault 2010). People with T2DM also have cognitive impairments, and effective treatment with diabetes medication improves these impairments (Gispen & Biessels 2000, Hoyer 2004). Conversely, insulin injected into the brain can improve performance in memory tasks in animals (Stockhorst et al. 2004). Treatments of diabetic animals with insulin also rescues the impairment in synaptic plasticity (Biessels, Bravenboer, & Gispen 2004, Gispen & Biessels 2000). The basis for this neuroprotective effect is that activation of neuronal insulin receptors has been shown to induce dendritic sprouting, neuronal stem cell activation, and general cell growth, repair, and additional neurotropic effects (Holscher 2005, Hoyer 2004, L. Li & Hölscher 2007, Stockhorst et al. 2004, van Dam & Aleman 2004). Therefore it is not surprising that insulin also improves brain function such as attention, memory and cognition in humans (Okereke et al. 2008, Reger, Watson, Green, Baker et al. 2008, Watson & Craft 2004, W. Q. Zhao et al. 2004).

In conclusion, the impairment of insulin signalling in the brain appears to play a role in the development of neurodegenerative disorders, as it leaves neurons more vulnerable to cytotoxic influences (S. Craft 2005, 2007, Hallschmid & Schultes 2009, Holscher 2005, Hoyer 2004).

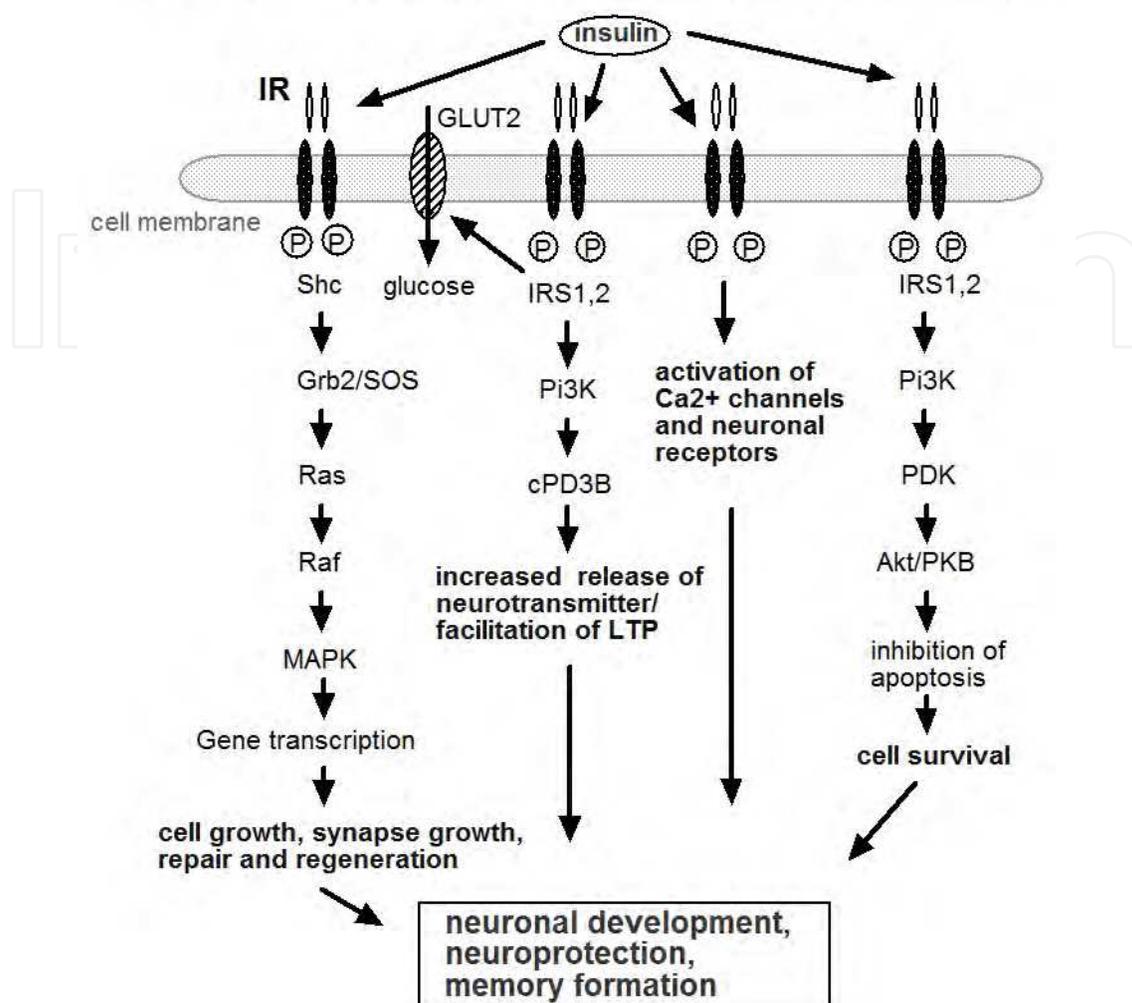## Pathways and functions of insulin receptor activation

