

EDITORIAL

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The therapeutic potential of glucagon-like peptide-1 analogs in the treatment of Alzheimer's disease

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“...preclinical evidence strongly supports the hypothesis that GLP-1 analogs can represent promising candidates for Alzheimer's disease treatment.”

Alzheimer's disease (AD) affects more than 25% of individuals over 80 years of age and its prevalence is expected to rise with the increase of life expectancy. Existing drugs only provide symptomatic benefits but there are no currently available disease-modifying therapies. However, evidence from preclinical studies indicates that several drugs approved for other indications could have beneficial effects on Alzheimer's pathology, and some of them are currently being evaluated in clinical trials [1].

In the last decades an increase in the incidence of both type 2 diabetes (T2D) and neurodegenerative disorders has been observed, posing a significant health and social challenge due to increased morbidity and mortality. T2D increases the risk of AD and there is an increased incidence of T2D in AD patients [2], probably due to common pathophysiological mechanisms shared between these diseases, and one that can be identified is insulin desensitization. Indeed, in AD brain, insulin signaling is desensitized, showing a molecular profile similar to that found in peripheral tissues of diabetic subjects [3]. Glucagon-like peptide-1 (GLP-1) is an incretin hormone with several effects on glycemic homeostasis, stimulating insulin and decreasing glucagon secretion. Currently, the GLP-1 receptor agonists exendin-4, liraglutide and lixisenatide are approved for treatment of T2D [4]. Besides its metabolic effects, GLP-1 has also been shown to act as a growth factor in the brain, inducing neurite growth and protecting against oxidative injury; GLP-1 receptor knock-out mice present with impaired hippocampal long-term potentiation of synaptic transmission [5]. The GLP-1 receptor is found in neurons throughout the nervous system, is maintained during aging and disease, and GLP-1 and its analogs effectively cross the blood–brain barrier.

In the context of AD-related brain amyloid pathology, the preclinical results of GLP-1 analogs have shown promising potential. Exendin-4 has been shown to reduce endogenous levels of β -amyloid in the mouse brain [6]. Liraglutide has also been shown to protect synapses from the detrimental effects of amyloid [7,8] and it was able to significantly reduce the β -amyloid plaque load and the total amount of β -amyloid in the brain of a transgenic mouse model of AD. Importantly, in a late-stage animal model of AD, liraglutide demonstrated restorative effects in both brain structure and function, reducing both β -amyloid plaques and soluble amyloid oligomers [9], suggesting that liraglutide could potentially influence the amyloid production. Moreover, GLP-1 analogs have been demonstrated to promote cell proliferation in the rat hippocampus and increase the number of neuronal progenitor cells in mouse models of diabetes. GLP-1R activators induce the differentiation of neuronal stem cell and stimulate neurite outgrowth in a manner similar to nerve

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growth factor, so it can be hypothesized that GLP-1 analogs might have a favorable impact on brain atrophy in AD patients [5]. Some data have also shown potential effects of GLP-1 analogs on brain metabolism. In particular, it has been demonstrated that in AD transgenic mice treated with liraglutide for 10 weeks, cortical glucose uptake was normalized. Compared to nontreated 12-month-old AD mice, in liraglutide-treated AD mice the uptake of glucose was maintained in the frontal brain. In the context of neuroinflammation, preclinical studies have demonstrated that GLP-1 analogs are not only neuroprotective, but also able to reduce the microglial activation by 50%. Both activated microglia and astrocytes induce GLP-1 receptor expression and GLP-1 treatment prevents endotoxin-induced release of inflammatory cytokines by these cells [10]. Moreover, chronic treatment of AD mouse models with liraglutide reduced the numbers of activated microglia in the brain [8].

Favorable results on the potential for GLP-1 analogs in neurodegeneration also derive from studies in Parkinson's disease (PD). In preclinical PD models the GLP-1 analogs have proven to exert favorable effects. In particular, exendin-4 enhanced neuronal progenitor cell proliferation in the subventricular zone, suggesting that new neurons may compensate for the loss of dopaminergic neurons in the substantia nigra [11]. Moreover, exendin-4 is able to protect PD animals from the loss of dopaminergic neurons and transmission and reduce functional impairment. In other experiments exendin-4 treatment increased the levels of dopamine measured in the basal ganglia and also increased dopamine production compared with controls [12].

Based on the encouraging preclinical results, clinical trials are ongoing, testing exendin-4 or liraglutide in AD patients, and exendin-4 in Parkinson's patients. Two large multicenter studies are underway evaluating GLP-1 analogs in mild AD, one US NIH study using exendin-4, and the other using liraglutide (ELAD study) at Imperial College London (London, UK). Recently, a single-blinded clinical trial of exendin-4

in PD patients has been completed, showing clinically relevant improvements in the treated group compared with the control group [13]. In the currently ongoing study at Imperial College London, primary and secondary outcomes will not only entail cognitive measures, but also changes in biomarkers of disease. In particular, the use of neuroimaging techniques for the evaluation of brain atrophy, metabolism, amyloid load and neuroinflammation in this study will provide further insight into the potential disease-modifying effects of GLP-1 analogs. The selection of a population of mild AD patients, with the exclusion of more advanced stages, might also allow accurate evaluation of the effects of these drugs on disease progression, at a stage when interventions are still likely to impact on the pathophysiological mechanisms of neurodegeneration.

Interestingly, liraglutide has been tested in non-diabetic populations and it was well tolerated [14]. However, this has not been tested in AD patients, hence particular caution should be taken in evaluating these subjects.

In conclusion, preclinical evidence strongly supports the hypothesis that GLP-1 analogs can represent promising candidates for AD treatment. Great expectations are posed on the results of currently ongoing clinical trials, whose rigor in the study design will hopefully prevent these potential failures.

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