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Evaluation of neuroprotective effect of glucagon-like peptide 1 analogs using neuroimaging

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Abstract There is increasing evidence to suggest that glucagon-like peptide 1 (GLP1) analogs are neuroprotective in animal models. In transgenic mice, both insulin and GLP1 analogs reduced inflammation, increased stem cell proliferation, reduced apoptosis, and increased dendritic growth. Furthermore, insulin desensitization was also observed in these animals, and reduced glucose uptake in the brain, as shown on FDG-PET imaging. In this review we discussed the role of PET and MRI in evaluating the effect of GLP1 analogs in disease progression in both Alzheimer's and Parkinson's disease. We have also discussed the potential novel PET markers that will allow us to understand the mechanism by which GLP1 exerts its effects.

Keywords: Glucagon-like peptide 1; Alzheimer's disease; Parkinson's disease; Liraglutide; Neuroimaging; FDG-PET; MRI; Neuroinflammation; Amyloid imaging

1. Introduction

Recent evidence has indicated there is a pathophysiologic link between type 2 diabetes mellitus (T2DM) and neurodegenerative disorders, and it is believed that insulin desensitization could be the final common pathway. In Alzheimer's disease (AD), brain insulin signaling is desensitized, showing a molecular profile similar to that found in peripheral tissues of diabetic subjects [1]. Glucagon-like peptide 1 (GLP1) is an incretin hormone with numerous effects on glycemic homeostasis, and GLP1 receptor (GLP1R) agonists exendin-4, liraglutide, and lixisenatide have been approved for treatment of T2DM [2]. In addition to its metabolic effects, GLP1 has been shown to act as a growth factor in the brain, inducing neurite growth and protecting against oxidative injury. Moreover, liraglutide and exendin-4 were both found to reduce endogenous levels of β-amyloid in the brain, and liraglutide not only prevents amyloid plaque formation in AD mice but can also reverse some key pathologic hallmarks of AD [3]. Furthermore, GLP1 analogs have demonstrated favorable effects in preclinical models of Parkinson's disease (PD) and have been tested in a pilot study of PD patients [4].

2. Imaging markers of neurodegenerative diseases

Along with the search for therapies that can modify the course of AD, there is a search for more reliable biomarkers to help in diagnosis and monitoring progression, with neuroimaging markers being among the most valuable tools for this purpose. According to recently revised criteria, the diagnosis of AD is made when there is both evidence of the clinical features and in vivo biologic evidence of underlying AD pathology [5]. Although in past decades computed tomography (CT) and magnetic resonance imaging (MRI) were mainly used to exclude other causes of dementia, newer imaging modalities have been developed, including structural and functional MRI and positron emission tomography (PET). Besides the study of cerebral metabolism with fluoro-deoxy-D-glucose (FDG)-PET, more newly developed tracers have made it possible to visualize the signatures of

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structural and functional cerebral alterations with amyloid imaging, microglial activation and neuroinflammation, cholinergic pathways, and, more recently, imaging tau and neurofibrillary tangles. By employing these techniques, we have improved our understanding of the timing of pathologic events in AD, with the great advantage that patients who do not fulfill a diagnosis of dementia, yet present brain lesions (prodromal AD), can be easily identified [5]. Moreover, there is a growing interest in clinical trials in patients in the prodromal stage of AD, although patient selection based only on clinical criteria may be challenging. Indeed, clinical criteria for mild cognitive impairment (MCI) are not consistent and most neuropsychological tests have shown substantial measurement variability [6]. In addition, clinical trials using progression to dementia as the main outcome may be underpowered because only a minority of MCI patients will develop dementia within 1–2 years of follow-up. However, these disadvantages may be overcome by the use of imaging biomarkers.

In this review we assess the role of neuroimaging techniques in evaluating the effects of GLP1 analogs in neurodegenerative diseases.

