● **INVITED REVIEW**

New drug treatments show neuroprotective effects in Alzheimer's and Parkinson's diseases

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Abstract

Type 2 diabetes is a risk factor for Alzheimer's disease and Parkinson's disease. Insulin signaling in the brains of people with Alzheimer's disease or Parkinson's disease is impaired. Preclinical studies of growth factors showed impressive neuroprotective effects. In animal models of Alzheimer's disease and Parkinson's disease, insulin, glia-derived neurotrophic factor, or analogues of the incretin glucagon-like peptide-1 prevented neurodegenerative processes and improved neuronal and synaptic functionality in Alzheimer's disease and Parkinson's disease. On the basis of these promising findings, several clinical trials are ongoing with the first encouraging clinical results published. This gives hope for developing effective treatments for Alzheimer's disease and Parkinson's disease that are currently unavailable.

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Current drug development strategies are ineffective

Alzheimer's disease (AD) and Parkinson's disease (PD) are progressive neurodegenerative disorders for which we do not have a cure. The current drug treatments are more designed to keep the symptoms at bay, but do not repair or prevent further degeneration.

There is a clear need for novel treatments, and the industry has invested billions of dollars in finding new drug treatments. However, in particular in AD, the efforts have been in vain, and a string of clinical trials that did not find any improvements have discouraged some drug companies from investing into further research. The immune response strategy to remove beta-amyloid by activating the patient's immune system or with the help of specific antibodies directed against amyloid had a string of failures, with the most recent one the antibody crenezumab developed by Eli Lilly (Cummings et al., 2014). The failure to ameliorate memory impairment with this strategy has led to discussion about the sensibility of this approach (Fuller et al., 2014). The second strategy to reduce the activity of the beta- and gamma-secretases that produce amyloid also has suffered a series of setbacks: avagacestat, (by Bristol-Myers Squibb), tarenflurbil (Flurizan, Myriad Genetics), LY2886721 and semagacestat (Eli Lilly and Company) (Extance, 2010; Brooks, 2013; Groves, 2013). This led to a discussion about the validity of the AD biomarker beta-amyloid (Armstrong, 2014).

Growth factors are neuroprotective in disease models

While these two main strategies have not been successful, another strategy has shown promising results for a fairly long time now. Instead of focusing solely on amyloid levels as a biomarker, the idea of supporting cellular repair by the use of growth factors has shown promising results.

Growth factors are required for the health and development of every cell. Growth factor signaling de-sensitization has been shown in the brains of people with Alzheimer's or Parkinson's disease (Holscher, 2014b). The reason for this is not entirely understood, but it may well be caused by the chronic inflammation that develops in these neurodegenerative disorders. Cytokines such as tumor necrosis factor-α (TNF-α) released in the inflammation response down-regulate growth factor signaling (Chertoff et al., 2011; Clark et al., 2012; Najem et al., 2014).

A wide range of growth factors have been tested in preclinical studies and have shown a range of protective effects. One of the first growth factors that show extensive neuroprotective properties in a mouse model of AD is nerve growth factor (NGF). NGF was found to protect synapses, synaptic plasticity, and learning abilities in AD mouse models or in nonprimate monkeys (Clarris et al., 1994; Kordower et al., 1997; Covaceuszach et al., 2009). However, NGF does not cross the blood-brain barrier (BBB), which severely limits the potential use of this growth factor to protect the brain (Bradbury, 2005; Heese et al., 2006; Schulte-Herbruggen et al., 2007; Covaceuszach et al., 2009). Brain derived neurotrophic factor (BDNF) also has been shown good effects in mouse models of AD. Injecting BDNF intracerebroventricular improved memory formation, reduced the impairments of synaptic plasticity in the hippocampus, and increased synaptic numbers (Blurton-Jones et al., 2009). Enhancing the BDNF levels in the brain by gene delivery vectors also has demonstrated neuroprotective property. The elevation

