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INSIGHT

Therapeutic Potential of Glucagon-Like Peptide-1 Cleavage Product for Alzheimer's Disease

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Alzheimer's disease (AD) is a devastating neurodegenerative disease and the most common form of dementia in the elderly. Concurrent with an aging population, the incidence of AD has been rising steadily and become a global threat to public health [1]. Unfortunately, there are currently no effective interventions that can cure AD or slow its progression, and recently finished clinical trials targeting brain amyloid-β (Aβ) accumulation have not succeeded in improving cognitive impairments in AD patients [1]. Thus, it is necessary and urgent to identify alternative disease-modifying strategies to alleviate AD pathophysiology. In this perspective article, we focus on glucagon-like peptide-1 (GLP-1), specifically its natural cleavage product GLP-1 (9-36), as a potential therapeutic approach for AD.

Biology of GLP-1

GLP-1 is an incretin hormone released from the L-cells of the distal ileum in response to nutrient ingestion. This proglucagon protein is a prohormone which gives rise to several hormones, and it is expressed in pancreatic α-cells, intestinal L cells, and in caudal brainstem and hypothalamic neurons. Proglucagon is post-translationally modified by prohormone convertase 1/3 (PC1/3) to produce glucagon-like peptide-1 (GLP-1) [2]. Additional proteolytic cleavage and amidation of GLP-1 by PC1/3 and peptidylglycine α-amidating monooxygenase (PAM), respectively, yields several forms of GLP-1: the biologically inactive forms GLP-1 (1-37) and GLP-1 (1-36)NH_2, and the biologically active GLP-1 (7-37) and GLP-1 (7-36)NH_2. In humans, the predominant circulating form is GLP-1 (7-36)NH_2 [GLP-1 (7-36) hereafter] [2].

Circulating GLP-1 (7-36) has a high binding affinity to the GLP-1 receptor (GLP1R), a heterotrimeric G-protein-coupled receptor. GLP1R is expressed in several organ systems and its activation results in a variety of physiological consequences, most of which are metabolic in nature (*e.g.* insulinotropic effects in pancreatic tissue and appetite suppression and gastric motility in the brain) [2, 3]. Thus it is not surprising that several GLP1R agonists have been approved for type-2 diabetes mellitus (T2DM) treatment and management [4]. Of note, T2DM has been identified as a risk factor, a comorbidity, and a putative mechanism for certain types of AD. Furthermore, examination of brain samples from AD patients and transgenic animal models of AD has revealed significant dysregulation of metabolic signaling pathways, including deficiency of insulin signaling [5, 6]. Such findings have driven research to investigate the potentially beneficial effects of treating AD with drugs that were initially developed for T2DM, such as GLP1R agonists [7].

Therapeutic Potential of GLP-1 and Its Cleavage Product GLP-1 (9-36) for AD

GLP1R is an essential component of learning and memory. Rats treated with GLP1R agonists display improved performance in learning and memory tasks, an effect

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negated by GLP1R antagonism [8]. GLP1R-knockout mice exhibit impaired memory and synaptic plasticity, which is rescued by *Glp1r* gene transfer [8, 9]. GLP1R agonism also improves memory and synaptic plasticity in a mouse model of AD [10]. Intracerebroventricular administration of GLP-1 (7-36) or a GLP1R agonist decreases endogenous Aβ production in mice and protects cultured rat hippocampal neurons against Aβ-induced cell death. In rats, GLP1R agonists prevent the Aβ-induced failure of long-term potentiation (LTP), a major form of synaptic plasticity and a cellular model for learning and memory [11, 12]. Moreover, administration of liraglutide, an acetylated form of GLP-1(7-36) and a GLP-1R agonist, has been shown to mitigate dementia and other behavioral defects in a mouse model of AD, in conjunction with improved synaptic plasticity and reduced neuronal damage, plaques, and oligomer formation [13]. Taken together, these results show that GLP-1 (7-36) and GLP1R are not only critical to memory function, but may also protect against Aβ-induced synaptic failure and cognitive impairment.

