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Invited review

Novel dual GLP-1/GIP receptor agonists show neuroprotective effects in Alzheimer's and Parkinson's disease models

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ABSTRACT

Type 2 diabetes is a risk factor for several chronic neurodegenerative disorders such as Alzheimer's or Parkinson's disease. The link appears to be insulin de-sensitisation in the brain. Insulin is an important neuroprotective growth factor. GLP-1 and GIP are growth factors that re-sensitise insulin and GLP-1 mimetics are used in the clinic to treat diabetes. GLP-1 and GIP mimetics initially designed to treat diabetes show good protective effects in animal models of Alzheimer's and Parkinson's disease. Based on these results, several clinical trials have shown first encouraging effects in patients with Alzheimer's or Parkinson' disease. Novel dual GLP-1/GIP receptor agonists have been developed to treat diabetes, and they also show good neuroprotective effects that are superior to single GLP-1 analogues. Several newer dual analogues have been tested that have been engineered to cross the blood –brain barrier. They show clear neuroprotective effects by reducing inflammation and oxidative stress and apoptotic signalling and protecting memory formation, synaptic numbers and synaptic activity, motor activity, dopaminergic neurons, cortical activity and energy utilisation in the brain. These results demonstrate the potential of developing disease-modifying treatments for Alzheimer's and Parkinson's disease that are superior to current single GLP-1 mimetics.

Contents

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1. A new dawn – novel drug targets for treating Alzheimer's disease

Our understanding what causes progressive neurodegenerative disorders such as Alzheimer's or Parkinson's disease (PD) is still sketchy. The findings of Alois Alzheimer when staining the brain of a patient showed distinct protein aggregates which appeared to define the disease (Alzheimer, 1907; Alzheimer et al., 1995). However, as a good scientist, Dr. Alzheimer cautioned to jump to conclusions and reminded readers that this does not prove that these aggregates actually cause the disease. Further research appeared to support the concept that amyloid is causal to the disease. Mutations in the APP gene and in presenilin genes were found in familial forms of AD, which demonstrated that these mutations accelerate disease progression (Hardy, 1997). However, since then, a number of clinical trials that tested antibodies directed against various sections and states of aggregation of amyloid or that inhibited secretases which produce the amyloid failed. In an active immunization trial, it was found that the vaccination was successful and cleared the brain of plaques. However, the disease progressed continued unhindered in these patients (Holmes et al., 2008). In the time period of 2002–2012, 413 clinical trials in AD were performed with a failure rate of 96% and only symptom modifying drugs reaching the market (Cummings et al., 2014). Sind then, numerous large scale phase III clinical trials that targeted amyloid in the brain failed to show clear improvements (De Strooper and Karran, 2016; Morris et al., 2014), see also Alzforum comment (Alzforum, 2016). Additionally, brain scans assessing the amyloid plaque load in AD patients did not show a clear correlation with disease progression as one would expect (Edison et al., 2008). These unexpected results led to a change in the concepts and hypotheses of what actually causes AD. New suggestions are bring proposed, eg. the important role that chronic inflammation in the brain plays in disease progression, and how to potentially halt this process (Butchart et al., 2015; Clark and Vissel, 2016; Morris et al., 2014). This review will focus on a different approach, using growth factor analogues as treatments.