Fig. 1. An overview of some of the roles and functions of insulin receptors (IR).
Traditionally, insulin is associated with its blood glucose lowering activity. This is achieved
by activating a glucose uptake transporter, eg. GLUT-2. This function is only one of many of
the IR. Recent research has uncovered a number of important roles in neuronal growth,
synaptic development, and direct control of neurotransmitter release. During neuronal
activity, insulin is released and binds to the a-subunit of the receptor. This activates the
tyrosine kinase phosphorylation of the b-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 (Biessels et al. 2006, Hoyer 1997).
2. IR activation has a direct effect on neurotransmission, and primes synapses for induction
of long-term potentiation of neuronal transmission (LTP) (Biessels et al. 2004). 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 (A. Z. Zhao et al. 2000). This would prime the
synapse for increased neurotransmitter vesicle release (de la Monte & Wands 2006).
Modulation of neurotransmission will influence memory formation, information processing,
and cognitive processes (C Hölscher 1999).

2. The incretins hormones: Glucagon-like Peptide-1 (GLP-1) and Glucose-dependent Insolinotropic Polypeptide (GIP)

As insulin receptors are desensitised in T2DM and in AD, and injection of insulin itself can have dangerous effects on blood sugar levels and loses its effectiveness over time, scientist in the field are investigating different strategies how to improve blood glucose level maintenance. In addition, it is not sensible to treat AD patients with insulin that do not have diabetes. However, other signalling pathways exist that also modulate blood glucose levels, eg. the incretin hormone signalling pathways – in particular GLP-1 and GIP (Frias & Edelman 2007, V. A. Gault, McClean et al. 2007).

GLP-1 is an endogenous 30-amino acid peptide hormone (fig 3a), which is released by intestinal L and K-cells after a meal. It has several physiological roles in the body to control cell metabolism (fig. 2). GLP-1 is a product of the glucagons gene which encodes the precursor peptide proglucagon. This peptide contains three glucagon-like peptides: glucagon, glucagon-like peptide 1 and glucagon-like peptide 2 (Baggio & Drucker 2007, B. D. Green et al. 2004). The GLP-1 receptor belongs to the class B family of G-protein coupled receptors. The receptors for glucagon, GLP-2 and GIP also belong to this group. Activation of the receptor activates an adenylate cyclase, increases IP3 levels, increases intracellular Ca^{2+} and affects levels of other second messengers (Baggio & Drucker 2007, Holscher 2010). GLP-1 receptor stimulation enhances beta-cell proliferation in the pancreas by activating stem cell proliferation, facilitates glucose-dependent insulin secretion and lowers blood glucose in patients with T2DM (B. D. Green et al. 2006, Lovshin & Drucker 2009).

GIP is a 42-amino acid incretin hormone which activates pancreatic islets to enhance insulin secretion and to help reduce postprandial hyperglycaemia, similar to GLP-1 (V. A. Gault, Flatt, & O'Harte 2003; Fig 3b). GIP also has been shown to promote pancreatic beta-cell growth, differentiation, proliferation and cell survival, documenting its growth-hormone properties (V. A. Gault et al. 2003). Therefore, research is ongoing to develop GIP as an therapeutic tool for T2DM treatment (Irwin et al. 2006) (see fig. 3b). GIP is a member of the vasoactive intestinal peptide seretin/glucagon family of neuroregulatory polypeptides which also include the pituitary adenylate cyclase activating peptide and the growth hormone releasing factor. It is expressed in pancreatic alpha cells, endocrine K and L cells, and also in neurons (Nyberg et al. 2005). Apart from the incretin effect of enhancing insulin release under hyperglycaemic conditions, GIPR activity in bone tissues enhances bode density, uptake of fat into adipose cells, and stem cell or neuronal progenitor cell proliferation (Baggio & Drucker 2007, Figueiredo et al. 2010). GIPR KO mice show a decrease in neuronal stem cell proliferation, and GIP analogues activate neuronal stem cells (E Faivre, McClean, & Hölscher 2010, Nyberg, Jacobsson, Anderson, & Eriksson 2007).

