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Beyond Glycemic Control: Exploring the Prospective of Exendin-4 Clinical Utility as a Disease-Modifying Agent in Alzheimer's Disease; Preclinical and Clinical Evidence

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Abstract: Amyloid-beta (Aβ) plaques, neurofibrillary tangles of hyperphosphorylated tau, and persistent neuroinflammation are the hallmarks of Alzheimer's disease (AD), a progressive neurodegenerative illness that frequently manifests symptoms of cerebral insulin resistance. The possible neuroprotective properties of Exendin-4 (Ex-4), a long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA) currently licensed for type 2 diabetes mellitus (T2DM), have attracted a lot of attention. Ex-4 effectively reduces (Aβ) buildup, mitigates tau hyperphosphorylation, and suppresses neuroinflammation and oxidative stress through the GLP-1 receptor (GLP-1R) pathway, as preclinical studies show. Although these data point to Ex-4 as a potentially effective disease-modifying drug, human clinical trials have so far shown conflicting findings about the cognitive and clinical effects of Ex-4 in moderate cognitive impairment (MCI) and early AD. The present body of evidence is summarized in this review, which also examines the known mechanisms of Ex-4 neuroprotection, examines the results of finished clinical studies, and talks about the direction of its clinical use in Alzheimer's disease.

Key Words: Exendin-4, Alzheimer's Disease, GLP-1 Receptor Agonist, Neuroprotection, Clinical Trials, Mild Cognitive Impairment

INTRODUCTION

Exendin-4: Discovery, Molecular Structure, and Glucagon-Like Peptide-1 (GLP-1) Receptor Signaling

In response to dietary intake, enteroendocrine L-cells in the gut release the hormone glucagon-like peptide-1 (GLP-1), a key incretin that promotes glucose-dependent insulin production and is essential for maintaining glucose homeostasis [1]. However, because of its quick enzymatic breakdown by dipeptidyl peptidase-4 (DPPIV), native GLP-1 has a relatively short physiological half-life (1.5–5 minutes), which limits its potential as a treatment for type 2 diabetes [2].

Exendin-4 (Ex-4) was discovered, which was a major pharmaceutical advance. A strong and persistent agonist of the GLP-1 receptor (GLP-1R), Ex-4 is a naturally occurring peptide. To overcome the drawbacks of native GLP-1, its synthetic equivalent, exenatide, was the first GLP-1R agonist authorized for the treatment of type 2 Diabetes [3].

Isolation from the Gila Monster

In 1992, Ex-4 was initially isolated and described from a biological source that appeared to be unrelated to human physiology: the saliva of the venomous Gila monster (*Heloderma suspectum*), a lizard that is indigenous to Mexico and the southwestern United States. The quest for peptides in the lizard's venom that controlled smooth muscle contraction and intestinal secretion served as the basis for this coincidental finding. Ex-4 and its shorter analog, Exendin-3, were found to be potent GLP-1R stimulators. A more pharmacologically stable therapeutic agent was modeled after this exogenous peptide. Ex-4 showed higher potency and a noticeably longer half-life in vivo, making it

an excellent place to start for drug development even though it only shared roughly 53% sequence identity with human GLP-1 (7-36) amide [3].

Molecular Structure and Enhanced Stability

With 39 amino acids, extendin-4 is a peptide that is marginally longer than native human GLP-1's active version, which has 30 or 31 amino acids. The variations in the N-terminal sequence are what give it its pharmacological advantage. His-Ala (residues 7 and 8 of the proglucagon sequence), which is the first sequence in native GLP-1, is easily broken down by the enzyme DPPIV [1].

Ex-4, on the other hand, contains a glycine residue (Gly2) at position two rather than the alanine present in GLP-1 (Ala8). A significant improvement over the minute-scale half-life of GLP-1, this particular Gly2-Glu3 sequence substitution makes the peptide nearly impervious to DPPIV cleavage, resulting in a prolonged plasma half-life of about 120 minutes in humans [1,3].

Ex-4 and GLP-1 have a structurally similar overall architecture, which is typical of peptide hormones that interact with Class B GPCRs. The structure has a central and C-terminal segment that adopts an α-helical conformation, as well as a flexible N-terminal tail. Its interaction with the receptor depends especially on the C-terminal helix [2].

Receptor Signaling and Mechanisms of Action

The GLP-1 Receptor (GLP-1R): A member of the Family B (or Class B) of G protein-coupled receptors (GPCRs), which also contains receptors for secretin, calcitonin, and parathyroid hormone, Ex-4 acts as a high-affinity agonist for the GLP-1 receptor (GLP-1R) [1]. The GLP-1R has two main functional domains: a large N-terminal extracellular domain (NTD) and the characteristic seven-transmembrane (7TM) bundle [4].

Peptide binding to the GLP-1R is described by a "two-site model":

- The C-terminal helical region of Ex-4 initially binds to the NTD of the GLP-1R, acting as an anchoring site.
- The N-terminal segment of Ex-4 then interacts with the 7TM core of the receptor, which is critical for inducing the conformational change necessary for receptor activation and intracellular signaling [2].

