Diabetes as a risk factor for Alzheimer's disease: insulin signalling impairment in the brain as an alternative model of Alzheimer's disease

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Abstract

Surprisingly little is known about the mechanisms that trigger the onset of AD (Alzheimer's disease) in sporadic forms. A number of risk factors have been identified that may shed light on the mechanisms that may trigger or facilitate the development of AD. Recently, T2DM (Type 2 diabetes mellitus) has been identified as a risk factor for AD. A common observation for both conditions is the desensitization of insulin receptors in the brain. Insulin acts as a growth factor in the brain and is neuroprotective, activates dendritic sprouting, regeneration and stem cell proliferation. The impairment of this important growth factor signal may facilitate the development of AD. Insulin as well as other growth factors have shown neuroprotective properties in preclinical and clinical trials. Several drugs have been developed to treat T2DM, which re-sensitize insulin receptors and may be of use to prevent neurodegenerative processes in the brain. In particular, the incretins GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insolinotropic polypeptide) are hormones that re-sensitize insulin signalling. Incretins also have similar growth-factor-like properties as insulin and are neuroprotective. In mouse models of AD, GLP-1 receptor agonists reduce amyloid plaque formation, reduce the inflammation response in the brain, protect neurons from oxidative stress, induce neurite outgrowth, and protect synaptic plasticity and memory formation from the detrimental effects caused by β-amyloid production and inflammation. Other growth factors such as BDNF (brain-derived neurotrophic factor), NGF (nerve growth factor) or IGF-1 (insulin-like growth factor 1) also have shown a range of neuroprotective properties in preclinical studies. These results show that these growth factors activate similar cell signalling mechanisms that are protective and regenerative, and suggest that the initial process that may trigger the cascade of neurodegenerative events in AD could be the impairment of growth factor signalling such as early insulin receptor desensitization.

Introduction

AD (Alzheimer's disease) is a progressive neurodegenerative disease for which there is no treatment at present. Despite enormous efforts, we still know very little about the processes that actually trigger the chain of events that eventually lead to extensive neuronal death. A number of rare inherited forms of AD do shed some light on what the underlying mechanisms may be. Numerous mutations of the APP (amyloid precursor protein) have been described that lead to AD, and also several mutations of the presenilin-1 gene, which codes for a part of the gamma-secretase that is involved in the synthesis of β-amyloid [1,2]. These mutations lead to an increase in production and deposition of amyloid and invariably lead to AD. In sporadic forms of AD, however, which form the vast majority of cases, we do not find such genetic mutations, and despite intense investigations by large international research groups, no clear picture of a genetic link has been found. The risk genes that have been identified up to now only account for a small percentage of the overall increased risk of developing AD in our population. Additional factors must exist that trigger the development of AD or at least push the system towards the development of AD.

Another approach of how to analyse potential links to the development of AD is the investigation into risk factors. A range of risk factors have been identified that increase the likelihood of developing AD. These include such surprising factors such as high cholesterol and T2DM (Type 2 diabetes mellitus) [3–6]. These rather surprising risk factors may shed light on underlying molecular processes that these conditions have in common, and may show us novel research avenues to pursue. In T2DM, insulin is no longer able to reduce the levels of blood glucose after a meal. The reason for this in most cases is that the insulin messenger signal no longer triggers the cellular cascade of events that leads to an increased uptake of glucose by cells [7]. Poor lifestyle choices appear to be the culprit, and a chronic overload with sugars leads to chronic increases of insulin, which eventually triggers the insulin desensitization [7]. How can

Key words: Alzheimer's disease (AD), central nervous system (CNS), glucagon-like peptide-1 (GLP1), insulin receptor substrate (IRS), Type 2 diabetes mellitus (T2DM).

Abbreviations used: AD, Alzheimer's disease; APP, amyloid precursor protein; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insolinotropic polypeptide; IRS, insulin receptor substrate; LTP, long-term potentiation; NGF, nerve growth factor; PS1, presenilin 1; T2DM, Type 2 diabetes mellitus.

