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Incretin Mimetics (GLP-1 Agonists) as an Addition to the Psychopharmacology Armamentarium

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ABSTRACT *~ The exploration of GLP-1 receptor agonists as pleiotropic agents in the treatment of neuropsychiatric disorders and substance use disorders is a rapidly evolving field. While early studies have shown promising results, much of the research is still nascent, and larger clinical trials are definitely needed to confirm the safety and efficacy of these agents on real grounds.* Psychopharmacology Bulletin. *2025;55(3):26–30.*

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) has been extensively studied for its role in glucose homeostasis and its therapeutic applications in type 2 diabetes. GLP-1 is a hormone released from the gut (mostly small intestine) after eating to decrease blood glucose by several mechanisms. GLP-1 is an incretin, i.e. hormone that increases insulin secretion. GLP-1 is not the only incretin, but it constitutes > 90% of all endogenous incretin function. Of note, GLP-1 and glucagon serve *opposite* functions.

GLP-1 action on target tissues involve-delayed gastric emptying (stomach), decreased gluconeogenesis (liver), increased insulin secretion and decreased glucagon secretion (pancreas), increased insulin sensitivity (muscles), cardioprotection (heart), and, decreased appetite, behavioral change, and neuroprotection (brain).

GLP-1 receptor agonists (GLP-1 RA), or GLP analogs, or incretin mimetics, include, inter alia, liraglutide (Saxenda®), semaglutide (Ozempic®), exenatide (Byetta®), and the twincretin agonist of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) tirzepatide (Mounjaro®).

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The Approval of GLP-1 receptor agonists for treatment of diabetes underscores the clinical significance of these incretin effects.[1]

Gastrointestinal side effects with GLP analogs are common. Rarely, these drugs may be associated with acute pancreatitis or cholelithiasis. Serious hypersensitivity reactions such as anaphylaxis and angioedema have occurred.

Thyroid tumors have been reported in rodents given GLP analogs and thyroid C-cell hyperplasia has been reported in humans.

Neuropsychiatric reactions have been reported with GLP analogs. A recent study should a significant association between GLP-1 RA treatment and a 98% increased risk of any psychiatric disorders. Notably, patients on GLP-1 RAs exhibited a 195% higher risk of major depression, a 108% increased risk for anxiety and a 106% elevated risk for suicidal behaviour.[2]

Anorexigenic Properties and Weight Management

Another significant feature of GLP-1 is its anorexigenic properties. Activation of GLP-1R has been shown to reduce both homeostatic and hedonic feeding, subsequently decreasing appetite. Given that some GLP-1R agonists also contribute to weight reduction, they have been approved for treating obesity.[3]

GLP 1 RA and Psychotropic-Related Weight Gain/Metabolic Syndrome

Psychotropic drug–related weight gain, defined by FDA as > 7% increase from baseline, is pretty common , highly associated with treatment non-adherence and intersects with the elevated risk for obesity and associated morbidity that has been amply reported in the psychiatric population. Evidence indicates that differential liability exists for antipsychotics, antidepressants, and anticonvulsants. Lifestyle, excercise and dietary modifications should be first-line. Metformin is the most studied pharmacological treatment in the prevention and treatment of psychotropic-related weight gain[4] with promising data are emerging for glucagon-like peptide-1 (GLP-1) receptor agonists.

A recent systematic review provided evidence suggesting that GLP-1RAs are effective in mitigating weight gain in persons prescribed psychiatric medication. It is hypothesized that GLP-1RAs may moderate weight change in persons prescribed psychiatric medication through direct effects on metabolism and cognitive processes implicated in hunger/satiety. The most studied agents were liraglutide and exenatide.[5]

Broader Physiological and Behavioral Effects

Beyond glucose regulation and appetite suppression, GLP-1 influences gastric emptying, cardiac functions, and various brain-related behaviors, such as reward, emotion, motivation, and learning. These broad effects highlight the peptide's complex physiological roles and potential therapeutic applications.[6]

GLP-1 and the Gut–Brain Axis

Recent attention has focused on the gut-brain axis, where GLP-1 plays a central role among numerous peptides. GLP-1 is critical for reducing food intake and body weight, maintaining glucose homeostasis, regulating gastrointestinal motility, and modulating insulin and glucagon release. Acute or repeated treatment with GLP-1R agonists has been shown to decrease alcohol consumption in rodents, suppress alcohol-induced hyperlocomotion, and reduce dopamine release in the nucleus accumbens, thereby affecting reward and alcohol-seeking behaviors.[7]

