

Are glucagon-like peptide-1 receptor agonists anti-consummatory drugs?

Perspective

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Abstract

Incretin-based treatments, such as glucagon-like peptide-1 receptor (GLP-1R) agonists (eg liraglutide and semaglutide), have rapidly transformed obesity treatment. The well-documented weight loss effect from these agents is considered to be primarily a result of their actions on food intake, but frequent anecdotal reports from varied sources have suggested that they might also broadly affect consummatory behavior, including alcohol and drugs of abuse, suggesting a potential modulatory effect on reward behavior. Herein, we critically review the extant literature on the behavioral effects of GLP-1R agonists in humans, including their impact on feeding behavior, alcohol/drug intake, and overall reward response. We also consider the physiological and neurobiological underpinnings of GLP-1 actions, with a focus on its distinct central and peripheral roles, as well as its relationships with the broader energy homeostasis network. We conclude with a discussion on the implications of this line of research on how behavior is conceptualized, and the potential future directions for research.

Highlights

- GLP-1R agonists promote weight loss through their effect on feeding behavior
- An overall modulatory effect of these agents on reward behavior has been proposed
- However, the evidence supporting this hypothesis in humans is very limited
- Metabolic signals, such as GLP-1, are known to modulate the reward neural circuits
- Better understanding of the brain–body connection can offer novel insights into behavior

Introduction

There has been increasing interest and speculation on the potential behavioral effects of incretin-based pharmacological agents. Glucagon-like peptide-1 receptor (GLP-1R) agonists (eg liraglutide and semaglutide) and the newer glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1R dual agonists (eg tirzepatide) are highly effective at reducing body weight.^{1–3} These agents have revolutionized obesity treatment, for individuals with or without type 2 diabetes mellitus (T2DM), and have been increasingly utilized off-label for a variety of conditions.⁴ The mechanisms underlying the weight loss effects of incretin-based treatments are incompletely understood, however, a reduction in food consumption has been consistently reported.^{5–8} Anecdotal reports from patients, healthcare providers, media, and scientific publications have also suggested that these agents might have overall anti-consummatory effects. Dual and GLP-1R agonists have been reported to reduce the intake of alcohol, tobacco, cannabis, cocaine, and opioids,⁹ as well as mitigate a range of addictive/compulsive behaviors, including shopping and hair-pulling.¹⁰ A number of clinical trials are currently underway to evaluate the efficacy of incretin-based agents for substance use disorders. As the best of our knowledge on these drugs rapidly evolves, what is actually known about the effects of GLP-1R agonists on behavior, and what does it tell us about its nature?

GLP-1 receptor agonists and behavior

The most robustly documented effect of incretin-based treatments is a sustained reduction in body weight. Weight loss is achieved when energy expenditure exceeds energy intake, that is a state of negative energy balance.¹¹ Any biological, behavioral, or environmental factor that affects body weight necessarily acts through one or more components of energy balance.¹¹ In humans, GLP-1 receptor agonists have been associated with neutral to negative effects on energy

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expenditure, including in volitional physical activity, thus it is likely that a decrease in caloric intake is the main driver of the negative energy balance.^{8,12} Studies using *ad libitum* (ieunrestricted) food intake assessments have documented a reduction of 30–40% in energy intake, compared to a placebo, in participants using an incretin-based treatment.^{5–8} This reduction in food intake has been similarly reported in healthy individuals.^{13,14} The distribution of nutrients (% energy consumed) was not significantly different, with reductions reported for all macronutrients (ie fat, carbohydrates, and protein),⁸ although separate studies have reported a decreased subjective preference for high-fat foods.¹⁵