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insulin insensitivity increase the risk of developing AD? Insulin is commonly known as a hormone that reduces blood glucose levels. However, insulin has a lot of important cell survival and growth functions, and should be called a growth factor. Insulin activates gene expression in the cells, induces stem cell proliferation, and reduces apoptosis in all cells [8]. Importantly, neurons are vulnerable to excitotoxic stress, and with some notable exceptions, there is very little neurogenesis in the brain. Most neurons will have to do their job for the whole life time of the person, and any increased stress or reduced repair mechanism can add up over the years.

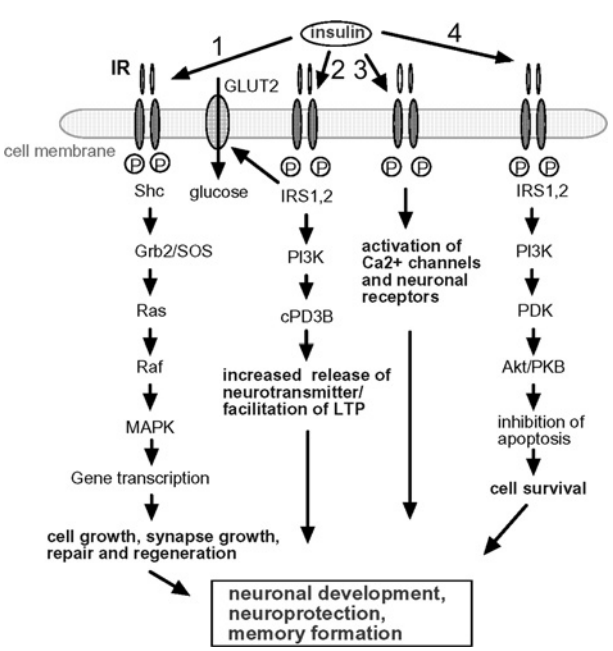
The impairment of insulin signalling in the brain could well play a role in the development of neurodegenerative disorders, as it leaves neurons more exposed to toxic influences.

Interestingly, insulin has direct effects on brain activity and cognitive processes. In animal models, a decrease in the insulin receptor signalling system produces cognitive impairments and a reduction in hippocampal synaptic neurotransmission [9,10]. Conversely, insulin injected into the brain intracerebroventricularly can improve performance in memory tasks in animals and also the performance of attention tasks in humans when applied via the nasal passage where it can enter the brain more directly [11]. This effect might be linked to the fact that LTP (long-term potentiation) of neuronal synaptic transmission is impaired if insulin signalling is affected, as shown in animal models of diabetes. Treatments of the diabetic animals with insulin rescued the impairment in neurotransmission [12–14]. People with T2DM also have cognitive impairments, and treatment with diabetes medication improves these impairments [5,12].

Reduced insulin sensitivity and efficacy are also observed in the majority of elderly people and contributes to the development of AD [5,15]. A recent study reported that insulin receptor levels are down-regulated in the brains of patients with AD. Insulin receptors were found to be internalized in neurons, and IRS (insulin receptor substrate)-1 and IRS-2 were reduced in total levels, but had increased levels of IRS-1 phosphorylation at Ser^{312}, which leads to reduced signalling activity [16]. 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. 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 [2,5,11,17–19] (see Figure 1 for details). Furthermore, insulin has potent neuroprotective factors, and also regulates GSK3β (glycogen synthase kinase 3β), a major tau kinase, which is the major component of neurofibrillary tangles found in the brains of AD patients [20,21]. Insulin also improves brain activity such as attention, memory formation and cognition in humans [22–25]. Nasal application of insulin, an application route where it enters the brain more directly, had clear effects on

