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GLP 1 RECEPTOR AGONISTS AND THEIR EFFECTS ON REWARD AND COMPULSIVE BEHAVIORS

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ABSTRACT

Background: Addiction and compulsive behaviors are widespread challenges that affect both individual and societal well-being. These behaviors involve persistent engagement in rewarding stimuli despite negative consequences. Glucagon-like peptide-1 (GLP-1) receptor agonists, initially developed for metabolic disorders, have been shown to modulate neural circuits involved in reward, motivation, and compulsive behavior.

Methods: To explore these questions, this review synthesizes evidence from animal studies, mechanistic neurobiological research, neuroimaging, and emerging human trials. The focus is on the effects of GLP-1 receptor activation on reward processing, motivation, and compulsive behaviors.

Results: Preclinical studies indicate that GLP-1 receptor agonists reduce drug- and food-related reward seeking, suppress relapse-like behavior, and modulate phasic dopamine signaling in mesolimbic circuits. Neurochemical and electrophysiological studies demonstrate coordinated activity between dopaminergic and inhibitory neurons. In humans, early trials suggest GLP-1 receptor agonists can reduce alcohol consumption and craving, and observational data hint at broader effects on other reward-related behaviors.

Conclusion: GLP-1 receptor signaling modulates central motivation and reduces maladaptive reward-seeking. These findings suggest GLP-1 receptor agonists have therapeutic potential for compulsive behaviors and addiction, relevant to behavioral science, psychiatry, and public health.

KEYWORDS

GLP-1 Receptor Agonists, Compulsive Behavior, Addiction, Dopamine, Motivation, Behavioral Neuroscience

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Introduction

Addiction and compulsive behaviors are characterized by persistent engagement in rewarding stimuli despite negative outcomes, diminished pleasure, or reduced goal relevance. These behaviors are associated with impaired behavioral flexibility, perseverative responding, and resistance to outcome devaluation. The societal burden of addiction includes health complications, economic costs, and impaired social functioning, highlighting the importance of identifying effective interventions [1–3].

At the neurobiological level, addiction reflects dysregulation of the mesolimbic dopamine system, a set of brain pathways that encode reward prediction, motivation, and the importance assigned to stimuli (salience). Traditional pharmacotherapies, treatments using drugs, often target withdrawal symptoms or specific substances and provide limited efficacy across a range of reward-seeking behaviors. There is, therefore, considerable interest in treatments that alter core brain circuits involved in compulsivity and reward processing.

Glucagon-like peptide-1 (GLP-1) is a hormone that regulates glucose levels in the body and influences appetite. In addition to its peripheral effects on glucose and appetite, GLP-1 acts centrally, with receptors in brain regions involved in reward. These regions include the ventral tegmental area (VTA, which produces dopamine and contributes to reward processing), the nucleus accumbens (NAc, involved in evaluating rewards), the lateral septum, the hypothalamus, the prefrontal cortex (involved in decision-making), the hippocampus, and the amygdala [4–6]. Activation of these receptors reduces food reward, diminishes drug-seeking, and modulates compulsive behavior. This suggests GLP-1 plays a broader role in controlling motivation and inhibitory control.

This review integrates evidence from animal studies, mechanistic research, and emerging human trials to provide a comprehensive overview of GLP-1 receptor agonists in the modulation of reward and compulsive behaviors. Building on the background outlined above, this work emphasizes neural mechanisms, translational implications and potential therapeutic applications.

Methods

We conducted a narrative review of literature published from 2010 to 2025. To ensure a comprehensive synthesis, we included preclinical rodent studies on self-administration, reinstatement, and binge-eating paradigms. We also included electrophysiological, neurochemical, and neuroimaging studies, as well as human clinical trials and observational studies. Inclusion criteria focused on studies of the effects of GLP-1 receptor agonists on reward-related behavior, motivation and compulsive actions. We synthesized evidence qualitatively to identify convergent findings and highlight translational relevance.

