Research and Practice 1

Title: GLP-1 Agonists and Alzheimer's: Hope or Hype?

Authors Antoine Sader, MD and Rita Khoury, MD

Department of Psychiatry, American University of Beirut, Faculty of Medicine & the Medical Center Beirut, Lebanon

Key highlights:

- Due to shared pathological processes between Alzheimer's disease (AD) and Type 2 Diabetes (T2D), Glucagon-like peptide-1 agonists (GLP-1A) are being investigated as a potential treatment (and prevention strategy) for AD.
- In animal models, GLP-1A enhances neuronal insulin sensitivity, reduces neuroinflammation, decreases beta-amyloid and tau accumulation, promotes neuronal repair, and protects synapses from degeneration.
- Cognitive and AD biomarker improvements with GLP-1A were primarily observed in preclinical trials and in specific groups of patients with diabetes and/or metabolic syndrome.
- These benefits have not been demonstrated yet in older individuals at high risk for AD or in those with AD without T2D.
- Low CNS penetration may necessitate higher doses for cognitive benefits, but this increases the risk of adverse effects and treatment discontinuation, particularly in older adults.
- Future randomized controlled trials should include large sample sizes, extended follow-up durations, and standardized baseline controls for AD severity, frailty scores, presence or absence of T2D, as well as specific GLP-1A dosages and formulations.

Introduction

Glucagon-like peptide-1 agonist (GLP-1A), an antidiabetic drug, is taking the medical world by storm! Celebrated as a game-changer for both weight loss and type 2 diabetes (T2D) management, its impact goes far beyond obesity and T2D [1]. Exciting new research is unveiling its powerful renal protective and cardioprotective effects, while also revealing its potential to curb addiction to nicotine, alcohol, and cocaine [2]. Currently approved and commonly used GLP-1 receptor agonists include exenatide, lixisenatide, dulaglutide, liraglutide, and semaglutide. Unlike endogenous GLP-1, GLP-1 mimetics resist degradation by dipeptidyl peptidase-4 (DPP-4), preventing

rapid inactivation. These drugs act as incretins, enhancing glucose-dependent insulin biosynthesis and secretion, slowing gastric emptying, reducing postprandial glucagon secretion, and suppressing appetite without increasing the risk of hypoglycemia [3]. GLP-1A also cross the blood-brain barrier, with receptors expressed in various brain regions, particularly the hypothalamus, which plays a key role in satiety regulation, explaining their anorexigenic effects [1, 3].

As the most prevalent neurodegenerative disorder, Alzheimer's disease (AD) is a leading cause of mortality, decreased quality of life, and disability [3]. Due to the shared pathological processes between AD and T2DM, including insulin resistance, oxidative stress, and neuroinflammation. several antidiabetic drugs—including GLP-1A—are being actively studied for their potential in combating this devasting neurodegenerative disease.

Mechanisms against AD and Pre-clinical studies

Given that GLP-1 receptors are expressed in multiple brain regions and that GLP-1 and its analogs can cross the blood-brain barrier, researchers have explored their effects on brain function and cognition. It is postulated that GLP-1 modulates key cellular processes disrupted in neurodegenerative diseases, particularly by restoring insulin signaling in neurons and preventing Oxidative stress [4]. In animal models, GLP-1A have been shown to increase insulin sensitivity in neurons, leading to a significant reduction in the expression of pro-inflammatory cytokines, which are typically elevated in hyperinsulinemic conditions [4]. This restoration of insulin sensitivity also leads to decreased tau hyperphosphorylation, a key hallmark of AD [4]. The anti-inflammatory properties of GLP-1A are further evident in studies where GLP-1 brain receptor overexpression enhances cognitive function in mice, whereas its knockout results in severe cognitive impairment [5]. Another striking effect of GLP-1 administration in AD models is the significant reduction of pro-inflammatory microglial cells and attenuation of reactive astrocytosis [3].

Beyond its role in neuroinflammation, GLP-1A improve cognition by reducing neuronal apoptosis, and suppressing neurotoxicity—especially by protecting hippocampal neurons from glutamate-induced excitotoxicity and hypoxic conditions [3].

More specifically, GLP-1A appears to directly target neurodegenerative processes in AD by decreasing beta-amyloid accumulation and tau hyperphosphorylation, either by interfering with their pathological formation or by enhancing autophagy and plaque clearance [5]. On the other hand, GLP-1 promotes neuronal growth and repair, functioning as a growth factor that stimulates stem cell proliferation and differentiation [5].