2.1 Incretins also play important roles in the brain

GLP-1 receptors are found on neurons in the brains of rodents and humans (Goke, Larsen, Mikkelsen, & Sheikh 1995, Perry & Greig 2005). They are predominately expressed on large size neurons, on the cell bodies and also on dendrites, indicating that they are located on the synapse (A Hamilton & Holscher 2009). Similar to insulin, GLP-1 is predominately known for its action on blood sugar levels. However, just as insulin, GLP-1 is principally a growth factor and has the main properties of all growth factors (Holscher & Li 2010). GLP-1 increases cell growth, proliferation and repair, and inhibits apoptosis (A. Hamilton, Patterson, Porter, Gault, & Holscher 2011, Perfetti, Zhou, Doyle, & Egan 2000). In the brain,
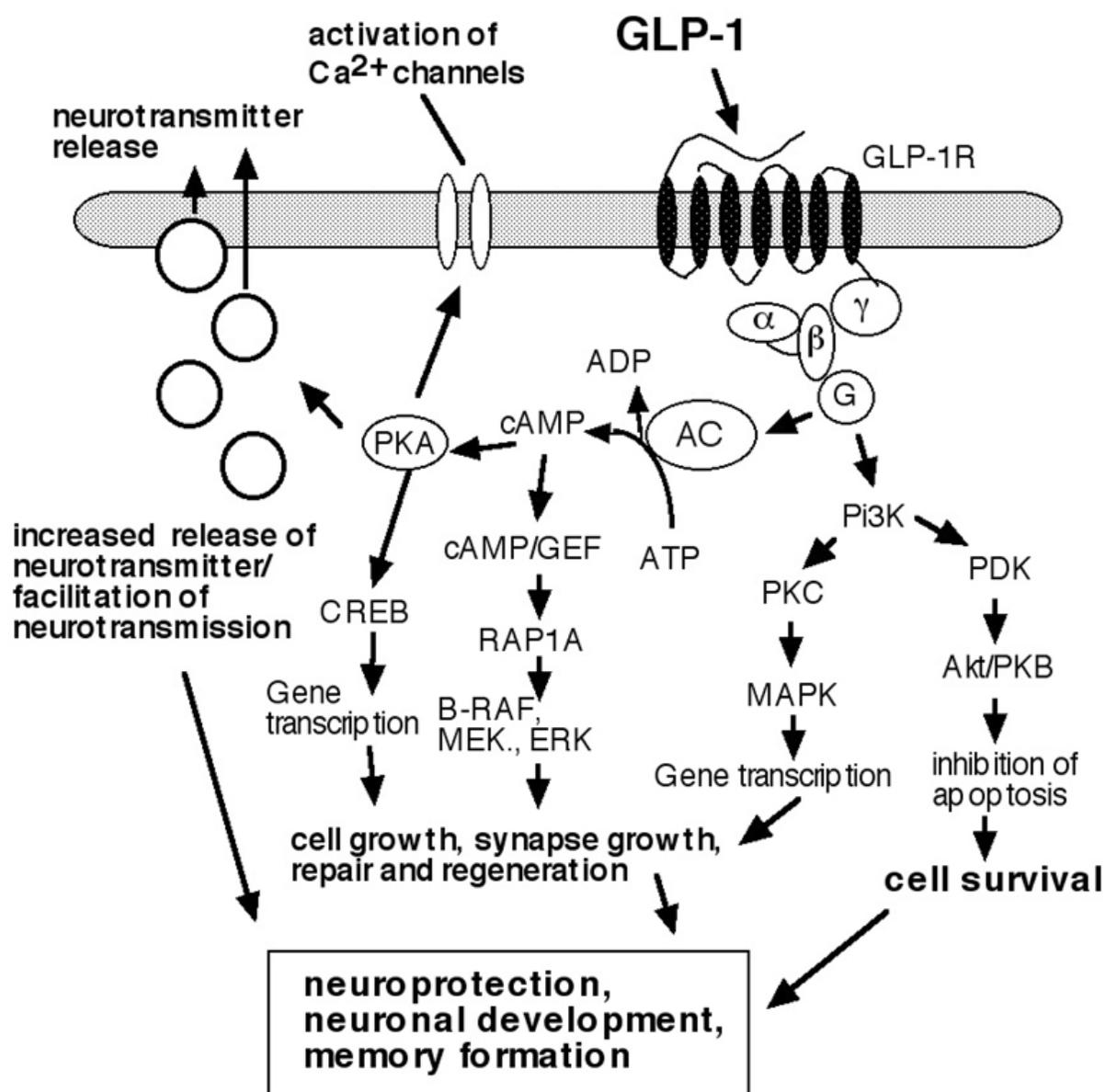
Activity of GLP-1 in neurons

Fig. 2. Overview of the main pathways induced by GLP-1 in neurons. As compared to fig. 1, the overall mechanisms are very similar. The main physiological effects of GLP-1 on cell growth, proliferation, regeneration and inhibition of apoptosis are identical. Differences can be seen in the control of vesicle release, which is glucose-dependent in ß-cells but not in neurons. For more details see (Holscher 2010, Holscher & Li 2010).

