Reshaping the Neural Architecture of Hunger

The Role of a GLP-1 Receptor Agonist

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Image courtesy of Getty Images, as featured in Young (2025).

Introduction

The World Health Organization reports that obesity rates have doubled in adults and quadrupled in adolescents over the last thirty years, and with obesity rates steadily rising immediate remedies to this global crisis have never been more urgent (Fasano, 2025). Yet since 2020, prescriptions for glucagon-like peptide-1 (GLP-1) receptor agonists, what many are calling the miracle drug for weight loss, have more than tripled, with approximately 11.8% of Americans reporting use of some form of GLP-1–based therapy (Bozick et al., 2025). These synthetic agents mimic the body's natural GLP-1 hormone, allowing them to bind to the same receptors and replicate its regulatory functions. Their easy access, self-moderated application, and efficient mass reduction makes losing weight feel effortless. Clinical trials have further demonstrated significant weight loss and cardiovascular benefits, and future directions show growing interest in applications for substance use disorders (Amorim et al., 2025).

However, as GLP-1 therapies continue to hit the market, conflicting information spreads alongside ongoing research, revealing just how much we have yet to uncover about GLP-1's actions and its long term effects. GLP-1 cells found in the brain, gut and nervous system all work together to reshape individuals' appetite, body weight, and regulatory processes. Utilizing an intricate signaling cascade, natural GLP-1 activates neural signals controlling motivation or suppression of hunger in the hypothalamus, and ultimately influences important neural pathways throughout the body. Examining not just GLP-1 receptor agonists' metabolic impact, but also its ability to modulate neural circuits that govern appetite and motivation, reveals potential long-term neuromodulatory consequences of chronically altering the brain's regulatory systems.

The Evolutionary Architecture of Hunger

Hunger is an adaptive, layered system evolutionarily conserved to optimize survival in energy-scarce environments (Lea et al., 2023). However, the emergence of agricultural farming and industrialization provided a solution to what once threatened our survival. Now, with overwhelming availability of food and little cost expended to acquire food, we are confronted with an evolutionary mismatch between our evolved biology and current environment (Ayyad, 2026). Humans must manage a system that persistently drives food intake even when energy needs are met.

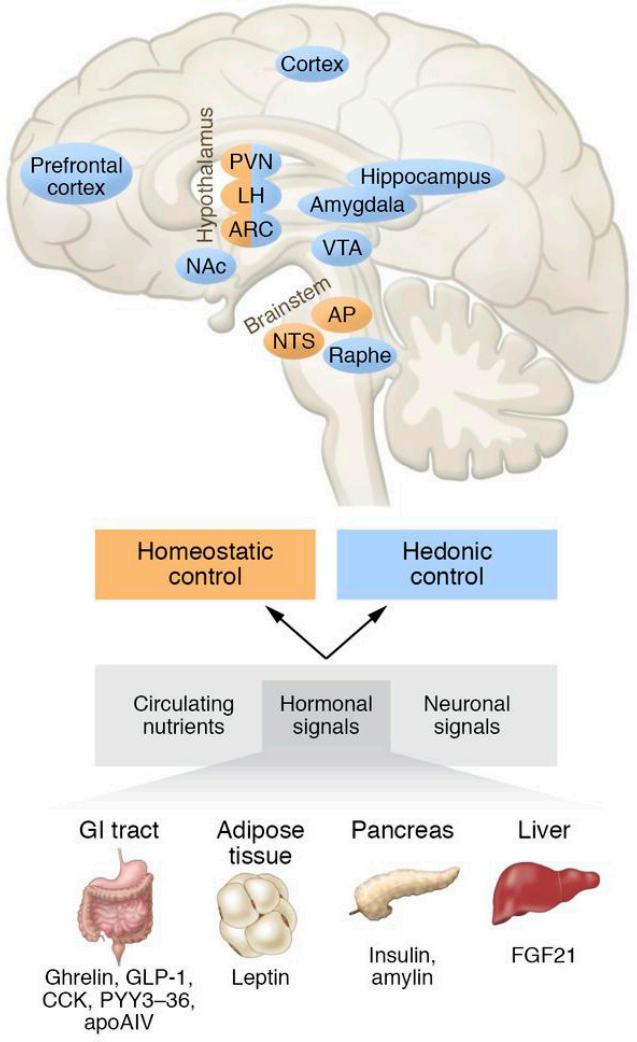


Figure 1. Key systems in appetite signaling. In orange is the homeostatic system, where physiological signals from vital organs send hunger level cues. In blue is the hedonic system that serves as a connection to reward centers responsible for food motivation (Stemmer et al., 2019).