Lastly, pre-clinical studies demonstrate that GLP-1A protects synapses from beta-amyloid plaque buildup, enhances synaptic plasticity, and ultimately supports memory formation, highlighting its potential as a neuroprotective agent in the treatment of AD [5].

Clinical trials: A Promise Yet to Be Proven?

Several clinical trials have investigated the efficacy and tolerability of GLP-1A in treating or preventing AD in both T2D and non-T2D older populations. The results are mixed. A 2023 systematic review examined the effects of GLP-1A on core AD biomarkers and cognitive performance in AD patients without T2D [6]. The review identified four randomized clinical trials (RCTs) and two pilot studies, none of which demonstrated significant improvements in AD biomarker endpoints or cognitive outcomes [6]. However, some neuroprotective benefits were noted, including mitigation of cerebral glucose metabolism decline and enhanced blood-brain glucose transport capacity [6].

These results contrast with the positive outcomes seen in animal models of AD. Several limitations may have influenced the findings of the reviewed RCTs, including small sample sizes, short study durations, variability in dosages and types of GLP-1A used, and significant heterogeneity in participant characteristics (e.g., different AD

stages, frailty, comorbid conditions) [6]. Furthermore, these studies did not include older participants with both AD and T2D, a critical subgroup that may exhibit different responses to GLP-1A treatment.

Particularly, a Swedish national registry study examining AD prevention in patients with T2D concluded that GLP-1A, compared to sulfonylureas and DPP-4 inhibitors, provided greater benefits in preventing AD [7]. However, this study had several limitations, including the lack of control over medication duration, diabetes duration, and the lag time between drug exposure and dementia onset. Hence, more data is needed to establish the role of GLP-1A in AD prevention among T2D patients [7].

Importantly, some research suggests that since only 1.5% to 2.0% of the administered dose reaches the CNS, a higher dose of GLP-1A may be needed to demonstrate cognitive benefits and AD biomarker improvement [3]. However, this may increase the risk of adverse effects and decrease the rates of adherence to treatment, given that older adults have generally higher discontinuation rates due to AEs [8]. Indeed, while no significant difference in AE incidence exists between age groups after GLP-1A treatment, older patients are particularly susceptible to common side effects like nausea and vomiting, which can lead to dehydration and falls [8]. Rapid weight loss may further increase fracture risk and exacerbate orthostatic hypotension. Close monitoring of kidney and liver function, hydration, and drug interactions is essential in geriatric patients [8].

Conclusion:

GLP-1A cognitive and AD biomarker improvement were primarily observed in preclinical trials using AD animal models and in specific groups of patients with diabetes and/or metabolic syndrome. However, these benefits were not consistently seen in older individuals at high risk for AD or in those with AD without T2D.

To clarify the potential role of GLP-1A in AD, future randomized clinical trials should include larger sample sizes, extended follow-up durations, and standardized baseline controls for AD severity, frailty scores, presence or absence of T2D, as well as specific GLP-1A dosages and formulations.

Ongoing research, particularly the phase 3 **EVOKE** (NCT04777396) and **EVOKE+** (NCT04777409), two multicenter, double-blind randomized controlled trials expected to conclude in 2026, will provide crucial insights into the effects of oral semaglutide in amyloid-positive older adults with mild cognitive impairment (MCI) due to AD.

With continued clinical trials and expanding research efforts, the role of GLP-1A in AD prevention and management remains a promising avenue. As we await more data, the prudent application of these agents in older adults must balance potential cognitive and metabolic benefits against known risks, ensuring that this innovative therapy is utilized safely and effectively.