GLP - 1 sequences

Native GLP - 1
HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

Asp(7)GLP - 1
DAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

Val(8)GLP - 1
HVEGTFTSDVSSYLEGQAAKEFIAWLVKGR

Pro(9)GLP - 1
HAPGTFTSDVSSYLEGQAAKEFIAWLVKGR

Exendin - 4
HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS

Lixisenatide
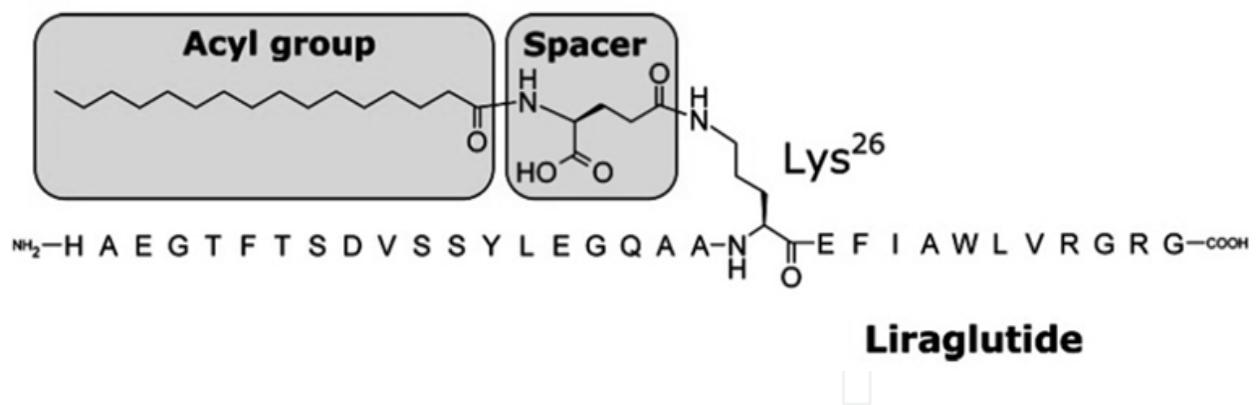HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPSKKKKKK - NH2

Fig. 3. a. Shown are the amino acid sequences of the native GLP-1 peptide and also of some modifications of GLP-1 designed to prevent degradation by the DPP-IV protease. Shown are amino acid substitutions at position 7, 8, or 9 (Holscher 2010), and a fatty acid addition to a modified GLP-1 peptide (liraglutide). Liraglutide has the amino acid sequence of native GLP-1 with one modification, Arg34, and are derivatised at position 26 with a spacer and an acyl group (Madsen et al. 2007). The natural GLP-1 analogue exendin-4 sequence is shown. This peptide is found in the saliva of the reptile Gila monster. A derivative of this sequence is Lixisenatide, which is a long-acting GLP-1 analogue currently in clinical trials as a treatment of T2DM (Christensen, Knop, Holst, & Vilsboll 2009).

GIP sequences

Native GIP
MVATKTFALLLLSLFLAVGLGEKKEGHFSALPSLPVGSHAKV

*d*Ala(2)GIP
MAATKTFALLLLSLFLAVGLGEKKEGHFSALPSLPVGSHAKV

Pro(3)GIP
MVPTKTFALLLLSLFLAVGLGEKKEGHFSALPSLPVGSHAKV

Fig. 3. b. Shown are the amino acid sequences of the native GIP peptide and also of some of the modifications of GIP to prevent degradation by the DPP-IV protease. Shown are amino acid substitutions at position 2 and 3. The analogue D-ALA(2)GIP acts as an agonist to the receptor, while the analogue Pro(3)GIP has antagonistic properties (V. Gault et al. 2005, V. A. Gault & C. Holscher 2008, V. A. Gault, Hunter et al. 2007).

GLP-1 has been documented to induce neurite outgrowth and to protect against excitotoxic cell death and oxidative injury in cultured neuronal cells (Perry et al. 2002, Perry et al. 2003). Neurons were found to be protected against cell death induced by beta-amyloid 1-42, the peptide that aggregates in the brains of Alzheimer patients, and against oxidative stress and membrane lipid peroxidation caused by iron (Perry & Greig 2005). In addition to this, mice that overexpress GLP-1 receptors in the hippocampus showed increased neurite outgrowth and improved spatial learning. Enhanced progenitor cell proliferation in the brain was also found in this study (During et al. 2003). The novel GLP-1 analogue Liraglutide also increases the division of neuronal progenitor cells in the brain, and even increases neuronal neogenesis in the brains of a mouse model of AD (P. McClean, Parthsarathy, Faivre, & Hölscher 2011) (see fig 4). These properties are typical growth factor effects, and by activating neuronal progenitor cell proliferation and neurogenesis it may be possible to regenerate parts of the lost brain tissue and to regain some of the lost cognitive functions in patients with AD (Sugaya et al. 2007).
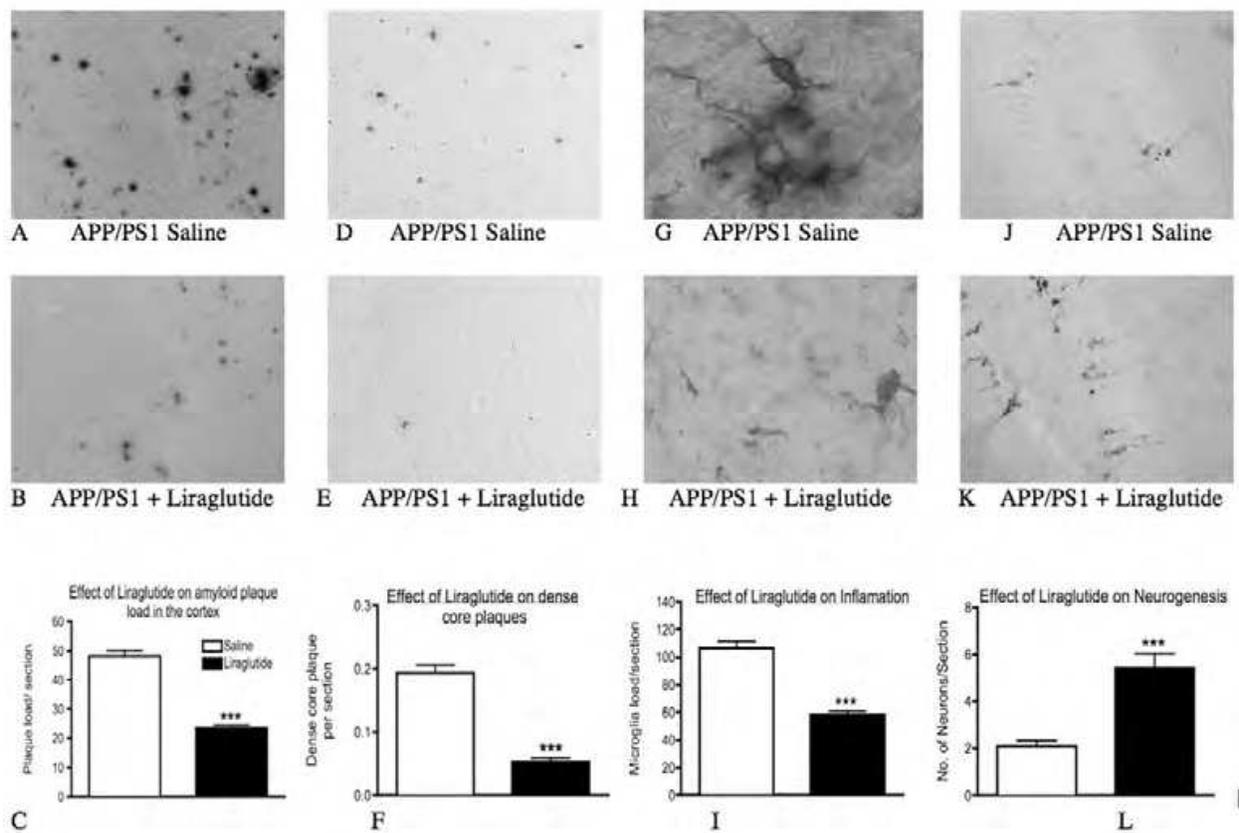