Intracellular Signaling Cascades

Adenylyl cyclase (AC) activation mediates the established signaling pathway for the activated GLP-1R. As a result, the intracellular second messenger cyclic adenosine monophosphate (cAMP) rises quickly [4].

The cAMP signal is central to Ex-4's main therapeutic effects:

- **Insulin Secretion:** Protein Kinase A (PKA) and Exchange Protein Activated by cAMP (Epac2) are activated in pancreatic β-cells when cAMP levels are raised. By improving glucose metabolism, these downstream effectors cause β-cell depolarization, KATP channel closure, Ca2+ ion inflow, and eventually the glucose-dependent exocytosis of insulin granules. Ex-4 has been demonstrated to primarily increase Ca2+ signaling during β-cell network activation and activity [5]
- **Cellular Survival and Proliferation:** Ex-4's signaling cascade also activates the PI3K/Akt pathway, which is essential for β-cell mass enhancement, apoptosis inhibition, and proliferation promotion. This process is essential for T2DM patients to regain β-cell activity [6]

The Neuro-Metabolic Link in Alzheimer's Disease

The most prevalent cause of dementia is Alzheimer's disease (AD), which poses a significant and expanding global public health concern. The extracellular buildup of amyloid-beta (Aβ) plaques and the intracellular buildup of hyperphosphorylated tau that forms neurofibrillary tangles are the traditional pathological features of AD. Due to severe cerebral insulin resistance and impaired glucose metabolism, AD is increasingly understood to have a significant metabolic component, commonly known as "Type 3 diabetes." [7].

There is a class of medications known as glucagon-like peptide-1 receptor agonists (GLP-1RAs), which includes Exendin-4 (Ex-4, or Exenatide), this class is effectively used to treat type 2 diabetes. Ex-4 is an incretin mimetic that functions as a strong and persistent agonist of the GLP-1 receptor (GLP-1R). It was first isolated from the venom of the Gila monster. Crucially, Ex-4 has been demonstrated to penetrate the blood-brain barrier, and GLP-1Rs are extensively expressed in important brain areas implicated in memory and learning, particularly the cortex and hippocampus. Ex-4 is a strong contender for repurposing as an AD treatment due to the combination of AD pathology with compromised cerebral insulin signaling and the proven pleiotropic effects of GLP-1RAs. [7,8].

Preclinical Evidence: Mechanisms of Neuroprotection

A large body of *in vitro* and *in vivo* studies, primarily using rodent models of AD, supports the neuroprotective potential of Ex-4. These studies demonstrate that Ex-4 directly intervenes in multiple pathological pathways characteristic of AD:

Modulation of Amyloid and Tau Pathology

Ex-4 has been demonstrated to lessen the toxicity and deposition of (Aβ). Ex-4 therapies can lessen (Aβ)-induced memory and spatial learning deficits in cellular and animal models [7]. Mechanistically, this effect is associated with increased synaptic plasticity and decreased (Aβ) oligomerization. Additionally, in the hippocampus of diabetic rat models, Ex-4 has been shown to decrease AD-associated tau hyper phosphorylation, especially at locations crucial for tangle formation. Key kinases are thought to be modulated in this way, including decreased activity of glycogen synthase kinase, a major tau-

phosphorylating enzyme, and increased activity of phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) [9].

Anti-inflammatory and Anti-Oxidative Effects

The development of AD is characterized by oxidative stress and chronic neuroinflammation, which is fueled by activated microglia and astrocytes. Ex-4 has strong anti-inflammatory qualities that make the neuronal microenvironment less harmful by inhibiting microglia activation and lowering the release of pro-inflammatory cytokines. Furthermore, Ex-4 strengthens anti-oxidative pathways that directly combat the harmful effects of reactive oxygen species (ROS), including thioredoxin reductase and glutathione peroxidase [10].

Promotion of Neuronal Survival and Synaptogenesis

Ex-4 has been demonstrated to protect against neuronal death and apoptosis in rat models of sporadic Alzheimer-like illness, as seen by lower levels of cleaved caspase-3 in hippocampus areas. Ex-4 may also have the ability to boost brain repair and connection in addition to protecting existing neurons by promoting cell proliferation (neurogenesis) and improving synaptogenesis. These effects are frequently associated with the activation of downstream signaling pathways, such as the brain-derived neurotrophic factor (BDNF) cascades and the cAMP response element-binding protein (CREB) [8].

Clinical Translation: Human Trials of Exendin-4 in AD

The compelling preclinical data paved the way for testing Ex-4 in human clinical trials for AD and MCI.

Completed Pilot and Phase 2 Trials

One notable pilot Phase II double-blind, randomized, placebo-controlled clinical study was conducted to assess the safety and preliminary evidence of Ex-4 in individuals with amnestic MCI or early. The study involved 27 participants randomized to receive Ex-4 (up to 10 μg) or placebo twice daily for 18 months, in addition to their standard AD medication [8].