3. FDG-PET and clinical outcome in AD

FDG-PET is a measure of cerebral glucose metabolism and an indicator of synaptic function [6]. Loss of synapses is an early feature of AD and is responsible for progressive cognitive decline. According to recent models of dynamic biomarkers in AD, hypometabolism has been shown to precede the appearance of cognitive symptoms and to predict the rate of progressive cognitive decline [7]. Patients with AD and MCI show well-documented patterns of reduced FDG uptake at rest in a network of posterior cingulate, hippocampus, and medial temporal regions [8]. The metabolic deficits in AD gradually worsen throughout the course of the disease. Although asymmetry can be observed in early stages, more advanced disease usually involves prefrontal association areas. Early longitudinal FDG-PET studies in AD and MCI showed that FDG-PET accurately predicts subsequent decline and conversion to AD [9–11].

Recent studies have further evaluated the potential use of FDG-PET as a biomarker of putative therapeutic treatments in clinical trials. Data from Alzheimer's Disease Neuroimaging Initiative (ADNI) studies have shown that FDG-PET accurately tracks AD progression and was able to suggest the numbers needed to provide adequate statistical power for intervention studies. ADNI investigators evaluated mean glucose metabolism uptake in a set of regions of interest (FDG ROIs) developed a priori (ROIs were chosen because they have been frequently found to show hypometabolism in AD in comparable studies), along with the clinical measurements ADAS-cog (Alzheimer's Disease Assessment Scale—cognitive subscale) and FAQ (Functional Activity Questionnaire) using a mixed-effects model. In the multicenter study, the statistical power of FDG-ROIs was compared with ADAS-cog and FAQ as potential outcome measurements of a putative treatment for AD symptoms [12]. Analysis for an MCI group and an AD group was carried out to assess the relationship between FDG-PET and clinical measures in these groups. In the multicenter study, power calculations were performed to determine sample sizes of AD and MCI subject groups that would be needed to detect 25% and 33% attenuation of decline in a clinical trial of a candidate treatment for symptoms of AD [12].

Overall, the study showed that lower baseline FDG-PET consistently predicted subsequent cognitive decline, and that longitudinal FDG-PET was associated with concurrent cognitive decline. These relationships were similar for functional outcomes. Importantly, an analysis of the statistical power of these measures to detect attenuation in decline for a putative AD treatment revealed that use of FDG-ROIs would require fewer AD subjects to detect attenuation in decline (103 subjects per group for 33% treatment effect) than ADAS-cog and FAQ. Based on data up to 12 months post-baseline, FDG-ROIs required the lowest number of AD subjects per group to detect a 25% treatment effect (180 subjects per arm) and a 33% treatment effect (103 subjects) [12]. Overall, these studies suggest that FDG-ROIs can reliably detect longitudinal change, and exceed the power of standard clinical outcome measures. Baseline and longitudinal FDG-ROI measures are sensitive to change in both the ADAS-cog and FAQ, validating the cognitive and functional relevance of longitudinal changes in FDG-PET measurements. Power analysis indicated that FDG-PET is a reliable and clinically useful measure of decline compared with ADAS-cog, particularly in AD patients. Strong associations observed between FDG-PET and ADAS-cog, in particular, indicate that FDG-PET could be useful in clinical trials for selecting subjects who are likely to decline, or as an outcome measure for monitoring clinically relevant change over time. Several other studies have evaluated FDG as a marker of progression of disease [13].

Only limited data are available on the effects of GLP1 analogs on brain metabolism. In particular, it has been shown that in AD transgenic mice treated with liraglutide (25 nmol/kg once daily) for 10 weeks, cortical glucose uptake was normalized. In nontreated, 12-month-old AD mice, the FDG signal was much reduced, whereas, in liraglutide-treated AD mice, uptake of glucose was maintained in the frontal brain. Thus, the changes in glucose uptake measured by FDG-PET are an established and clinically relevant outcome measure to evaluate the possible efficacy of GLP1 analogs in clinical trials (unpublished data).

Two large multicenter studies are underway evaluating GLP1 analogs in mild AD, one using exendin-4 at the National Institutes of Health (NIH) and an other using liraglutide (ELAD Study) at Imperial College London. In the latter study, change in FDG-PET using arterial input analysis is the primary endpoint of the study.