Similar to other systems such as the visual and olfactory systems, hunger uses a form of parallel processing where multiple pathways can be activated simultaneously to create a unified response for addressing hunger signals. Our hedonic system influences

the psychological factors of appetite processing (Fig.1). It is responsible for regulating our motivations towards food signals, and the gratification of eating. Feelings of temptation or desire are governed by this system, both due to the abundance of highly saturated food, but also because of the presence of dopamine signaling, which amplifies the pleasure and incentive value of food (Kinasz et al., 2017).

This system is counterbalanced by our homeostatic system that activates based on physiological signals, relying on metabolic cues to trigger a response (Fig. 1). When someone experiences hunger, ghrelin hormone signals are activated from the gut and travel through the endocrine system to alert the body that it requires food (Fasano, 2025). Simultaneously, agouti-related peptide (AgRP) neurons, which strongly promote food consumption, respond to this energy deficit by expressing a persistent signal to seek out immediate sustenance (Chen et al., 2016).

Together, these primal systems drive food-seeking behavior and support the body's ability to restore nutritional balance. Yet, in the modern day, our psychological needs can override our physiological state due to constant food cues from endless food advertisements, or the oversaturation of fast food establishments. Together these low cost, high reward options prevent clear distinctions between hunger and satiety (Fasano, 2025). As a result, homeostatic signaling may remain chronically active or dysregulated, further contributing to excessive intake. Prolonged imbalance of hunger signals causes the body to become defensive of vital organs such as the heart and the brain. (Kim et al., 2025; Fasano, 2025).

Recognizing hunger as a tightly regulated system designed to resist energy deficits demonstrates its evolutionary complexity and reveals how clearly tied it is to our survival. Pharmacological suppression of GLP-1 receptor agonists intervene directly within this naturally selected arrangement, and present the potential to not simply correct a seemingly dysfunctional system, but rather intervene in regulatory systems meant to maintain internal balance. If these signals are chronically dampened, their long-term influence may extend beyond appetite reduction and into the broader scheme of human energy regulation.

Pharmacokinetics and GLP-1 Mechanism

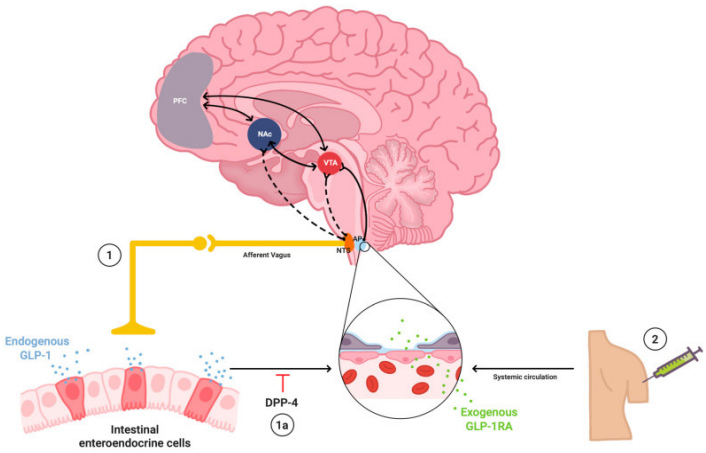


Figure 2. Endogenous GLP-1 is secreted in the body and is inhibited by DPP-4 (Amorim et al., 2025).

As part of this evolutionarily conserved architecture, satiety signals are designed to be brief and tightly regulated, preventing prolonged suppression of this critical system. Availability of endogenous GLP-1 is important for ensuring adequate regulation of blood sugar, and with a half-life of one to two minutes, approximately 10-20% of naturally produced GLP-1 is available for use (Peri et al., 2025). Hence, GLP-1 agonists' prolonged activation overcompensates for natural GLP-1's succinct signaling mechanism by elevating GLP-1 concentration.