Central Distribution of GLP-1 Receptors

GLP-1 receptors are present throughout the brain, especially in regions involved in reward, motivation, and emotion, such as the ventral tegmental area (VTA), nucleus accumbens (NAc), lateral septum, hypothalamus, prefrontal cortex, hippocampus, and amygdala [4–6]. Most GLP-1–producing neurons originate in the nucleus tractus solitarius (NTS) and send projections to forebrain structures linked to reward [5,6].

Within the VTA, GLP-1 receptors are found on both dopamine-producing and other neurons, allowing the system to influence dopamine output in several ways [4,5].In the NAc, GLP-1 receptors can influence reward processing primarily by modulating dopaminergic inputs to medium spiny neurons [5,6]. Receptor expression in the lateral septum and hypothalamus also helps integrate signals about energy state, stress, and motivation, showing that GLP-1 links homeostatic needs with reward-driven behavior [6].

At the cellular level, GLP-1 receptors are G protein–coupled and mainly activate stimulatory Gs proteins, increasing intracellular cyclic AMP and triggering protein kinase A pathways [4]. These signals affect how neurons fire, release neurotransmitters, and regulate gene expression [4–6]. Studies in rodents show that activating GLP-1 receptors reduces burst firing of VTA dopamine neurons, partly via local GABAergic interneurons, which, in turn, lower dopamine release in the NAc during reward-seeking behaviors [9–11,14,15].

Importantly, GLP-1 signaling helps balance homeostatic and reward-driven control. By connecting hypothalamic appetite circuits with mesolimbic and cortical reward pathways, GLP-1 receptor activation promotes satiety and reduces the drive to pursue rewards [4–8]. Unlike many traditional addiction treatments, GLP-1 receptor agonists modulate the perceived value of rewards rather than merely decreasing consumption.

Results

Animal Studies

Rodent studies consistently show that GLP-1 receptor activation reduces both drug-seeking and consumption. When GLP-1 receptor agonists are administered systemically or directly into key brain regions such as the ventral tegmental area (VTA) or nucleus accumbens (NAc), animals consume less alcohol, cocaine, nicotine and opioids under standard self-administration schedules [7–12]. In tests in which animals must work harder to obtain the drug, such as progressive-ratio schedules, willingness to obtain the drug decreases, indicating reduced motivation for reward [11-12, 20].

Models of relapse simulate reinstatement of drug-seeking triggered by cues, stress, or small priming doses. These models show that GLP-1 receptor activation can suppress such behaviors across multiple substances [12, 13, 21]. Importantly, these effects persist even after controlling for general locomotor activity. This suggests a direct effect on the reward system, rather than on overall activity or nausea.

In addition to drug-related findings, GLP-1 receptor agonists also reduce maladaptive eating behaviors. In rodent models of binge eating, activation of GLP-1 receptors reduces consumption of highly palatable foods and attenuates repetitive, perseverative responses to food rewards [6, 8]. These findings indicate that GLP-1 signaling influences motivational drive, not just the act of consumption.

Mechanistic Evidence

Studies exploring the underlying neural mechanisms show that GLP-1 receptor activation dampens activity in mesolimbic dopamine circuits. Fast-scan cyclic voltammetry in the nucleus accumbens shows rapid decreases in phasic dopamine release during reward-seeking after receptor activation [14–16]. Fiber photometry confirms that dopamine signaling remains reduced over longer periods in freely moving animals. Simultaneous recordings reveal increased activity in inhibitory GABA neurons that regulate dopamine output [15, 16].

Electrophysiological recordings in live animals show lower burst firing of VTA dopamine neurons. This pattern is consistent with reduced reward signaling. In addition, imaging studies, including functional MRI, show decreased activity in the VTA, NAc, and prefrontal cortex following GLP-1 receptor activation. They also reveal changes in connectivity between these regions [17,18]. Together, these results suggest that GLP-1 receptors reduce the motivational value of rewards by balancing excitatory dopaminergic signals with inhibitory control.

