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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.

4. MRI in AD

The current National Institute on Aging-Alzheimer's Association (NIA-AA) standards include volumetric MRI measurement as a criterion for the evaluation of AD. In evaluating disease progression, progressive hippocampal and cortical atrophy are considered as a valid measure of neurodegeneration and neuronal loss [14]. The areas progressively affected by atrophy in AD are the hippocampus and medial temporal lobe, then the temporal neocortex and all neocortical association areas; atrophy can be detected in the preclinical phase of the disease—indeed, in patients with MCI, the entorhinal volumes are already reduced by 20%–30% and hippocampal volumes by 15%–25% [15]. Longitudinal MRI studies have shown that, in asymptomatic subjects who subsequently develop AD, hippocampal volumes are already reduced by about 10% at least 3 years before diagnosis of dementia [16,17]. Moreover, assessment of medial temporal atrophy on MRI has been shown to have positive predictive value for AD, with a sensitivity and specificity of 80%–85% in differentiating AD from normal aging, and it correlates with cognitive decline [14]. Given these results, the atrophy rates on MRI have a major role as outcome measures of disease modification effects in clinical trials, with a greater power to detect a disease-modifying effect compared with clinical measures.

GLP1 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. Moreover, GLP1R activators induce the differentiation of neuronal stem cells and stimulate neurite outgrowth in a manner similar to nerve growth factor, so it can be hypothesized that GLP1 analogs may have a favorable impact on brain atrophy in AD patients [18]. MRI measures of brain atrophy can provide evidence of whether these therapeutic modalities have a disease-modifying effect that can be translated into clinical outcomes. In the multicenter clinical studies using GLP1 analogs, volumetric change in MRI is considered an endpoint.

5. Amyloid imaging

The most important advancement provided by the development of amyloid imaging in the context of AD is that amyloid PET can serve as an in vivo surrogate marker of amyloid pathology. Notably, the greatest potential of amyloid imaging is its ability to detect amyloid in MCI as well as asymptomatic subjects, where pharmacologic interventions may be more effective in slowing disease progression.

These amyloid imaging agents specifically bind to fibrillar amyloid and different molecules have been developed and tested in humans, including 11-labeled Pittsburgh Compound B ([^{11}C]PiB), 18-labeled Flutemetamol ([^{18}F] Flutemetamol, or [^{18}F]Florbetaben), [^{18}F]Florbetapir, [^{11}C] AZD2184, [^{18}F]AZD4694, [^{11}C]SB13, and [^{11}C]BF-227. Extensive data currently available derive from [11C]PIB studies [19]; however, there have also been recent data on [^{18}F]Flutemetamol and [^{18}F]Florbetaben. Different PiB-PET studies have shown that PiB retention in AD subjects is twofold higher than that of healthy controls. Using region-of-interest and/or voxelwise analysis, it has been observed that AD subjects have the highest tracer uptake in prefrontal cortex, precuneus, and posterior cingulate cortex, followed by lateral parietal and temporal cortex [20]. Recent reviews on amyloid PET on clinically diagnosed AD patients have indicated that, globally, 96% of AD patients were amyloid-positive. PiB-PET has been used in longitudinal studies evaluating disease progression and it has been established that amyloid deposition reaches a plateau in the early clinical stages of the disease, with dissociation between the amyloid load, which remains relatively stable and maintains clinical status [21,22]. In fact, because amyloid deposition is an early event in AD pathogenesis, amyloid PET cannot be used as a reliable marker of progression in the clinical phase of the disease, as structural MRI and FDG-PET are more suitable for monitoring disease progression.

