GLP-1 RECEPTOR AGONISTS: A POTENTIAL TREATMENT FOR AUD

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ABSTRACT
Alcohol use disorder (AUD) is a chronic substance use disorder characterized by uncontrolled alcohol consumption. According to the National Institute on Alcohol Abuse and Alcoholism, it affects roughly 28.9 million people in the US (2024) and was linked to 2.6 million preventable deaths worldwide in 2019 (World Health Organization, 2024). One major roadblock in treating AUD is the limited availability of prescribable medications—only three are currently approved in the United States. Consequently, a major focus of current research is finding suitable therapeutic agents. Recent clinical studies suggest GLP-1 receptor agonists (GLP-1 RAs), which are normally used to treat Type 2 diabetes, may be potential candidates.

WHAT IS GLP-1?

Glucagon-like peptide-1 (GLP-1) is a peptide hormone vital to regulating energy homeostasis in humans. Derived from proglucagon, GLP-1 is secreted in response to food consumption. It binds to a G-protein coupled receptor called GLP-1R. This triggers a signaling pathway which leads to an increase in an intracellular second messenger molecule known as cAMP, resulting in a variety of downstream effects including regulation of insulin secretion, glucagon secretion, and proliferation of pancreatic β cells (Zheng et al., 2024). Essentially, these changes lead to decreased levels of glucose in the blood, feelings of "fullness," and slowed digestion.

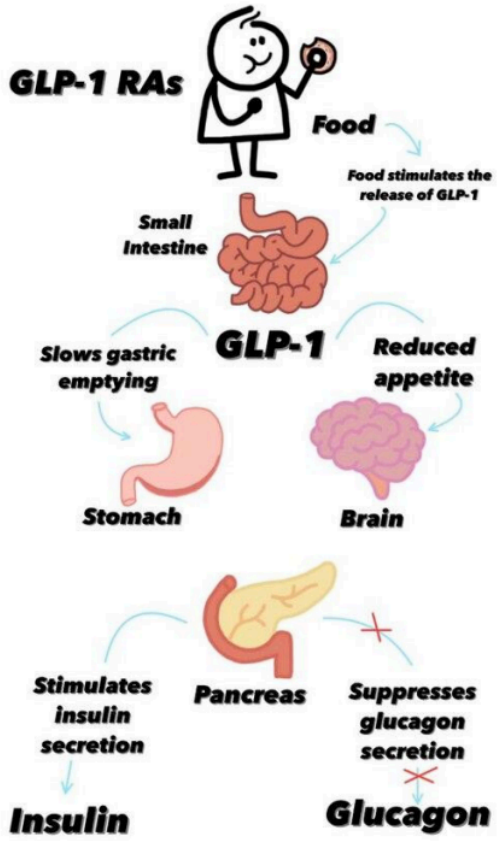

Figure 1: A diagram summarizing the process through which GLP-1 modulates hunger and digestion, which involves several different pathways in different areas of the body (Myluckynumber7, 2024)

GLP-1 RECEPTOR AGONISTS REDUCE ALCOHOL CRAVINGS

A recent randomized clinical trial showed that patients with AUD who were treated with low doses of semaglutide, a GLP-1 receptor agonist, experienced significantly reduced weekly alcohol cravings (Hendershot et al., 2025). GLP-1 receptor agonists are structurally modified versions of naturally produced GLP-1. Changes to specific amino acids in human GLP-1 endow these synthetic peptides with a variety of advantages, including less susceptibility to degradation by dipeptidyl-peptidase-4, which typically breaks down GLP-1, leading to longer-lasting effects (Zheng et al., 2024). These drugs have conventionally been used to treat type 2 diabetes due to their stronger ability to modulate hunger and blood-glucose levels compared to naturally produced GLP-1. This clinical study underscores other preclinical and observational studies which suggest GLP-1 plays an important role in regulating dopamine homeostasis in response to nutrient consumption. Multiple studies have shown that both systemically and locally administered GLP-1RAs can reduce the dopamine release triggered by alcohol in the nucleus accumbens region of the brain, which is part of the reward system neural circuitry (Vallöf et al., 2015; Egecioglu et al., 2013).

MECHANISTIC THEORIES AND A PROMISING OUTLOOK

However, the precise mechanism of how GLP-1RAs modulate the reward system is still under investigation. One theory is that GLP-1RA stimulation may lead to increased expression of dopamine transporter (DAT) in the brain, which has been tested in rodents (Reddy, 2016). Dopamine transporter is a protein which essentially promotes the reuptake of dopamine back into the neuron from which it was secreted. So far, there has been conflicting evidence to support this theory, with a few studies finding no such effect (Fortin, 2017). Other theories suggest presynaptic and postsynaptic mechanisms are both involved in the role of GLP-1 in the reward system (Kruse Klausen et al., 2022). Despite the uncertainty of how GLP-1 may modulate the reward system, there is increasing interest in adapting current GLP-1RAs to help treat substance use disorders, and several more clinical studies are underway which hope to assess patient outcomes. Much of the GLP-1RA discussion to this date has centered around their ability to treat type 2 diabetes, but these emerging discoveries could potentially lead to the development of a powerful tool to treat AUD.

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