Feeding behavior is complex and multidimensional. It has been parsed in multiple constituent elements, starting with hunger and the incentive salience of food (ieanticipation and valuation), to the consummatory, including the hedonic response, and termination (ie satiation) phases, all modulated by cognitive (eg learning and memory), and decision-making processes. The effects of incretin-based treatments have been primarily assessed by exploring the subjective impression of participants on their eating behavior, using standardized questionnaires and visual analogue scales. Multiple studies have reported a reduction in feelings of hunger, and increased fullness and satiety. These effects are independent of nausea, a common side effect of GLP-1R agonists.^{5–7,16} Additionally, decreased prospective food consumption (ie how much people think they could eat), and better control of eating, with fewer and less strong food cravings, and less difficulty resisting food, have been consistently documented.^{5–7,16} Furthermore, neuroimaging studies have reported decreased anticipatory responses, to food cues or consumption of highly palatable foods, in various brain regions (eg parietal and orbitofrontal cortex, insula, putamen, and amygdala).^{17,18} In contrast, the hedonic response to food seems to be preserved, with reports of no change in palatability or general food aversion.⁶ A recent neuroimaging study reported that treatment with liraglutide did not result in an altered hedonic experience or neural response while consuming a high-calorie food.¹⁹

Accumulating preclinical evidence has indicated that the administration of a GLP-1 receptor agonist results in a reduction in the intake of alcohol and drugs of abuse.⁹ However, evidence from clinical studies, albeit very limited, is more mixed. A recent non-controlled study documented a lower self-reported intake of alcohol and decreased frequency of binge drinking episodes in obese individuals on semaglutide or tirzepatide.²⁰ Dulaglutide was reported to reduce alcohol intake in a secondary analysis of a randomized clinical trial (RCT) testing this GLP-1 receptor agonist as a therapy for smoking cessation.²¹ The primary outcome of this RCT was negative, as dulaglutide was not more effective than a placebo at promoting abstinence from smoking.²² In the only published RCT in patients with alcohol use disorders, exenatide was not superior to placebo at reducing the number of heavy drinking days and total alcohol intake, although an exploratory analysis suggested a significant effect of the treatment in a subgroup with comorbid obesity.²³ In patients with a cocaine use disorder, acute treatment with exenatide, when compared to placebo, did not change cocaine self-administration, self-reported euphoria, or wanting of cocaine.²⁴

Hitherto, 2 studies assessed the effects of liraglutide on reward behavior (ie the responses to positive stimuli) using objective tasks.^{25,26} Hanssen et al. (2021)²⁵ evaluated how the drug affected the willingness to exert physical effort for food and monetary rewards, using a task whereby varying amounts of food and money could be earned by squeezing a handgrip device. The results indicated that liraglutide increased the motivation to work for both

food and monetary rewards in insulin-resistant participants, restoring it to a similar level when compared to insulin-sensitive individuals. Hanssen et al. (2023)²⁶ probed adaptive learning, through a paradigm that assessed the ability of participants to learn associations between auditory cues and subsequent visual outcomes, which shifted in predictability throughout the experiment. The key finding was that insulin-resistant participants exhibited a reduced adaptive learning rate (ie the extent to which participants learned from their errors), which was then normalized by a one-time liraglutide administration.

Therefore, the emerging picture is that incretin-based agents affect food intake, primarily through a modulation of the anticipation and valuation of foods, rather than a hedonic action. Evidence on consummatory behavior of non-foods is more uncertain, but with potential effects on motivation to work and learning reported, specifically in subgroups with metabolic dysfunction (ie obesity and/or insulin resistance). Whereas the connection between incretin function and food intake is more direct, if not necessarily straightforward, it is worth questioning further why and how would this system also affect the consumption of non-food rewards, which have vastly different physiological roles (or, in the case of drugs, are thought to work by “hijacking” the reward neurocircuitry, but still through targets that are not necessarily involved in the signaling of nutrient availability).