Amyloid PET has great potential in the preclinical stages of the disease, as it can potentially identify early AD pathology in MCI, helping predict the rate of progression from MCI to dementia. Various studies have demonstrated that PiB uptake in MCI could be intermediate between AD and controls, but with a predominantly bimodal distribution (a subset of patients showing AD-like uptake ratios with the other subset showing uptake levels similar to controls), with the amnestic MCI subjects having the highest PiB uptake [23–25]. Data from longitudinal studies are not unequivocal, with some studies showing nonsignificant elevations in PiB uptake despite significant progression in hippocampal atrophy in MCI subjects developing AD, yet others reporting significant increases in overall amyloid burden in MCI subjects at 2-year follow-up [26–29].

Several studies in MCI subjects have clearly demonstrated that the highest baseline PiB uptake is associated with the fastest conversion to AD. Forsberg et al. found that about one third of MCI subjects with elevated PiB uptake converted to AD at clinical follow-up, whereas individuals with normal baseline PiB uptake did not progress to AD [30]. Similarly, Okello et al. demonstrated that PiB-positive subjects with MCI are significantly more likely to convert to AD than PiB-negative patients, with faster converters having higher baseline PiB retention than slower converters [31]. These findings have been replicated in several other studies by the ADNI groups [32]. Thus, early detection of brain amyloid pathology is of paramount importance as it could help identify MCI subjects who are more likely to progress to AD. Several intervention studies have prescreened MCI subjects with amyloid imaging before enrollment into the study, and it is anticipated that 50% of amyloid-positive MCI subjects will develop AD in 2 years time [32].

In the context of brain amyloid pathology, the preclinical results of GLP1 analogs have shown promise. Exendin-4 has

been found to reduce endogenous levels of β-amyloid in the mouse brain [33]. Also, liraglutide has been shown to protect synapses from the detrimental effects of amyloid [34,35] and, when tested in the transgenic mouse model of AD, it was able to significantly reduce the β-amyloid plaque load and the total amount of β-amyloid in the brain. 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 [3]. It can be thus hypothesized that liraglutide is able to modulate amyloid clearance in brain. In clinical trials evaluating the disease-modifying effects of these new drugs in AD, the use of amyloid imaging offers the potential to identify and measure brain amyloid content in vivo. In one ongoing liraglutide clinical trial in AD patients, the change in cerebral amyloid deposition by PiB-PET is the primary outcome measure [36].

6. Imaging microglia in neurodegenerative diseases

Progressive neurodegenerative diseases induce a chronic inflammation response in the brain. Given the role of activated microglia in neurodegeneration, imaging them in vivo represents a tool to quantify and localize neuroinflammation and to evaluate the potential of novel therapeutic interventions. PET is the most widely used in vivo method of evaluating microglial activation. Microglial activation is associated with upregulated expression of mitochondrial translocator protein (TSPO), previously known as peripheral benzodiazepine binding receptor. It is found throughout the body and in the central nervous system (CNS) it is expressed at low levels. TSPO also has a role in cholesterol transport and steroid production, but its exact function in the CNS needs to be further elucidated [37]. In animal models, it has been shown that TSPO expression is associated with either activated microglia or reactive astrocytes, depending on the nature of the neuronal insult [38,39]. In rat models of focal ischemia, TSPO expression increases in microglia and is subsequently followed by a rise in astrocyte activation, indicating that a temporal relationship exists between TSPO expression in microglia and astrocyte activation [40]. In human postmortem studies, TSPO–radioligand binding was associated with activated microglia in patients with stroke, multiple sclerosis, AD, and frontotemporal dementia [41].

Most studies have used [^{11}C](R)PK11195 [1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide] PET, which was first reported in 1986 [42]. This agent has been used extensively in a number of neurologic diseases in humans and animals. Immunologic studies have shown that activated microglia colocalize with amyloid plaques and hyperphosphorylated tau, both in postmortem human AD [43,44] and animal [45] studies. [^{11}C]PK11195 PET detects in vivo microglial activation in brains in mouse [44] and human [46,47] studies of AD. In AD patients, [^{11}C]PK11195 PET reveals microglial activation throughout the cortex in a similar distribution to that of amyloid plaque deposition [47]. Increased cortical [^{11}C]PK11195 binding can be detected in around 60% of mild to moderate AD patients and around 40% of subjects with amnestic mild cognitive impairment (aMCI) [48]. Levels of cortical [^{11}C]PK11195 signal have shown an inverse correlation with Mini-Mental State Examination (MMSE) scores [47], suggesting involvement of microglial activation in neuronal dysfunction and cognitive impairment. However, not all series have detected increased [^{11}C]PK11195 binding in aMCI and mild to moderate AD [49], which may reflect different sensitivities of the imaging devices and analytical approaches used.