Fig. 4. Histological hallmarks of AD are improved with Liraglutide. Histological analysis of the liraglutide-injected APP/PS1 mice showed a reduction in the number of plaques in the cortex and hippocampus of Liraglutide-treated APP/PS1 mice was halved (A, B, C). The number of Congo-red positive dense core plaques was reduced to 25% (D, E, F). The inflammatory response, as shown by activated glia (IBA-1stain), was also halved (G, H, I). Mice treated with Liraglutide also had a significant increase in neurogenesis (Doublecortin positive cells) 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) (P. McClean et al. 2011).

GIP is expressed in neurons and used as a neurotransmitter, and GIP receptors are also found in the brain (V. A. Gault & C. Holscher 2008, Nyberg et al. 2005, Nyberg et al. 2007). Even less is known about the roles of GIP in the brain than about the roles of GLP-1. GIP enhances neuronal progenitor proliferation in the dentate gyrus and affects learning, as discussed below (E. Faivre, Gault, Thorens, & Holscher 2011, E Faivre & Hölscher 2011).

2.2 Effects of incretins on synaptic transmission

Insulin as well as the incretins not only have growth-factor like properties in the brain, but also modulate synaptic activity. Neurons communicate via synaptic activity, and this activity can be enhanced for longer periods of time (long-term potentiation of synaptic transmission, LTP (C Hölscher 1999). One study showed that the injection of GLP-1 into the basal ganglia increased the synaptic release of the neurotransmitter glutamate (Mora, Exposito, Sanz, & Blazquez 1992). GLP-1 also increased the spontaneous firing rate of pyramidal neurons in the hippocampus (J. I. Oka, Goto, & Kameyama 1999). Interestingly, beta-amyloid fragments can directly affect synaptic transmission and impair the use-dependent upregulation of synaptic transmission (LTP). Since such a mechanism could be a used for storing information in the brain (C. Hölscher 2001), this amyloid-induced block of LTP may be in part responsible for impaired memory formation in patients with AD (Freir, Holscher, & Herron 2001, C Hölscher, Gengler, Gault, Harriott, & Mallot 2007). In addition, a recent study has shown that soluble beta-amyloid fragments directly bind to and decrease insulin receptor densities on neuronal dendrites (Xie et al. 2002, W. Q. Zhao et al. 2008). This may be a mechanism how insulin signalling in the brain becomes impaired in people with AD.