GLP-1 physiology and behavior

Incretins are multifaceted peptides. Endogenous GLP-1 acts both as a gut hormone and as a neuropeptide within the central nervous system (CNS).²⁷ The central and peripheral GLP-1 systems are considered to be, at least partially, functionally separate.^{28,29} GLP-1 originates from 2 separate locations, the enteroendocrine L cells of the intestine and the preproglucagon (PPG) neurons in the nucleus tractus solitaries (NTS).^{28,30} Gut-derived hormonal GLP-1 is synthesized and secreted after nutrient ingestion,³¹ it stimulates pancreatic insulin secretion and biosynthesis in a glucose-dependent manner, in addition to having numerous regulatory effects.³¹ Central GLP-1 secretion is stimulated by gastric distension, or endocrine factors, such as leptin and oxytocin.²⁷ The central GLP-1 system is probably not directly activated by peripheral endogenous GLP-1, as PPG neurons do not express GLP-1Rs,²⁹ and active GLP-1 in the circulation is rapidly metabolized to inactive by the enzyme dipeptidyl peptidase 4 (DPP-4); it is unlikely then that GLP-1 released by the intestine reaches the brain.³² PPG neurons are the main source of brain GLP-1.³³ These are projecting neurons; their axons containing GLP-1 vesicles are present in varied regions of the brain. Neuronally produced GLP-1 is transported to the axon terminals and stored in synaptic vesicles until its eventual release.³⁴ GLP-1Rs are widely expressed in the CNS and are thought to modulate, directly or indirectly, multiple regions. These include “homeostatic” feeding areas (eg brainstem–hypothalamic circuit), associative networks (eg parietal cortex) as well as regions relevant to motivation (eg mesolimbic pathway) and general cognitive function (eg hippocampus).^{17,35–38}

The effects of GLP-1 on food intake are considered to result from the activation of its receptors in the CNS.^{28,30,39} Evidence indicates that the peripheral and central GLP-1 systems suppress food intake independently, through distinct behavioral mechanisms.^{29,30} Postprandial release of intestinal GLP-1 is thought to convey a satiation signal, primarily mediated by vagal afferent neurons,^{40,41} thus reducing *ad libitum* energy intake.⁴² In contrast,

physiological central GLP-1 signaling does not seem to be involved in *ad libitum* feeding, glucose tolerance, or long-term energy balance, but is instead activated by different forms of metabolic and psychogenic stressors, including unusually large meals and prolonged fasting, as well as acute stress, modulating stress-induced hypophagia.^{29,33} Systemically administered GLP-1R agonists are degradation-resistant and long-acting, and are thus considered to mimic the action of postprandial gut-derived GLP-1. These agents additionally access GLP-1Rs within the CNS, although the extent to which they access the areas protected by the blood–brain barrier (BBB) is still unclear.^{43–45} Therefore, it is unclear if GLP-1R agonists are also correlated with central GLP-1 actions. Preclinical evidence indicates that liraglutide and semaglutide do not activate PPG neurons, nor require them for their feeding suppression effects.²⁹ Interestingly, concurrent activation of PPG neurons was shown to augment semaglutide's effects on eating behavior, indicating that brain-specific GLP-1 action might not be fully reflected by existing GLP-1R agonists, and could be additional pharmacological targets.²⁹

A reasonable synthesis of the extant literature is that peripheral GLP-1 is involved in day-to-day energy balance, serving as a meal termination signal. Elevating the tone of peripheral GLP-1 signal with long-acting and degradation-resistant GLP-1R agonists would then promote feelings of satiety, facilitating the cessation of feeding (improving subjective feelings of control), and decreasing the subjective value of food (reducing the anticipation and valuation of food rewards), which are all consistent with the reported behavioral effects of incretin-based treatments. On the other hand, central GLP-1 is more context-dependent and is activated by stressful situations, whereby the termination of feeding behavior is more urgent. Based on the reported inputs to NTS PPG neurons, these can be related to somatic signals (e.g. excess gastric distention), but also to metabolic stress and perceived imminent threats.⁴⁶ Conceivably, these could also be disease states and/or intermediate phenotypes, such as the excess accumulation of adipose tissue or insulin resistance. Evidence indicates that central GLP-1 signaling can promote feelings of satiety even in conditions of negative energy balance,²⁹ suggesting that it is activated in situations where responding to a threat, internal or external, takes priority over replenishing energy resources.⁴⁶ Nonetheless, despite interest in the role of the GLP-1 system in the overall response to stress,⁴⁷ the behavioral correlates, in humans, of these actions have not been directly explored. If, and to what extent, the currently documented behavioral effects of GLP-1R agonists in humans are attributable to central versus peripheral GLP-1 activation is still to be determined.