Circulating GLP-1 (7-36) is extremely unstable (half-life < 2 min), and is rapidly broken down by dipeptidyl peptidase-4 into GLP-1 (9-36)NH_2 [GLP-1 (9-36) hereafter], which is the major circulating metabolite of GLP-1 (7-36) [2]. Unlike its precursor, GLP-1 (9-36) has a weak affinity for the GLP1R and does not induce insulinotropic activity. Consequently, GLP-1 (9-36) has been labeled as an inactive waste-product. However, there is a growing body of evidence that suggests otherwise. One of the most interesting properties of GLP-1 (9-36) is that it protects against oxidative stress, a putative pathophysiological mechanisms underlying AD-associated synaptic failure and cognitive decline [14]. For example, GLP-1 (9-36), but not GLP-1 (7-36), suppresses the reactive oxygen species production in human aortic endothelial cells induced by high glucose or high free-fatty-acids [15]. Moreover, application of GLP-1 (9-36) blunts the increase of mitochondrial superoxide in the hippocampus associated with an aged mouse model of AD, or induced by exogenous synthetic human Aβ [16]. In agreement with the findings on mitochondrial superoxide, impairments of synaptic plasticity (LTP as well as long-term depression, another form of synaptic plasticity) and cognition (spatial memory and conditioned fear memory) associated with the aged mouse AD model are also significantly improved by treatment with GLP-1 (9-36) for two weeks using a microosmotic pump [16].

Aside from a decrease of mitochondrial superoxide, the detailed molecular signaling mechanisms through which GLP-1 (9-36) alleviates synaptic plasticity impairments and memory loss in mouse AD models remain unclear. As discussed above, it is unlikely that GLP-1 (9-36) exerts such effects (behavioral and electrophysiological) *via*

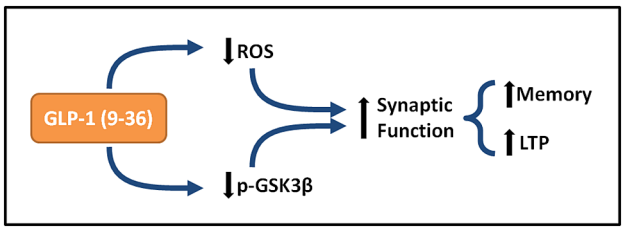

Fig. 1 Schematic of the working hypothesis that GLP-1 (9-36) improves memory and synaptic plasticity.

GLP1R activation or insulin secretion. Of note, it has been shown that the AD-associated increased activity of glycogen synthase kinase-3β (GSK3β), as indicated by decreased GSK3β phosphorylation at the Ser9 site, is reversed by GLP-1 (9-36) treatment [16]. While GSK3 was originally identified as a regulator of glycogen metabolism, it is now clear that GSK3 signaling is involved in many cellular processes and plays a critical role in neuronal function. Abnormally high GSK3β activity leads to synaptic plasticity impairments, and conversely, suppression of GSK3β activity facilitates the induction of LTP [17, 18]. Of interest, overactive GSK3 has been linked to several aspects of AD pathology and accordingly, inhibition of GSK3 activity has been proposed as a potential therapeutic intervention strategy for AD, although controversy has arisen on the exact roles of the different GSK3 isoforms (GSK3α *versus* GSK3β) in AD pathogenesis [19, 20]. Moreover, GSK3 upregulation results in suppression of the signaling pathways controlling *de novo* protein synthesis, which is known to be required for the maintenance of long-term memory and synaptic plasticity [18].

In conclusion, our working hypothesis, based on studies on animal models, is that the natural GLP-1 cleavage product GLP-1 (9-36) is a potential therapeutic agent for AD and other neuronal disorders with cognitive impairments (Fig. 1). Future studies on human populations (clinical trials) are critical to determine the effectiveness of the GLP-1 cleavage product in alleviating AD-associated dementia syndrome.

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Conflict of interest The authors declare no conflict of interest.

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