[^{11}C]PK11195 has been used for two decades, but, because of the low signal-to-background ratios and short 20-minute half-life, several second-generation TSPO markers have been developed. These include [^{18}F]FEPPA, [^{18}F]FEDAA1106, [^{11}C]vinpocetine, [^{11}C]DAC, [^{11}C]DAA1106, [^{11}C]N1-methyl-2-phenylindol-3-ylglyoxylamide ([^{11}C]31), [^{11}C]CLINME, [^{11}C]DPA-713, [^{18}F]DPA-714, [^{18}F]PBR06, and [^{11}C]PBR28. These radiotracers are in various stages of development and are being evaluated in humans.

[^{11}C]PBR28 is a radioligand with an 80-fold higher affinity for TSPO than PK11195, a lower signal-to-noise ratio, and slower pharmacokinetics [50]. However, it was discovered that patients exhibited different binding affinities for TSPO, falling into high-affinity, low-affinity, or mixed affinity-binding groups [51]. This variable binding was mapped to expression of a specific polymorphism in the TSPO gene, which permits prediction of binding potential [52]. This variability in binding affects modeling of radioligand binding as a proxy for microglial activation, to the extent where some investigators have chosen only to use high-affinity binders, representing around 50% of Caucasians, to make their analysis more robust.

Preclinical studies have demonstrated that GLP1 analogs are not only neuroprotective but can also reduce microglial activation by 50% in animal models. Both activated microglia and astrocytes induce GLP1R expression and GLP1 treatment prevents endotoxin-induced release of the cytokine interleukin-1β (IL-1β) by these cells [53]. Moreover, long-term treatment of AD mouse models with liraglutide reduced the numbers of activated microglia in the brain [35]. In a large-scale phase II clinical trial with liraglutide in early AD patients, the change in microglial activation is considered a secondary endpoint.

7. PET in PD

PD is a neurodegenerative disease characterized by dopaminergic cell loss from the substantia nigra and formation of intracellular Lewy inclusion bodies. Currently, no imaging biomarker of Lewy bodies is available, but the detection of altered striatal dopamine terminal function is possible by ^{18}F-Dopa PET, which measures striatal aromatic amino acid decarboxylase (AADC) activity, whereas