of BDNF levels reverses synapse loss, improves synaptic plasticity and restores learning abilities of a mouse model of AD (Nagahara et al., 2009; Poon et al., 2009). However, BDNF does not cross the BBB and therefore it would need to be injected into the brain in order to be effective (Schulte-Herbruggen et al., 2007; Zuccato and Cattaneo, 2009). Other growth factors that do cross the BBB are leptin and ghrelin, which also have shown protective effects on synapses and memory formation and protect against oxidative stress (Perez-Gonzalez et al., 2011; Tan and Bloom, 2013; Gomes et al., 2014; Sharma and Hölscher, 2014). In PD, glia-derived neurotrophic factor (GDNF) has shown good effects and is under intense research to develop a new treatment (Broome et al., 1999; Drinkut et al., 2012; Kordower and Bjorklund, 2013). As GDNF does not cross the BBB either, new strategies such as nasal application are being tested (Migliore et al., 2014).

The growth factors insulin and insulin-like growth factor 1 (IGF-1) also have shown good effects in protecting synapses and synaptic function and memory formation. In a mouse model of AD, a systemic slow-release formulation of IGF-1 enhanced cognitive performance, decreased amyloid levels, protected synapses and reduced inflammation (Carro et al., 2006). In mouse models of AD, insulin and IGF signaling was found to be impaired, and a reversal of this is neuroprotective (Bomfim et al., 2012; Long-Smith et al., 2013).

Based on this observation, drugs initially developed to treat diabetes have been tested in animal models of AD and PD. The growth factors glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) show good effects in animal models of diabetes and have shown good effects in several mouse models of AD (Holscher, 2014a). Three GLP-1 mimetics have been licenced and are very effective in treating type 2 diabetes (Campbell and Drucker, 2013). They cross the BBB (Hunter and Holscher, 2012) and have shown good effects in animal models of AD and PD (Holscher, 2013, 2014b).

First clinical data demonstrating protective effects in patients with AD or PD

Insulin treatment shows effects

Based on the encouraging preclinical results, several clinical trials are ongoing to test insulin of GLP-1 mimetics in AD and PD patients. Considering that a long list of drugs that initially showed effects in preclinical tests had shown disappointing results in subsequent clinical trials, it is noteworthy that initial data has been published that demonstrate positive clinical effects of growth factor analogues in AD and PD.

Biochemical tests of brain tissue demonstrate that insulin signaling in the brain is de-sensitized in AD patients, and the brain tissue shows key biochemical markers of insulin signaling failure (Moloney et al., 2010; Talbot et al., 2012). A study showed that in brain tissue of AD patients, IGF-1 and insulin signaling was strongly de-sensitized. Phosphorylation of the insulin receptor β chain was reduced at positions IRβ pY1150/1151 and IRβ pY960, while the insulin receptor substrate 1 (IRS-1) was hyperphosphorylated at positions IRS-1

pS616 and IRS-1 pS636. Furthermore, when incubating AD brain tissue with insulin, it revealed a reduced downstream second messenger cascade (Talbot et al., 2012). Incubating the brain tissue with the GLP-1 mimetic liraglutide also reversed some of the insulin signaling impairments (Talbot et al., 2011). Currently, it is believed that the insulin receptor desensitization is triggered by amyloid-oligomers. *In vitro* cell culture experiments showed that oligomers bind to and activate receptors which are then taken up into the cell (Zhao et al., 2008; De Felice et al., 2009). Infusion of oligomers into the brains of monkeys also show these effects and trigger α local inflammatory response (Lourenco et al., 2013). Interestingly, GLP-1 analogues that prevent the insulin desensitization can prevent this oligomer-induced effect (Bomfim et al., 2012; Lourenco et al., 2013).

Building on the observation that insulin signaling is impaired, nasal application of insulin has been tested in patients with mild cognitive impairment (MCI), which develops further to AD in the majority of cases.