Human Evidence

Early clinical studies support these preclinical findings. Randomized trials using semaglutide in people with alcohol use disorder report reductions in overall alcohol intake, number of heavy drinking days and craving compared to placebo [19]. Functional imaging studies show that GLP-1 receptor agonists decrease activation in reward-related brain regions in response to food or drug cues [17,18]. Observational data also suggest that patients taking GLP-1 receptor agonists for diabetes or obesity may experience reduced cravings and reward-driven behaviors. Further controlled studies are needed to confirm these effects.

Summary

In summary, across animal and human studies, GLP-1 receptor activation consistently reduces reward-seeking behaviors. In rodents, these effects include lower intake of drugs and palatable foods, reduced motivation for rewards, and suppression of relapse-like behavior. Mechanistic studies demonstrate that these behavioral changes are linked to the modulation of dopaminergic and inhibitory circuits. Early human studies align with preclinical results, suggesting that GLP-1 receptor agonists may provide a novel strategy for reducing compulsive reward-seeking behaviors.

Discussion

Our review highlights that GLP-1 receptor agonists consistently reduce reward-seeking behavior across species. In rodent models, these agents lower the consumption of drugs of abuse, decrease motivation to obtain rewards, and reduce relapse-like behaviors. Mechanistic studies indicate that these effects are mediated by modulation of dopaminergic and inhibitory circuits in the mesolimbic system, particularly in the VTA and nucleus accumbens. This suggests that GLP-1 signaling can recalibrate the neural circuits that drive compulsive reward-seeking.

Evidence from human studies, although still limited, supports the translational potential of these findings. Semaglutide has been shown to reduce alcohol intake and craving in individuals with alcohol use disorder. Functional imaging studies in humans demonstrate decreased activation of reward-related brain regions in response to food cues; evidence for effects on drug-related cues is emerging but remains preliminary. Together, preclinical and clinical data suggest that GLP-1 receptor agonists act on both the motivation to seek rewards and the hedonic value of those rewards.

These findings point to a broader role for GLP-1 signaling as a neuromodulator that integrates homeostatic and hedonic information. By reducing the incentive salience of rewards while promoting satiety and metabolic balance, GLP-1 receptor agonists offer a complementary approach to traditional addiction therapies, which often target specific neurotransmitter pathways or particular substance use disorders..

Despite these promising results, several questions remain. Long-term effects of GLP-1 receptor agonists on reward processing in humans are not well understood. Optimal dosing strategies, the duration of therapeutic effects, and efficacy across different types of addictive or compulsive behaviors require further investigation. Moreover, the relative contributions of direct central nervous system effects versus peripheral metabolic signals remain unclear. Continued research combining behavioral, neurochemical and neuroimaging approaches will be essential to establish causal links and guide clinical applications.

Conclusions

GLP-1 receptor agonists represent a promising class of compounds for reducing compulsive reward-seeking behavior. In preclinical studies, these agents lower the intake of drugs and palatable foods, reduce motivation for rewards, and attenuate relapse-like behavior. Mechanistic studies in rodents indicate that these effects are largely mediated by modulation of dopaminergic and GABAergic circuits within mesolimbic pathways. Early human evidence, although limited, aligns with these preclinical findings, suggesting potential clinical applications in substance use disorders and maladaptive reward-related behaviors.

Overall, GLP-1 receptor agonists offer a unique approach that targets both the motivational and hedonic components of reward. By modulating neural circuits that integrate homeostatic and reward-related signals, these agents bridge metabolic regulation and compulsive behaviors in a way distinct from conventional pharmacotherapies. With further research, GLP-1 receptor agonists may become a valuable addition to treatment strategies for addiction and other disorders characterized by maladaptive reward-seeking.

Conflict of Interest Statement: The authors declare no conflicts of interest.

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