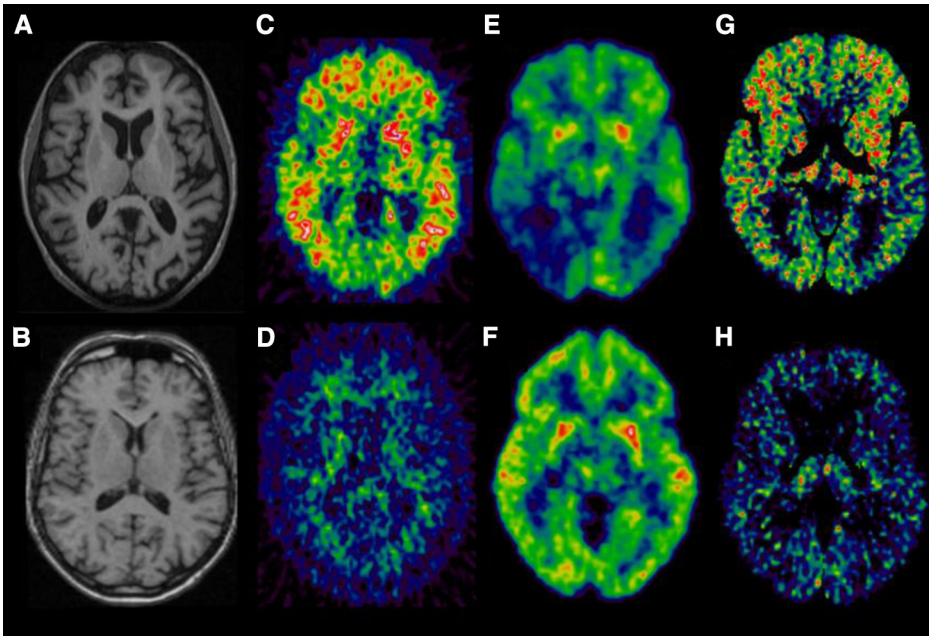

Fig. 1. Representative transveral image sections from a control subject and an AD patient. MRI scan in an AD patient (A) and a control subject (B). [^{11}C]PiB-PET scan in AD (C) and control (D) showing increased uptake of in the cortical areas of the AD patient. FDG-PET scan in AD (E) and control (F) subjects indicating hypometabolism in AD. [^{11}C]PK11195 PET scans in AD (G) and control (H) subjects revealing microglial activation in AD.

dopamine transporter function in PD can be assessed with PET, using tropane-based tracers, or single-photon emission computed tomography (SPECT), with ligands including ^{123}I-β-CIT, ^{123}I-FP-CIT, and ^{123}I-IPT [54]. ^{18}F-Dopa uptake in PD striatum has been shown to reflect the number of remaining nigral dopaminergic neurons in both human and in animal models [55,56]. It has been demonstrated that loss of striatal ^{18}F-DOPA uptake occurs more rapidly in PD patients than in age-matched controls and its decrease in putamen is about 10%/year. Moreover, ^{18}F-DOPA uptake has shown a significant inverse correlation with the degree of disability, degree of rigidity, and bradykinesia [57,58]. Because PET can objectively document the loss of dopamine terminal function in PD, it is a valuable tool for monitoring the efficacy of putative agents.

In preclinical PD models, GLP1 analogs have proven to exert favorable effects. In particular, exendin-4 enhanced neuronal progenitor cells proliferation in the subventriclar zone, suggesting that new neurons may compensate for the loss of dopaminergic neurons in the substantia nigra [59]. Moreover, exendin-4 can protect PD animals from the loss of dopaminergic neurons and transmission and reduce functional impairment. In other experiments, exendin-4 treatment was found to increase the levels of dopamine measured in the basal ganglia and also increased dopamine production compared with controls [60]. Recently, a single-blind clinical trial of exendin-4 in PD patients was completed. Exenatide was well tolerated, and the treated group showed clinically relevant improvements across motor and cognitive measures compared with the control group [4]. The subgroup of patients given exenatide had an [^{123}I] FP-CIT SPECT scan performed at baseline and repeated at 12 months, with the aim of identifying whether this may serve as a biomarker of responsiveness to exenatide.

8. Conclusion

In recent decades, neuroimaging techniques have given us a greater understanding of the pathophysiology of neurodegenerative diseases. Brain imaging has the great advantage of providing a "window" to the brain, identifying in vivo the structural and functional abnormalities of neurodegeneration and allowing us to track them in disease progression or even in the prodromal phases (Fig. 1). Due to recent advances in neuroimaging, new hypothetical models based on AD biomarkers have been hypothesized. It should be noted that no single technique provides all the information in these complex disorders, and the use of different biomarkers is complementary. Moreover, improved standardization should be the goal for all neuroimaging analyses.

In the search for therapies that can modify the course of neurodegenerative diseases, such as GLP1 analogs in AD and PD, imaging markers can serve not only as adjunct marker for patient selection but also as outcome measures in clinical trials, especially in the early phases.

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