Figure 1 | An overview of some of the roles and functions of insulin receptors

Insulin action is associated with its blood glucose lowering activity. This is achieved by activating a glucose uptake transporter, e.g. GLUT4 [68–70]. There are other important roles in neuronal growth, synaptic development and direct control of neurotransmitter release. During neuronal activity, insulin binds to the α-subunit of the receptor. This activates the tyrosine kinase phosphorylation of the β-subunit. Then, several intracellular signalling cascades can be activated. (1) Activation of the insulin receptor-Shc (Src homology collagen peptide)-MAPK (mitogen-activated protein kinase) pathway activates gene expression. These genes code for proteins that are required for cell growth, synapse growth and for cell repair and maintenance [10,71]. (2) Insulin receptor activation has a direct effect on neurotransmission and primes synapses for induction of LTP of neuronal transmission [13]. This pathway probably involves binding of IRS-1 and IRS-2 to PI3K (phosphatidylinositol 3-kinase). Then, the cPD3B is activated [72]. This would prime the synapse for increased neurotransmitter vesicle release [73]. Modulation of neurotransmission will influence memory formation, information processing and cognitive processes [74]. (3) Insulin receptors furthermore modulate neurotransmission directly by altering glutamatergic and GABAergic receptor activity. NMDA (*N*-methyl-D-aspartate) glutamate receptors can be phosphorylated to increase the opening of the associated Ca^{2+} channel [75]. IR activation also affects GABA (γ-aminobutyric acid) transmission by recruiting functional GABA receptors to the postsynaptic site [76]. (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 (phosphoinositide-dependent kinase) and protein kinase B (Akt/PKB), which suppresses the induction of apoptosis and thereby protects neurons [68,77,78]. For further details see [35]. Abbreviations: Akt/PKB, protein kinase B complex; cPD3B, cyclic phosphodiesterase 3β; Grb2/SOS, growth factor receptor-binding protein 2/son of sevenless protein.



attention and memory formation [24,26,27]. 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 (colony-stimulating factor) amyloid 1–40/1–42 ratio, and showed enhancement of cortical activation in PET (positron-emission tomography) scans, and an improvement in cognitive tasks [28].

In conclusion, the impairment of insulin signalling in the brain could well play a role in the development of neurodegenerative disorders, as it leaves neurons more exposed to degenerative influences [5,27–29].

However, treating AD patients with insulin over longer periods of time does not appear sensible, in particular, as this may exacerbate the insulin receptor desensitization.

The incretins: GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insolinotropic polypeptide)

As insulin receptors are desensitized in T2DM and in AD, and injection of insulin itself loses its effectiveness over time, researchers are investigating different strategies concerning how to improve blood glucose level maintenance. In addition, it is not safe to treat AD patients with insulin if they are not diabetic. However, other signalling pathways exist that also modulate blood glucose levels, e.g. the incretin hormone signalling pathways, in particular GLP-1 and GIP [30,31].

GLP-1 receptors are found on neurons in the brains of rodents and humans [32,33]. They are predominately expressed on large-sized neurons, on the cell bodies and also on dendrites, indicating that they are located on the synapse [34]. Similar to insulin, GLP-1 is predominately known for its use in treating T2DM. However, like insulin, GLP-1 is principally a growth factor and has the main properties of all growth factors [35]. GLP-1 increases cell growth, proliferation and repair, and inhibits apoptosis [36] (see Figure 2). In the brain, GLP-1 has been documented to induce neurite outgrowth and to protect against excitotoxic cell death and oxidative injury in cultured neuronal cells [37,38]. Neurons were found to be protected against cell death induced by β-amyloid 1–42, the peptide that aggregates in the brains of Alzheimer patients, and against oxidative stress and membrane lipid peroxidation caused by iron [32]. In addition, GLP-1 showed neuroprotective properties in pyridoxine-induced peripheral neuropathy [39]. Furthermore, mice that overexpress GLP-1 receptors in the hippocampus showed increased neurite outgrowth and improved spatial learning [40]. Enhanced progenitor cell proliferation in the brain was also found in this study. 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 [41]. Theoretically, it may be possible to regenerate neuronal tissue and to regain some of the lost cognitive functions in patients with AD similar to the regeneration of β-cells in the pancreas [42].

