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Review

New roles for insulin-like hormones in neuronal signalling and protection: New hopes for novel treatments of Alzheimer's disease?

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Abstract

Type 2 diabetes has been identified as a risk factor for Alzheimer's disease (AD). This is most likely due to the desensitisation of insulin receptors in the brain. Insulin acts as a growth factor and supports neuronal repair, dendritic sprouting, and differentiation. This review discusses the potential role that insulin-like hormones could play in ameliorating the reduced growth factor signalling in the brains of people with AD. The incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) have very similar properties in protecting neurons from toxic effects, and are capable of reversing the detrimental effects that beta-amyloid fragments have on synaptic plasticity. Therefore, incretins show great promise as a novel treatment for reducing degenerative processes in AD.

Keywords: Alzheimer; LTP; Transgenic mouse model; Insulin; Synaptic plasticity; Synaptic transmission; Hippocampus; Growth factor

1. A surprising connection between diabetes and Alzheimer's disease

Recently, type 2 diabetes has been identified as a risk factor for Alzheimer's disease (AD). Epidemiological studies of patient cohort data sets have found correlations between type II diabetes and the likelihood of developing AD or other neurodegenerative disorders (Luchsinger et al., 2004; Ristow, 2004; Haan, 2006). An analysis of the Mayo clinic patient database showed a clear correlation between AD and type II diabetes. 85% of AD patients also had diabetes or at least increased fasting glucose levels, compared to 42% in age matched controls (Janson et al., 2004). Reduced insulin sensitivity, the borderline situation before developing T2DM, is also observed in the majority of elderly people and appears to directly contribute to the development of AD (Carro and Torres-Aleman, 2004; Hoyer, 2004). This connection between T2DM and AD set off research initiatives to identify what the basis is for this. Insulin is well known for its role in reducing blood sugar levels. However, current research demonstrates that insulin has many more functions in the body. Its role is that of a growth factor, and neuronal insulin receptors have been found to induce dendritic sprouting, neuronal stem cell activation, of exert neuroprotective effects (Hoyer, 2004; Li and Hölscher, 2007). Insulin also exerts important actions within the brain, and functions as a messenger with growth factor like properties (van Dam and Aleman, 2004; Cohen et al., 2007). Furthermore, insulin and the related insulin-growth factor (IGF-I) are potent neuroprotective factors, and also regulate levels of phosphorylated tau, the major component of neurofibrillary tangles found in AD (Carro and Torres, 2004; Li et al., 2007).

In type II diabetes (T2DM), the insulin receptors have become desensitised, and the insulin signal to increase cell metabolism and cell growth and repair appears to be functionally impaired. Recently, it was shown that insulin receptors in the brain are desensitised in AD patients, and this condition even has been named 'type 3 diabetes' by some authors

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(Steen et al., 2005; Lester-Coll et al., 2006). 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 affects on brain activity and cognitive processes as well. In animal models, a decrease in insulin receptor signalling system produces cognitive impairment and a reduction in hippocampal synaptic neurotransmission (Trudeau et al., 2004; Biessels et al., 2006). Conversely, insulin injected into the brain can improve performance in memory tasks in animals and also performance of attention tasks in humans when applied via the nasal passage where it can enter the brain more directly (Stockhorst et al., 2004). This effect might be linked to the fact that long-term potentiation (LTP) 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 (Gispen and Biessels, 2000; Biessels et al., 2004), for a review on the connection between diabetes and AD see (Li and Hölscher, 2007).

2. Insulin-like messengers: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)

Since insulin receptors are often desensitised in T2DM, and injection of insulin itself loses its effectiveness in a lot of cases, researchers are investigating different strategies how to improve blood glucose level maintenance. Fortunately, several parallel signalling systems exist, e.g. the incretin hormone signalling pathways: GLP-1 and GIP.

GLP-1 is an endogenous 30-amino acid peptide hormone, which is released by intestinal L-cells and binds to the GLP-1 receptor coupled to the cAMP second messenger pathway (Green et al., 2004). GLP-1 receptor stimulation enhances beta-cell proliferation, glucose-dependent insulin secretion and lowers blood glucose in patients with type II diabetes mellitus (Green et al., 2006). GLP-1 receptors are found on neurons in the brains of rodents and humans (Goke et al., 1995; Perry and Greig, 2005). 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, 2003). Also, neurons were 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 and Greig, 2005). In addition, GLP-1 showed protective properties in an induced form of peripheral neuropathy (Perry et al., 2007). Furthermore, mice that overexpress GLP-1 receptors in the hippocampus (a brain area that is involved in memory formation) showed increased neurite growth and improved learning (During et al., 2003). Moreover, GLP-1 and exendin-4, a more stable analogue of GLP-1, have been shown to reduce endogenous levels of beta-amyloid in the mouse brain, and to reduce levels of beta-amyloid precursor protein (APP) in neurons (Perry et al., 2003). This neuroprotective effect is most likely due to the modulation and control of calcium influx into neurons, which limits the neurotoxic effects of kainate exposure (Gilman et al., 2003). These results suggest that treatment with GLP-1 or a related peptide beneficially affects a number of the therapeutic targets associated with AD, such as impaired neuronal communication, neurodegenerative processes and reduced neuronal regeneration.

GIP also is a gastrointestinal hormone that is secreted in response to food intake. It has modulating effects on blood sugar levels similar to GLP-1 or insulin (Gault et al., 2003, 2007). Recently, it has been found that GIP receptors are also expressed in neurons in the CNS (Nyberg et al., 2005). In addition, GIP receptors are found on neuronal progenitor cells (Nyberg et al., 2007). In the pancreas, GIP increases cell count of β-cells, most likely by the activation of stem cell proliferation and differentiation (Irwin et al., 2004). Insulin receptors (and most likely GLP-1 receptors) are also located on stem cells (Ye and D'Ercole, 2006), underlining the importance of these signalling pathways in development and repair. The effect of insulin analogues on stem cell proliferation and their differentiation to neurons offer a new opportunity of treating AD patients by replacing lost neurons. Theoretically, it might be possible to regenerate neuronal tissue and to regain lost cognitive functions (Sugaya et al., 2007).

GLP-1 and GIP only have a half-life of minutes in the blood stream. In order to treat T2DM in a more effective way, long-lasting analogues have been developed that are not broken down by the endogenous protease DPP-IV(Green et al., 2003b; Irwin et al., 2005b; Gallwitz, 2006). A GLP-1 analogue that has been extracted from the saliva of the Gila monster lizard has entered the market as a treatment for T2DM (exendin-4, *Exenatide*) (Murphy and Bloom, 2007). Since GLP-1 analogues readily cross the blood brain barrier (Kastin et al., 2002; Kastin and Akerstrom, 2003), such compounds could affect neuronal activity and survival, and even cognitive function. However, no data are available to date on these effects.

2.1. Synaptic transmission is directly modulated by beta-amyloid, GLP-1 and GIP

Another surprising observation is that insulin, GLP-1 and GIP not only have growth-factor properties in the brain, but also modulate synaptic activity. The injection of GLP-1 into the basal ganglia increase the release of glutamate transmitter (Mora et al., 1992). GLP-1 also increased the spontaneous firing rate in the hippocampus (Oka et al., 1999). As shown previously, beta-amyloid fragments can directly affect synaptic transmission and LTP (Freir et al., 2001; Hölscher et al., 2007) (Fig. 1), most likely by affecting voltage-dependent calcium channels (VDCC) (Mattson et al., 1992; Freir and Herron, 2003), NMDA glutamate receptors (Cullen et al., 1996), nicotinergic receptors, and others. In addition, a recent