Researchers have attempted to directly block GLP-1 inhibitor dipeptidyl peptidase-4 (DPP-4) as a manner to elevate GLP-1 concentration, but this has resulted in only a modest increase in GLP-1. This is caused by DPP-4 inhibition relying on meal-stimulated hormone release, but due to low baseline levels of natural GLP-1 in the body, inhibiting only results in minimal increase of GLP-1 concentration even when unsuppressed (Gilbert, 2020). For that reason, therapeutic GLP-1 receptor agonists today are structurally engineered to resist degradation and act independently of endogenous GLP-1 secretion (Fig. 2).

The development of these long lasting receptors is derived from the saliva of the Gila monster lizard, which contains a protein structurally analogous to GLP-1 (Deane et al., 2010). By synthetically replicating the venom, GLP-1 is modified from its intermittent signaling to produce prolonged receptor activation extending signaling from minutes to hours or even days. At the molecular level, this prolonged response prevents satiety signals from being turned off, causing meal-triggered GLP-1 responses to be stacked upon each other. At the physiological level, this sustained response dulls intracellular machinery that processes "I am eating" signals, and as a result fundamentally alters modulatory signaling of both blood sugar and hunger signaling (Gilbert, 2020).

Yet, with prolonged activation comes a shift in the appetite regulation system. Calcium signaling, essential for insulin secretion and metabolic balance, is disrupted by the active GLP-1 signal mimicked by the receptor agonist. This disruption consequently affects the signaling cascade in charge of indicating hunger or satiety (Kim et al., 2025). Under natural signaling, food is processed in short bursts as the meal gets digested, hence why we often feel full mid-meal, but hungry again within a few hours. However, with prolonged receptor engagement, signals from intracellular messengers are extended beyond their typical duration, and result in repeated activation of pathways that present a sense of fullness to the individual (Peri et al., 2025). It is precisely this shift from pulsed to sustained signaling that positions GLP-1 receptor agonists not just as metabolic regulators, but as key neurological moderators of appetite and reward processing.

Neuromodulation and Reward Pathways

Furthermore, the extended signaling of GLP-1 receptor agonists can influence more than just the intracellular processing of hunger, but neural pathways beyond appetite regulation alone. Through activation of established hunger pathways, coupled with prolonged signaling, GLP-1 receptor agonists can influence neuromodulation of reward circuits, and intervene directly in the brain's reward system to alter how motivation is processed. The mesocorticolimbic dopamine system is the brain's primary reward circuit network responsible for gratification, motivation, and in some cases, addiction. It comprises

the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC) (Amorim et al., 2025). Both receptors and GLP-1 producing neurons appear in these regions of the brain, which positions GLP-1 to be highly influential over motivational aspects of feeding (Mietlicki-Baase, 2014).

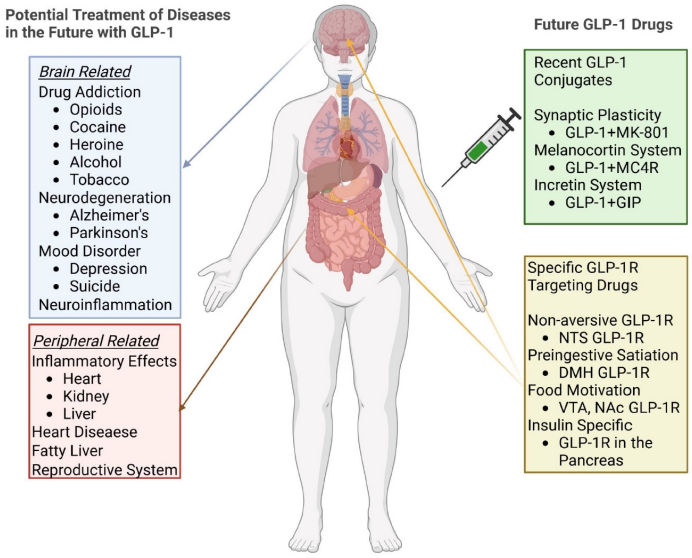


Figure 3. The potential applications of GLP-1 to medical treatments beyond diabetes and weight loss (Kim et al., 2025).