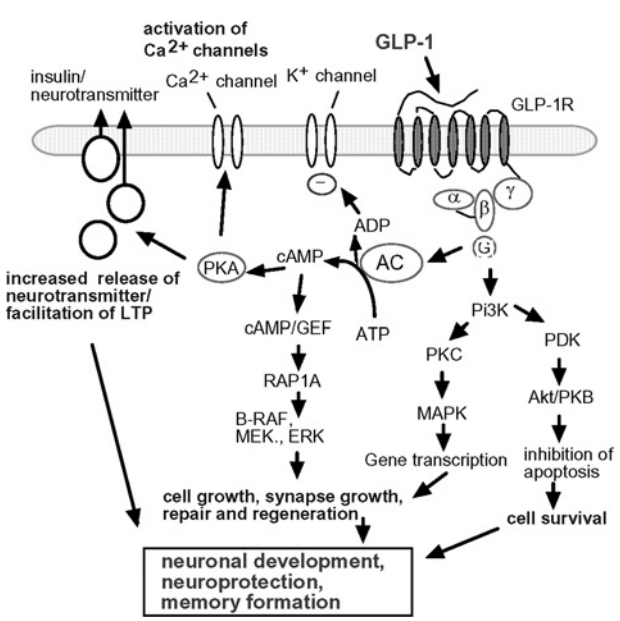
Incretin receptor agonists have neuroprotective effects in mouse models of AD

Importantly, agonists of GLP-1 receptors have shown neuroprotective properties in mouse models of AD. In one study, the GLP-1 receptor agonist 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 PS1 (presenilin 1). When injecting Val^8-GLP-1 chronically intraperitoneally, synaptic plasticity in the hippocampus was protected from the effects of plaque formation and those treated did not differ from littermate wild-type control mice. LTP was completely protected even at 18 months of age compared with wild-type controls. 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 with controls, indicating that GLP-1 analogues also protect the brain to some degree from age-related synaptic degenerative processes [43].

Recently, the GLP-1 analogue exendin-4, which is currently on the market as a treatment for T2DM, was tested in a triple transgenic mouse model of AD [44]. This model also expresses the Swedish mutated form of human APP and PS1, 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, β-amyloid production had increased and plaque formation in the brain was enhanced. The treatment with exendin-4 treated the diabetes, and reduced β-amyloid production and plaque formation [44]. In another study, the novel GLP-1 analogue liraglutide, which is also on the market as a T2DM treatment, enhanced memory formation and synaptic plasticity in the brain of a APP/PS1 AD model after intraperitoneal injection (25 nmol/kg of body weight, 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, 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, normalizing the number of young neurons when compared with wild-type controls [41]. GIP analogues have shown similar effects in an APP/PS1 mouse model of AD. Injection of the GIP peptide intraperitoneal had protective effects on spatial learning in memory tasks and also reduced plaque formation and amyloid load [45].

Figure 2 | An overview of the roles and functions of the GLP-1 receptor

Activation of the GLP-1 receptor (GLP-1R) activates a G-protein, which in turn activates the adenylate cyclase (AC) system [79]. The Gα subunit of the GLP-1 receptor stimulates AC, which leads to an increase in intracellular cAMP and activation of PKA (protein kinase A). PKA activity can increase vesicle release in β-cells to enhance glucose-stimulated insulin secretion, or, as postulated in this review, can increase the release of synaptic neurotransmitter and enhance LTP in neurons. ADP that is also produced by AC during cAMP production acts on ATP-sensitive K^+ channels. This leads to a slow depolarization of the cell membranes following closure of K^+ channels and reduced re-polarization of neuronal membranes [80]. This can increase the opening of voltage-dependent L-type Ca^{2+} channels and increases cytosolic Ca^{2+}, which in turn acts as a second messenger. One of the many effects that increased cytosolic Ca^{2+} can have is the increase of transmitter release [81]. Activation of GLP-1 receptors also leads to an increase in cytosolic Ca^{2+} levels as a result of activation of voltage-dependent L-channels following phosphorylation of PKA and/or mobilization of intracellular Ca^{2+} stores. An increase in phosphatidylinositol 3-kinase (PI3K) levels via G-protein activation also can activate intracellular Ca^{2+} stores [82]. It has been proposed that the fast action of GLP-1 (and furthermore of GIP or insulin) on synaptic transmission is mediated by these fast, ion channel and vesicle release-dependent processes. The G-protein-dependent increase in PI3K levels also activates MAPK (mitogen-activated protein kinase). This pathway activates gene expression, which controls the expression of peptides that are required for cell growth, repair and differentiation of β-cells and also in neuronal cells. Inhibition of PI3K (with LY294002) or MAPK (with PD98059) reduced GLP-1-stimulated neurite outgrowth (for a review, see [39]. GLP-1-mediated activation of PI3K and downstream transcription factors regulate expression of the genes that encode insulin, β-cell growth and differentiation phenotype [83–85]. cAMP activates multiple intracellular messenger systems via PKA or independently of PKA activation (shown here). A PKA-independent pathway had been found in β-cells, which involves cAMP-GEFs. GEFs are activated by binding to cAMP and activation of Rap1A [86]. Rap1A activates PKC (protein kinase C) and B-Raf, leading to activation of MAPK [87]. Abbreviations: AC, adenylate cyclase; cAMP-GEF, cAMP-guanine-nucleotide-exchange factor; ERK, extracellular signal-regulated kinase; MEK, MAPK/ERK kinase; PDK, phosphoinositide-dependent kinase; PKB, protein kinase B.