Further studies showed that direct injection of GLP-1 or long-lasting GLP-1 analogues into the brain markedly enhanced LTP in the hippocampus, a brain area that is involved in memory formation. Agonists such as Val^8-GLP-1 showed a clear upregulation of LTP, while the selective GLP-1 antagonist exendin(9-36) blocked LTP (V. Gault & C. Holscher 2008). The novel GLP-1 analogue liraglutide that has been released onto the market as a treatment for T2DM also upregulated LTP (P. L. McClean, Gault, Harriott, & Holscher 2010). Importantly, GLP-1 analogues were able to prevent the impairment of LTP that was induced by beta-amyloid fragments (V. Gault & C. Holscher 2008, Gengler, McClean, McCurtin, Gault, & Holscher 2010, P. McClean et al. 2011). These effects are most impressive and underline the fact that beta-amyloid has numerous independent effects on cell physiology; some of which may occur very early on in AD, long before amyloid aggregates appear and neuronal death is observed (Gong et al. 2003, Townsend, Shankar, Mehta, Walsh, & Selkoe 2006). Moreover, GLP-1, liraglutide and exendin-4 have been shown to reduce endogenous levels of beta-amyloid in a mouse model of AD, and to reduce levels of beta-amyloid precursor protein (APP) in neurons (P. McClean et al. 2011, Perry et al. 2003). In contrast, the elimination of the GLP-1R in a KO mouse model severely impaired learning abilities and also strongly reduced synaptic plasticity (Abbas, Faivre, & Hölscher 2009). Interestingly enough, spatial learning and synaptic plasticity is also impaired in mouse models of diabetes, and exendin-4 is able to reverse these impairments (V. A. Gault et al. 2010). These results suggest that treatment with GLP-1 or long-lasting analogues beneficially affect a number of the therapeutic targets associated with AD, such as impaired memory, impaired neuronal synaptic transmission, increased neurodegenerative processes and reduced neuronal regeneration.

Interestingly, GIP receptors are also expressed in the brain and are found on larger neurons such as the pyramidal cortical neurons (Nyberg et al. 2005), which is similar to the pattern of expression of GLP-1 receptors (A Hamilton & Holscher 2009). The peptide GIP is also expressed in neurons and serves as a neuronal transmitter (Nyberg et al. 2007). Stable analogues such as D-ala^2-GIP or N-glyc-GIP facilitate synaptic plasticity in the hippocampus, while the antagonist Pro^3-GIP impairs LTP (V. A. Gault & C. Holscher 2008). Impressively, GIP analogues can prevent the LTP impairment that beta-amyloid fragments induce on synaptic transmission in the brain (V. A. Gault & C. Holscher 2008). In a GIPR-KO mouse strain, LTP was also much reduced, and paired-pulse facilitation showed an effect on the presynapse, indicating that the release of synaptic vesicles is reduced (E. Faivre et al. 2011). The long-lasting GIP analogue D-Ala^2-GIP also had neuroprotective effects in an APP/PS1 mouse model of AD. In 12 months old mice, synaptic plasticity in area CA1 of the hippocampus and spatial memory formation was impaired in control APP/PS1 mice but was unimpaired in D-Ala^2-GIP treated APP/PS1 mice. In addition, the amyloid plaque load was much reduced, showing impressive effects in reducing the main hallmarks of AD (E Faivre & Hölscher 2011). This suggests that these analogues have neuroprotective properties in AD and protect synapses from the detrimental effects of beta-amyloid. The receptor distribution in the brain and also the effects of analogues on LTP is very similar when comparing GLP-1 analogues with GIP analogues. This would suggest that the physiological roles of these incretins may also be very similar. However, the clear results in impairing LTP (and learning) in the GLP-1R KO or GIPR KO mice show that one incretin cannot compensate the impairment or receptor loss of the another. This suggests that both incretins play distinctive roles that we currently know very little about, but also show very similar growth-factor-like effects.

2.3 Effects of incretins on memory formation

GLP-1 and longer acting analogues that can cross the BBB have beneficial effects on cognition. A behavioural study showed that the GLP-1 analogue exendin-4 can prevent the learning impairments induced by the injection of beta-amyloid fragments (J. Oka, Suzuki, & Kondo 2000). The GLP-1 analogue Val^8-GLP-1 also prevented the detrimental effect of beta-amyloid injected icv. has on learning a water maze task (Wang et al. 2010). Another study showed that GLP-1 when injected *icv.* can enhance memory formation. The study also showed that the GLP-1 analogue Ser(2)exendin(1-9) can enhance learning of a spatial task when injected *ip.*, indicting that this analogue crosses the BBB (During et al. 2003). The overexpression of the GLP-1 receptor also enhanced learning of a spatial task, while the deletion of GLP-1 receptor in KO mice impaired learning (During et al. 2003). In a different study, GLP-1 receptor KO mice were impaired in learning spatial and recognition tasks, while LTP in the hippocampus was severely impaired (Abbas et al. 2009). These results show that GLP-1 receptors do play an important role in cognitive processes in the brain, and that GLP-1 analogues can enhance learning even when injected *ip.*

Recent studies have shown that stable GIP analogues such as D-ala^2-GIP or Pro^3-GIP cross the BBB and also enhance neuronal stem cell proliferation in the brain (E Faivre et al. 2010). Furthermore, GIP analogues have clear effects on memory formation, with the GIP receptor agonist D-Ala^{2}GIP facilitating memory, and the GIP receptor antagonist Pro^3-GIP impairing memory (E Faivre et al. 2010). GIP analogues also have clear effects on synaptic plasticity in the brain. They enhance synaptic plasticity in the hippocampus, a mechanism considered by some to represent the cellular level of memory formation. Importantly, beta-amyloid

impairs synaptic plasticity, and injection of GIP analogues protect synapses from the detrimental effects of beta-amyloid(25-35) (V. A. Gault & C. Holscher 2008). In another study, icv. infusion of Abeta1-40 in mice produced impairments in a water maze test, and the infusion of GIP icv. prevented the amyloid induced impairment in spatial learning (Figueiredo et al. 2010).