The hedonic system, our evolutionarily established system for reward signaling, functions as a component of the larger mesolimbic system that regulates reward. The hedonic pathways serve as the behavioral output of food motivation, while the mesocorticolimbic system expresses the biological mechanism underlying our behavioral drive to seek and consume it (Amorim et al., 2025; Fasano, 2025). To better understand the function of reward circuits and desire-seeking behavior induced by GLP-1, researchers tested rats' behavioral response to blocking GLP-1. In one experiment, rats learned to associate a location with a reward, yet after GLP-1 administration, they lost preference for that location, not because of forgotten association, but reduced motivation. Similarly, rats that had previously worked for rewards by pressing a lever showed no interest in doing so following GLP-1 suppression (Dickson et al., 2012). These studies offer insight into how motivational and hedonic values are transformed by GLP-1 blocking.

Previously, scientists believed dopamine signaling was the strongest explanation for reward modulation, associating increased levels of dopamine with higher levels of motivation (Alhadeff et al., 2012). However, emerging models suggest that manipulating the signaling of glutamate, the brain's primary excitatory neurotransmitter, may play a key role in motivation processing. With GLP-1 receptors positioned in the VTA, NAc, and PFC, their activation stimulates presynaptic glutamate neurons, increasing glutamate release. These elevated glutamate levels then signal target neurons, particularly medium spiny neurons in the NAc, which integrate incoming signals to determine behavioral responses (Mietlicki-Baase, 2014). This suggests that while dopamine signaling explains how motivation levels increase or decrease, glutamate signaling demonstrates how motivation is evaluated and ultimately shapes goal-guided behavior.

This proposed model is particularly relevant in the context of addiction, as the same mesolimbic circuits that govern food-related reward also underlie substance-seeking behavior. Through glutamate mediated signaling, GLP-1 receptor agonists can expand the modulation of reward circuits, and extend signaling to the regions of the brain responsible for emotional processing and decision making. These regions intersect in hunger signaling through the gut-brain axis, which is a bidirectional system capable of regulating mood, motivation and reward seeking behavior via endocrine, neural, and immune pathways (Kinasz et al., 2017).

This broader neuromodulatory capacity has also opened avenues for exploring GLP-1's role in pain regulation. The dorsal horn acts as an initial relay center that determines how strongly pain signals are transmitted to the brain. Alterations in spinal excitatory synaptic transmission can therefore modify pain communication. Across species, pain levels are reduced after eating, and researchers have tried to explain this phenomenon with GLP-1 processing (Go et al., 2024). Studies in rats reveal that GLP-1 can attach to TRPV1 pain receptors, directly influencing the threshold at which the nervous system registers pain and discomfort. These synthetic agonists reduce excess excitation in the horn, thereby dampening the intensity of pain signals (Go et al., 2024).

Together, these findings point to a broader role for GLP-1 as a regulator of neural excitability across multiple systems involved in motivation, reward, and sensory experience. GLP-1's ability to simultaneously influence reward circuits, appetite pathways, and pain thresholds suggests that it is more than just a regulator for blood sugar, but also a multipurpose hormone with the potential of addressing more than just weight management, but chronic migraines, and addiction recovery (Go et al., 2024; Mietlicki-Baase, 2014).

Conclusion

GLP-1 signaling is tightly connected to the neural circuits that influence both metabolism and motivation, and the neuromodulatory effects of controlling this system requires further exploration. Its ability to effectively suppress hunger and assist with appetite regulation has increased its public standing as a strong weight loss therapeutic. GLP-1's presence within reward pathways, neurotransmitter signaling, and pain thresholds reflects how deeply integrated this hormone is within the body. GLP-1 receptor agonists alter this evolutionary stable system by dampening endogenous signaling with prolonged activation, and disrupting modulation of key reward centers.

As research continues to expand the therapeutic scope of GLP-1 receptor agonists, the methods of application used to administer the drug should adapt alongside it. Currently, GLP-1 receptor agonists extended activation provides the body with suppression of neural circuits, but ultimately returns back to its regular mechanism when treatment is halted. Therefore, people are obligated to take repeated dosages of GLP-1 receptor agonists at stronger concentrations without the system being corrected (Deane et al., 2010). Given the limited amount of present data on this rather novel drug, a growing list of common physiological side-effects is emerging under this current method.

Developing future approaches that avoid prolonged and ramped dosages, reduce indefinite suppression of the system, and recalibrate its relationship with metabolism and reward may be the first step towards reshaping our neural architecture of hunger.

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