These findings confirm that incretin analogues have effects in the CNS (central nervous system) when injected peripherally and have pronounced neuroprotective effects in these mouse models.

Other growth factors show neuroprotective effects

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 β-amyloid are very similar to the neuroprotective effects of other growth factors. For example, BDNF (brain-derived neurotrophic factor) has been shown to protect synapses in mouse models of AD. Injecting BDNF intracerebroventricularly improved cognition, prevented impairments of LTP and led to an enhancement of hippocampal synaptic density [46]. 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 [47,48]. It is of interest to note that the effects of BDNF are therefore very similar to those of Val(8)GLP-1 and liraglutide. This suggests that growth factors have common modes of action. There is, however, one vital difference: BDNF does not cross the BBB (blood–brain barrier), and therefore a gene delivery system to the brain has to be developed, or it has to be injected directly into the brain [49,50]. This clearly limits the application of BDNF as a treatment for AD.

A different growth factor that has shown promise as a treatment for neurodegenerative disorders is NGF (nerve growth factor). Again, NGF was found to protect synapses, LTP, and learning abilities in AD mouse models or in non-primate monkeys without affecting amyloid plaque load [51–53]. However, NGF does not cross the BBB either, and therefore gene delivery systems have been developed to be able to use NGF as a treatment for CNS disorders. Such attempts to increase the amount of NGF production in the CNS have not been successful so far [50,52,54,55]. Still, clinical trials are ongoing to test the effects of gene delivery via a viral vector when injected in the brains of patients [56]. A different clinical trial tests the effects of the implantation of cells that express NGF into the basal brain (mucleus basalis) of patients with AD, in the hope that the observed degeneration of cholinergic neurons in AD will be prevented [57].

Other growth factors have similar protective effects on neurons in AD models, e.g. IGF-1 (insulin-like growth factor 1) [58,59], VEGF (vascular endothelial growth factor)

[60–62], and glial cell line-derived growth factor [GDNF (glial-derived neurotrophic factor)] [63]. These growth factors have shown promising results in protecting neurons from the effects of β-amyloid, promoting cell repair and protecting synaptic functions and cognitive performance. Again, the main stumbling block for these growth factors is the fact that they do not readily cross the BBB. As a consequence, special delivery systems are under development to deliver them, which opens up a whole range of problems [60,61,63–66].

The similarity of the activity profile of these different growth factors is surprising. It is possible that they activate similar or identical signalling mechanisms in neurons and synapses. It suggests that the lack or loss of one growth factor signalling pathway (e.g. insulin) can be compensated for using a range of alternative growth factors. Importantly, two GLP-1 analogues are already on the market as a T2DM treatment and show few side effects in chronic use [67]. Currently, clinical trials testing the effects of exendin-4 are ongoing in Parkinson's patients and also in AD patients (see http://www.clinicaltrials.gov for details).

The fact that insulin desensitization can increase the risk of developing AD, and the observation that insulin, incretins and other growth factors actually show clear protective effects in models of AD suggests that the initial mechanism that impairs the ability of neurons to repair and regrow and perhaps starts the cascade of events that ends in neuronal death is an impairment of growth hormone signalling. Insulin has been strongly implicated in this, as insulin receptors in the brain are desensitized early on in the development of AD, but other growth factors may contribute to the slow development of neurodegenerative processes.

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