These properties make GIP analogues a promising target for the development of novel treatments of AD. As described earlier, spatial and non-spatial learning was greatly impaired in a GIPR- KO mouse strain, showing that the lack of GIP signalling plays an important role in memory formation, and cannot be compensated for by the still functioning insulin and GLP-1 signalling pathways (E. Faivre et al. 2011).

2.4 Novel incretin analogues have neuroprotective effects in mouse models of AD

As an important pre-clinical test, novel analogues of GLP-1 have shown neuroprotective properties in mouse models of AD. In one study, the GLP-1 analogue Val^8-GLP-1 had neuroprotective effects in a mouse model of AD that overexpresses the human Swedish mutated form of APP and a human mutated form of presenelin-1. The mice develop high densities of beta-amyloid plaques in the cortex and hippocampus, starting at 3 months of age (Radde et al. 2006). When injecting Val^8-GLP-1 chronically ip. at a dose of 25nmol/kg *ip.* once-daily for 3 weeks, synaptic plasticity in the hippocampus was protected from the effects of plaque formation and did not differ from littermate wildtype control mice. LTP was completely protected even at 18 months of age. In addition, the number of Congo red positive dense-core amyloid plaques in the brain was reduced. LTP was also improved in 18 month old *wild-type* mice when compared to controls, indicating that GLP-1 analogues also protect the brain to some degree from age-related synaptic degenerative processes (Gengler et al. 2010). Furthermore, the GLP-1 analogue exendin-4 which is currently on the market as a treatment of T2DM (Byetta®) had been tested in a triple transgenic mouse model of AD. This model also expresses the Swedish mutated form of human APP and a PS-1, and in addition expresses a mutated form of tau protein. The mice develop plaques at around 12-14 months. They also show hyperphosphorylated tau, similar to humans with AD. Exendin-4 was applied subcutaneously via osmotic pumps. To test the effects of a combination of diabetes and AD, a group of transgenic mice were made diabetic by injection of streptozotocin. The main findings were that in the diabetic mouse model of AD, beta-amyloid production had increased and plaque formation in the brain was enhanced. The treatment with exendin-4 treated the diabetes, reduced beta-amyloid production and plaque formation (Y. Li et al. 2010).