2. The protective roles of growth factors

Another key area of research that has shown promise in the past is the research are of growth factors and their roles in cell repair, synaptic protection and maintenance of their functionality, enhanced gene expression of key proteins that normalise energy utilisation, deal with oxidative stress, normalise autophagy, re-sensitise growth factor signalling, block apoptotic signalling, enhance DNA repair, and inhibit chronic inflammation in the brain, see also Figs. 2 and 3 (Allen et al., 2013; Blurton-Jones et al., 2009; Bradbury, 2005; He et al., 2013; Holscher, 2014b; Mickiewicz and Kordower, 2011; Olson, 1993; Yang et al., 2017). Growth factors have shown a range of neuroprotective properties in a large number of studies and in different disease models. However, the main stumbling block for the implementation of the findings into the clinic is that they do not cross the blood-brain barrier (BBB). The highly protective growth factor Brain Derived Neurotrophic Factor (gene delivery systems are under development to circumvent this barrier. The injection of BDNF directly into the brain is not a suitable treatment for the clinic. No such clinical trial has been successful so far (Beck et al., 2005; Gao et al., 2016; Lopes et al., 2017; Schulte-Herbruggen et al., 2007; Zuccato and Cattaneo, 2009) NGF was found to protect memory formation, synapse numbers and LTP in AD mouse models or in nonprimate monkeys (Clarris et al., 1994; Covaceuszach et al., 2009; Kordower et al., 1997). Gene delivery systems have been developed to be able to use NGF as a drug to treat AD. Clinical trials testing this technique have not been successful so far (Bradbury, 2005; Covaceuszach et al., 2009; Heese et al., 2006; Mandel, 2010; Rafii et al., 2014; Schulte-Herbruggen et al., 2007). In PD, glial-cell line derived neurotrophic factor (GDNF) has attracted considerable interest, as it protects dopaminergic neurons from stress and degeneration, and has shown considerable neuroprotective effects in preclinical tests. However, as it does not cross the BBB either, and the same obstacles of enhancing GDNF levels in the brain exist (Blits and Petry, 2016; Tenenbaum and Humbert-Claude, 2017). Ideally, a growth factor that can cross the BBB and has similar neuroprotective effects should be used.

2.1. New opportunities: growth factors that can cross the BBB

Fortunately, there are growth factors that can cross the BBB. Insulin is an important growth factor that is essential for the control of energy metabolism, cell growth and cell repair in neurons (Freiherr et al., 2013; Holscher, 2014b) (see also the reviews on this topic in this special issue). Insulin can cross the BBB (Banks, 2004; Banks et al., 1997). Type 2 diabetes is a risk factor for developing AD, and a potential driver for the progressive neurodegeneration in AD and PD is the loss of insulin signalling in the brain (Arvanitakis et al., 2004; Baker et al., 2011; Biessels et al., 2006; Schrijvers et al., 2010; Talbot et al., 2012). Cell growth, repair and energy utilisation gradually decays and may be a key mechanism that underlies the progressive degenerative process. A biochemical analysis of brain tissue of AD patients showed a clear profile of insulin desensitisation, even in people that were not diabetic (Lester-Coll et al., 2006; Moloney et al., 2010; Steen et al., 2005; Talbot et al., 2012). It was found that insulin receptor subunits and IRS1/IRS2 was found to be hyper-phosphorylated and inactivated, a biochemical profile also seen in diabetics in the periphery (Moloney et al., 2010; Talbot et al., 2012). In PD, insulin desensitisation was also observed in central brain areas such as the basal ganglia and substantia nigra (Moroo et al., 1994; Morris et al., 2008, 2011; Pellecchia et al., 2014). Energy utilisation, mitochondrial function, insulin signalling and dopamine transmission was found to be impaired (Morris et al., 2008, 2011; Numao et al., 2014). These effects were also found in non-diabetic subjects and are therefore unlikely to be caused exclusively by diabetes. However, clinical tests showed that a higher percentage of PD patients are diabetic or glucose intolerant compared with age-matched controls (Aviles-Olmos et al., 2013b).

2.2. Treating AD patients with insulin – proof of concept trials

Just as insulin improves diabetes, treating AD patients with insulin shows improvements in cognition, attention, reducing levels of biomarkers for AD, and normalising cortical activity and brain energy utilisation (Okereke et al., 2008; Reger et al., 2008a; Watson and Craft, 2004; Zhao et al., 2004). Insulin cannot be given to people who are not diabetic. Delivering insulin by nasal application where it enters the brain more directly with causing only little increases in blood levels can circumvent the problem of inducing hypoglycaemia. Nasal application of insulin improved attention and memory formation even in non-diabetic people (Craft, 2007; Reger et al., 2008a, 2008b). A phase II clinical trial in AD patients showed improved cognition in patients with mild cognitive impairments (MCI). It furthermore improved the amyloid1-40/1–42 ratio in the cerebrospinal fluid and increased brain activation as seen in ^{18}FDG-PET scans which measure brain activity and energy utilisation, and furthermore showed improvement in mental tasks (Claxton et al., 2015; Craft, 2010; Craft et al., 2012). However, as in patients with diabetes, insulin appears to enhance brain insulin desensitisation and worsen cognitive decline in some patients (Claxton et al., 2015). For a review, see (Freiherr et al., 2013; Holscher, 2014a).

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