A pilot study testing nasal application of insulin in MCI/AD patients included 26 memory-impaired subjects (13 diagnosed with early AD and 13 with MCI) and 35 controls randomly allocated to groups with a double-blind design. They received three intranasal treatments consisting of placebo or insulin (20 or 40 IU). The insulin treatment had no effect on plasma insulin or glucose levels. Insulin facilitated recall on two measures of verbal memory in memory-impaired apolipoprotein E epsilon4 (APOEe4) carriers. These effects were stronger for memory-impaired non-APOEe4 carriers than for memory-impaired APOEe4 carriers and control subjects. These findings are a proof of concept and demonstrate that insulin can indeed improve memory impairments in AD/MCI patients (Reger et al., 2006). A follow-up pilot study with 24 AD/MCI patients confirmed these effects of insulin (Reger et al., 2008b). In a follow up study, 33 AD/MCI patients and 59 control subjects received intranasal treatments of insulin or placebo. Insulin improved verbal memory in memory-impaired non-APOEe4 carriers. In contrast, memory-impaired APOEe4 carriers displayed a decline in verbal memory. Interestingly, insulin also affected plasma amyloid-beta levels in memory-impaired subjects and controls (Reger et al., 2008a).

Following this, a randomized, double-blind, placebo-controlled clinical pilot trial was conducted. 104 patients with either MCI ($n = 64$) or mild to moderate AD ($n = 40$) were tested. Treatment with 20 IU of insulin improved memory, and both doses of insulin (20 and 40 IU) preserved caregiver-rated functional ability. Both insulin doses also preserved general cognition as assessed by the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) score for younger participants, and functional abilities as assessed by the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) scale for adults with AD. Placebo-assigned participants showed decreased 18-fluoro-2-deoxyglucose with positron emission tomography ([18]FDG-PET) uptake in the brain, demonstrating that neuronal metabolism was deteriorating. Importantly, the improvements in episodic

memory were still present two months after cessation of treatment (Craft et al., 2012).

In a recent clinical trial, AD/MCI patients received insulin analogue detemir (40 IU/d Levemir) and showed improvements in memory if they had high levels of insulin resistance at baseline (Craft, 2013). Larger clinical trials are in preparation.

This series of studies demonstrate that improving insulin signaling in the brains of AD patients has indeed positive effects on key disease parameters and biomarkers. This is a welcome change from previous experience, where encouraging effects with novel drugs in preclinical studies could not be repeated in clinical studies.

GLP-1 mimetics show effects

The treatment of patients with insulin is unlikely to be the best strategy, as it may well enhance insulin de-sensitization if taken over longer time periods. In diabetes, the problem of progressing insulin de-sensitization by treatment with insulin is well described (Inoue et al., 1996). In order to prevent this in diabetic patients, the GLP-1 treatment had been developed which uses a different receptor pathway (Lovshin and Drucker, 2009). The positive preclinical results of GLP-1 in animal models of AD and PD motivated several clinical trials.

A clinical trial of the GLP-1 mimetic exendin-4 in PD patients had been conducted. This proof of concept study tested the effects of exendin-4 in a randomized open label trial. Drug treated patients showed improvement at 12 months in motor tasks, compared with control patients. Most interestingly, exendin-4 showed a clear improvement in the Mattis DRS-2 cognitive score, suggesting that exendin-4 has beneficial effects on cognition (Aviles-Olmos et al., 2013). Impressively, this effect was still visible 12 months after the clinical trial (Aviles-Olmos et al., 2014). This result demonstrates the potential of these drugs, and confirms that the results from animal studies can be found in humans as well. The long lasting drug effect suggests that the effect is due to the normalization of growth factor signaling and the growth of new synapses and increased dopamine synthesis and release, rather than based on a short-term drug effect on synaptic release (Bertilsson et al., 2008). A larger study has started which has a larger number of patients and a double-blind placebo controlled study design (Clinical trial identifier NCT01971242).

To test the effects of these drugs in AD, a randomized, double-blind clinical trial of Exendin-4 treatment in MCI patients/early phase AD by the NIH/NIA is on the way (clinical trial identifier NCT01255163).

Furthermore, a phase II clinical trial of the effects of the GLP-1 analogue liraglutide in MCI/AD patients has started (clinical trial identifier NCT01843075).

Conclusion

In contrast to current drug treatment strategies supported by the drug industry which have not produced any protective effects in clinical trials in twenty years, the strategy of using growth factor analogues that can cross the BBB has shown first effects in humans and appears to be superior and

worth investing into. Currently, the drug trials of insulin and GLP-1 analogues are funded by non-profit and government agencies only. The lack of funding has hampered the tests of new treatments, and there is a clear need to rethink current research strategies and a shift of research targets. The development of new growth factor analogues is currently the strategy with the greatest promise of success.

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