Key Findings from Pilot Stud

- **Safety and Tolerability:** Ex-4 was generally safe and well-tolerated, with an expected increase in gastrointestinal side effects such as nausea and decreased appetite
- **Cognitive and Clinical Outcomes:** The study showed no significant differences or trends between the Ex-4 and placebo groups across major clinical and cognitive measures, including the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-cognitive Subscale (ADAS-Cog)
- **Biomarkers:** While cerebrospinal fluid (CSF) and plasma biomarkers (Aβ) and tau showed nonsignificant change,Ex−4treatmentresultedinareductionof (Aβ) levels in plasma neuronal extracellular vesicles (EVs). This finding, although needing validation, suggests a possible biological effect on amyloid processing in the brain that may not be captured by traditional CSF/plasma measures. The study was, however, underpowered due to early termination, preventing firm conclusions on efficacy

Other GLP-1RA Trials and Implications for Ex-4

Although the results of Ex-4 trials in AD have been conflicting, research on the larger class of GLP-1RAs is still ongoing. Additionally, there was no overall positive impact on cognitive function in a 32-week proof-of-concept study that used the long-acting formulation of Exenatide (slow-release Ex-4, 2 mg once-weekly) in patients with MCI. It's interesting that this study found a gender-based interaction, with women randomized to Ex-4 experiencing a decline in their ADAS-Cog score. However, it's important to exercise caution when interpreting this single finding [11].

The results are in opposition to certain observational data. Exenatide use was linked to a lower incidence of AD when compared to non-users, according to a retrospective cohort analysis of Medicare beneficiaries with type 2 diabetes. This suggests that exenatide may have a long-term protective effect, especially in the T2DM group [12]. Different drug pharmacokinetics (ability to cross the blood-brain barrier), treatment duration, cohort stage (MCI vs. late-stage AD), and the presence of underlying metabolic disorders (T2DM/obesity) may all have a significant impact on outcomes, according to the inconsistent results across GLP-1RA trials, including those involving liraglutide and semaglutide [8,11].

Discussion and Future Directions

Ex-4's transformation from a diabetes treatment to a possible AD treatment demonstrates the paradigm shift in approach to treating metabolic dysfunction in neurodegeneration. There is strong and very encouraging preclinical evidence for its multi-target action, which includes amyloid, tau, inflammation, and neuronal survival.

A key obstacle, though, is the conflicting and mostly insignificant results from the early, smaller clinical trials of Ex-4 in MCI and early AD. The discrepancy between preclinical success and clinical outcomes could be caused by a number of variables:

- **Stage of Disease:** Neuroprotective agents are hypothesized to be most effective during the very early or pre-symptomatic stages of AD, before extensive neuronal loss has occurred. The cohorts in the completed Ex-4 trials, despite being "early-stage," may have already had irreversible brain damage
- **Trial Power and Duration:** The pilot studies were small and, in one case, prematurely terminated, limiting the statistical power to detect subtle but clinically meaningful effects over the relatively short trial period (18 months) for a slow-progressing disease

- **Dose and Formulation:** Optimization of dose and the selection of the most effective GLP-1RA formulation (e.g., long-acting once-weekly vs. twice-daily) for brain penetration and sustained target engagement are ongoing areas of refinement [11]

Larger, longer-term clinical trials concentrating on particular, at-risk populations are probably going to define the future clinical utility of Ex-4 and other GLP-1RAs in AD. The likelihood of success may be boosted by focusing on people with pre-symptomatic or pre-MCI phases, those with existing type 2 Diabetes, or obese people who are at a higher risk for AD [12]. Additionally, a possible avenue for advancement is the creation of new GLP-1R agonists or dual/triple agonists, which combine GLP-1R with additional incretin receptors, such as GIPR, and provide better CNS penetration and stability. Despite the absence of cognitive effect, the pilot study's positive biomarker signal of decreased (Aβ) in neuronal EVs emphasizes the significance of using sensitive, disease-modifying biomarkers in subsequent studies.

CONCLUSION

Exendin-4 remains a compelling molecule in the landscape of AD research due to its multifaceted neuroprotective mechanisms. It is still a fascinating molecule in the study of AD because of its several mechanisms of actions, which have been demonstrated in preclinical models. Despite the lack of conclusive evidence of cognitive benefit in early AD/MCI, limited clinical trials have confirmed the medication's safety profile in this cohort and generated encouraging biomarker data. The therapeutic application of Ex-4 in Alzheimer's disorders will need the successful completion of meticulously designed, adequately powered, longer-duration trials that focus on appropriate patient populations and incorporate sensitive, disease-modifying endpoints. For pharmacological repurposing, Ex-4 and the entire class of GLP-1RAs continue to be a primary goal in order to address the debilitating issue of Alzheimer's disease.

Conflicts of Interest

The authors declare no conflict of interest.

Data Availability

The data are available upon request.

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