GLP-1 Pathway in Alcohol Use Disorder (AUD)

Preclinical studies suggest that GLP-1R activation reduces the motivation to consume alcohol, diminishes alcohol-seeking behaviors, and alleviates withdrawal symptoms. These effects are observed in brain areas processing reward, such as the nucleus of the solitary tract, where GLP-1 is produced and projects to reward-related regions. Polymorphisms in GLP-1-related genes may be associated with AUD, and GLP-1R agonists have shown promise in reducing alcohol consumption in a sub-population of obese AUD patients.

Broader Implications for Addiction

GLP-1R agonists have also demonstrated modulatory effects on responses to other addictive substances, such as nicotine, opioids, amphetamine, and cocaine.[8] For instance, GLP-1R activation blocks nicotine-induced activation of the mesolimbic dopamine system and reduces nicotine intake in animal models. Similarly, GLP-1R agonists influence the behavioral responses to opioids, although the effects vary across different opioids.

The clinical potential of GLP-1R agonists in addiction medicine is underscored by their ability to modulate both behavioral and neurochemical responses to addictive substances. Future research should focus on distinguishing the central versus peripheral actions of GLP-1,

exploring its effects in various brain regions, and understanding the impact of different GLP-1R agonists on drug and alcohol-related responses. Given the complexity of addiction, further studies are needed to elucidate the specific roles of GLP-1 and its receptors in both preclinical and clinical settings.

As such, GLP-1 and its receptor agonists represent a promising avenue for treating addiction and related disorders. Their multifaceted physiological roles and effects on the gut-brain axis, reward pathways, and ingestive behaviors highlight their potential in addressing the complex mechanisms underlying addiction.

GLP 1RA for Mood and Anxiety Disorders

Preclinical studies have provided preliminary evidence of GLP-1 RAs' antidepressant and anxiolytic properties. Animal models have demonstrated that GLP-1 receptor activation promotes neurogenesis, enhances synaptic plasticity, and modulates stress response pathways in mood disorders.Furthermore, GLP-1 RAs have been shown to attenuate neuroinflammation and oxidative stress, processes implicated in the pathophysiology of depression and anxiety.

Human trials have also yielded promising results, with several clinical studies reporting improvements in depressive symptoms following treatment with GLP-RAs In a recent systematic review and meta-analysis,[9] adults treated with GLP-1RAs showed significant reductions in the depression rating scale scores compared to those treated with control. Moreover, preliminary evidence suggests potential benefits in conditions such as bipolar disorder and schizophrenia, hinting at the broad spectrum of psychiatric disorders that could potentially benefit from GLP-1-based interventions.[10]

GLP 1RA for Binge-Eating Disorder

Small pilot studies previously showed GLP-1RAs like liraglutide reduce binge eating, body weight, and comorbidities in binge eating disorder and bulimia nervosa. Mechanisms may involve effects on satiety signaling, food reward pathways, and brain areas mediating feeding behaviors. A recent systematic review[11] suggested larger placebo-controlled trials are needed to firmly establish efficacy and safety of GLP-1RAs for reducing binge eating as well as dosing studies required to optimize GLP-1RA therapy and comparisons to existing pharmacological options would clarify relative effectiveness.

GLP 1RA for Alzheimer's Disease

LP-1 mimetics exhibit neuroprotective effects by crossing the blood–brain barrier, reducing β-amyloid plaques, preventing synaptic loss, improving memory impairments, and decreasing oxidative stress and inflammation in the brain.[4] Preclinical research indicates that semaglutide exhibits potential in the treatment of Alzheimer's disease (AD) and Parkinson's disease (PD). The AD models demonstrate the restoration of cell viability, enhanced autophagy, and decreased apoptosis.[12] Multiple studies showed that liraglutide improved cognitive functions and MRI volume in patients with Alzheimer's disease.

Conclusion

The exploration of GLP-1 receptor agonists in the treatment of neuropsychiatric disorders and substance use disorders is a rapidly evolving field. While early studies have shown promising results, much of the research is still nascent, and larger clinical trials are definitely needed to confirm the safety and efficacy of these agents on clinical grounds. ✤

Disclosures

Authors have nothing to declare.

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