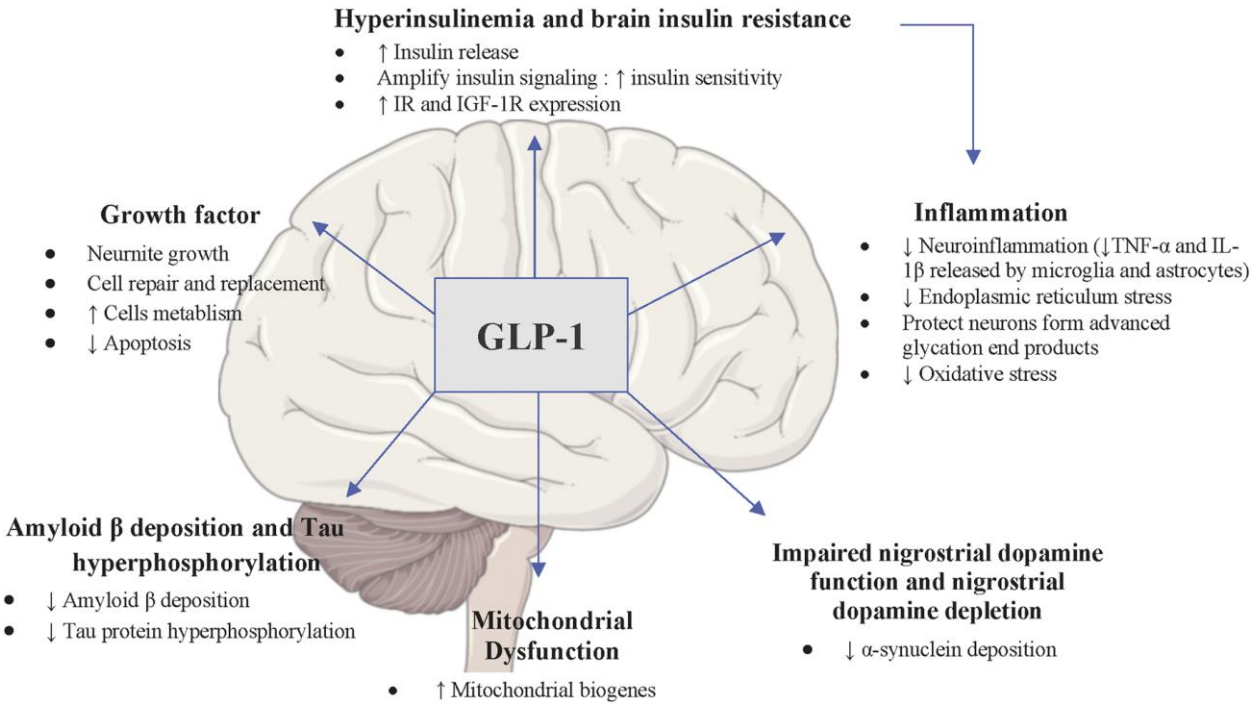

Fig. 1. GLP-1 central effects retrieved from [3]

References:

1. Zheng, Z., et al., Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Signal Transduct Target Ther, 2024. 9(1): p. 234.
2. Klausen, M.K., et al., The role of glucagon-like peptide 1 (GLP-1) in addictive disorders. Br J Pharmacol, 2022. 179(4): p. 625-641.
3. Monney, M., F.R. Jornayvaz, and K. Gariani, GLP-1 receptor agonists effect on cognitive function in patients with and without type 2 diabetes. Diabetes Metab, 2023. 49(5): p. 101470.
4. Yaribeygi, H., et al., GLP-1 mimetics and cognition. Life Sci, 2021. 264: p. 118645.
5. Du, H., et al., The mechanism and efficacy of GLP-1 receptor agonists in the treatment of Alzheimer's disease. Front Endocrinol (Lausanne), 2022. 13: p. 1033479.
6. Liang, Y., et al., Clinical Evidence for GLP-1 Receptor Agonists in Alzheimer's Disease: A Systematic Review. J Alzheimers Dis Rep, 2024. 8(1): p. 777-789.
7. Tang, B., et al., Comparative effectiveness of glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, and sulfonylureas on the risk of dementia in older individuals with type 2 diabetes in Sweden: an emulated trial study. EClinicalMedicine, 2024. 73: p. 102689.
8. Wang, Y., et al., Efficacy and safety of glucagon-like peptide-1 receptor agonists in the elderly versus non-elderly patients with type 2 diabetes mellitus: insights from a systematic review. Endocrine Journal, 2024. 71(6): p. 571-582.

Antoine Sader, MD, holds a medical degree from the University of Balamand and has been a Research Fellow in the Department of Psychiatry at the American University of Beirut since 2023. His primary research interests are neuropsychiatric symptoms associated with neurodegenerative diseases, particularly Alzheimer's and Parkinson's, and novel interventional treatments for Alzheimer's disease. Email: as326@aub.edu.lb

Dr. Rita Khoury is an adult and geriatric Psychiatrist, Assistant Professor of clinical psychiatry at the American University of Beirut, Lebanon. Email: rk224@aub.edu.lb