In another study, the novel GLP-1 analogue liraglutide that is also on the market as a T2DM treatment (Victoza®) enhanced memory formation and synaptic plasticity in the brains of APP/PS1 mice after ip. injection (25nmol/kg bw, once daily) for 8 weeks, at a dose that is comparable to the dose given to T2DM patients (0.9-1.8 mg subcutaneously once-daily). The learning impairments observed in untreated AD mice were reversed by liraglutide (fig. 5), and the impairment of hippocampal synaptic plasticity that develops over time in untreated mice was also prevented. More importantly, amyloid plaque formation was reduced to 50%, and the formation of Congo-red dense core plaques was reduced to 30%. In addition, the inflammation response (activated microglia) was also halved. Furthermore, increased neurogenesis was observed in the dentate gyrus of these mice, normalising the number of young neurons when compared to wild type controls (fig. 4). The level of soluble amyloid-oligomers was also greatly reduced (P. McClean et al. 2011).
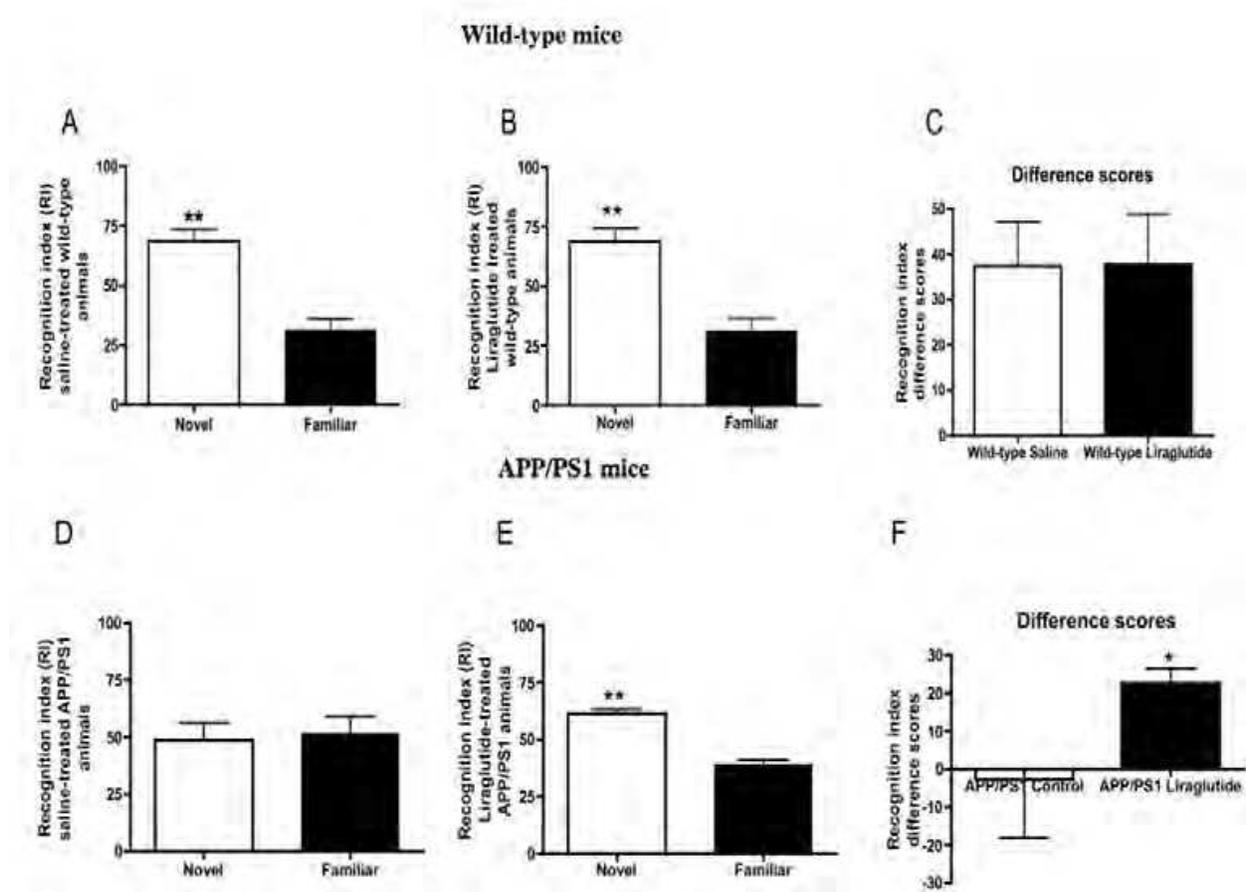
Fig. 5. Effect of the diabetes drug Liraglutide on recognition memory in APP/PS1 mice. In the object recognition task two identical objects were shown to mice for 10min, after 56 days treatment with either 0.9% Saline or Liraglutide (25nm/kg bw). After a 3h interval mice were exposed to one novel and one familiar object. Shown is the recognition index (RI) which is the % time spent exploring the novel object vs. the overall exploration time. Liraglutide treatment made no difference to the learning ability of wild-type mice (A, B), with overall difference scores comparable (C). In contrast Liraglutide rescued the recognition memory of APP/PS1 mice (E), with controls unable to discriminate between novel and familiar objects (D). Overall difference scores were significantly increased in APP/PS1 Liraglutide-treated mice. (F, student's t-test, *p<0.05, **p<0.01; all groups n=12) (P. McClean et al. 2011).

GIP analogues have shown similar effects in a APP/PS1 mouse model of AD. Injection of the GIP peptide ip. had protective effects on spatial learning in memory tasks and also reduced plaque formation and amyloid load (Figueiredo et al. 2010). In 12 months old APP/PS1 mice, spatial memory formation and object recognition memory as well as LTP was impaired in control APP/PS1 mice but was unimpaired in D-Ala^2-GIP treated APP/PS1 mice. In addition, the amyloid plaque load was much reduced, showing clear effects in reducing the main hallmarks of AD. The numer of neuronal progenitor cells in the dentate gyrus was also increased by D-Ala^2-GIP (E Faivre & Hölscher 2011).

These findings confirm that incretin analogues cross the BBB when injected peripherally and have pronounced neuroprotective effects on the main hallmarks and symptoms of AD as observed in these mouse models. This suggest that treating AD patients with novel stable

GLP-1 analogues has the potential to prevent or prolong the early phase of neurodegeneration, and potentially prevent the late phase of degeneration altogether. Since two such GLP-1 analogues are already on the market as T2DM treatment, the use of such drugs to treat neurodegenerative conditions is most promising. Importantly, clinical trials of the effects of exendin-4 in patients with Parkinson's disease (UCL, London, UK) have been started, and clinical trials in patients with MCI or early-phase AD are on their way (NIH/NIA, USA) (see an update on www.clinicaltrials.gov).

3. Acknowledgement

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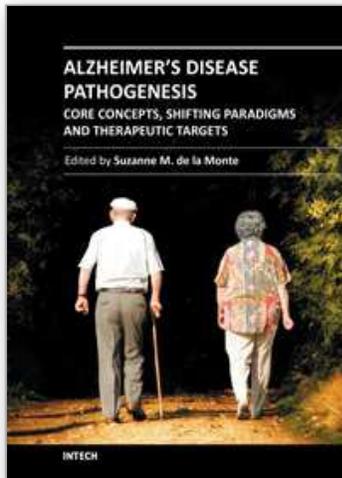
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Edited by Dr. Suzanne De La Monte

Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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