How could then the GLP-1 system affect the intake of non-foods, as well as overall reward behavior? One of the underlying concepts is that responses to food and non-food rewards converge on a common neural network, the mesolimbic pathway.⁴⁸ Mesolimbic regions, such as the ventral tegmental area and the nucleus accumbens, express GLP-1R and receive projections from NTS PPG neurons.²⁷ Activation of GLP-1R in the mesolimbic pathways has been shown to modulate dopaminergic neurotransmission, one of the key molecular mediators of reward response, in preclinical models.⁹ Conversely, studies have reported that the effects of GLP-1 on alcohol and drug intake in animals are mediated by central rather than peripheral mechanisms.⁹ Notably, the effects of GLP-1 on alcohol intake seem to be related to modulation of its rewarding/reinforcing properties, rather than a byproduct of GLP-1 overall influence on nutrient and fluid intake, as a study showed that a GLP-1R agonist was able to attenuate intravenous ethanol self-administration in mice.⁴⁹

Nonetheless, findings from human studies have been mixed. Two studies failed to document an effect of GLP-1R agonists on an indicator of dopamine function *in vivo*, the availability of striatal dopamine transporter (DAT), measured using molecular neuroimaging (e.g. positron emission tomography); Jensen *et al.* (2020)⁵⁰ following the acute administration of exenatide in healthy volunteers and Athauda *et al.* (2017)⁵¹ following 48 weeks of exenatide treatment in patients with Parkinson's disease, despite improvement in motor symptoms. In contrast, Klausen *et al.* (2022)²³ reported a decrease in striatal DAT availability after 26 weeks of treatment with exenatide in patients with alcohol use disorder. These discrepant findings might be a result of methodological limitations from the aforementioned studies, including relatively small sample sizes. It is also worth considering the possibility that these might reflect the distinct roles of the central and peripheral GLP-1 system. The more context-dependent nature of central GLP-1 signaling indicates that its activation, which is likely necessary for the potential broader effects on reward behavior, might only be meaningful in specific situations, determined by certain physiological and/or environmental conditions. Indeed, reinforcing this hypothesis, the effects of GLP-1R agonists on non-food reward in humans, including alcohol intake and response to monetary rewards, have hitherto only been shown in individuals with obesity and/or insulin resistance.^{23,25,26}

An additional explanation for the potential role of the GLP-1 system on non-food reward might be in the non-specific properties of GLP-1 signaling. Activation of GLP-1 receptors has been consistently associated with neuroprotective effects in preclinical models, including preventing or reversing the effects of a range of toxic conditions on neuronal survival, by decreasing apoptosis and increasing neurogenesis, angiogenesis, and cerebral blood flow.^{52–54} Some of these actions seem to be mediated by the modulation of oxidative stress and inflammatory processes; recent work documented that central GLP-1 signaling was required for the anti-inflammatory effects of GLP-1R agonists.⁵⁵ These actions have substantiated the hypothesis that GLP-1R agonists may also have pro-cognitive effects, which has been tested in diverse clinical populations.^{56–59} Conversely, the GLP-1 system has been implicated in the regulation of cerebral glucose metabolism. The human brain is highly dependent on glucose as its primary substrate and is considered to be particularly vulnerable to fluctuations in glucose supply and consumption. Evidence from human studies indicates that GLP-1 modulates the transport of glucose across the blood–brain barrier and the cerebral metabolic rate of glucose, in a glucose-dependent manner.⁶⁰ In a 6-months RCT testing the use of liraglutide as a treatment for Alzheimer's disease (AD), the GLP-1R agonist was shown to prevent the decline of cerebral glucose metabolism, a pathological feature of AD's progression, although the trial failed to document treatment effects on its primary outcome, cognitive function.⁶¹

In an attempt to reconcile these broad and relatively disparate functions attributed to the GLP-1 system, it should be considered that GLP-1, and the concerted effects of physiological or pharmacological GLP-1 activation, can also function as a signal of energy availability. Extensive literature indicates that energy substrates (ie glucose) and its accompanying network of regulatory peptides, including, but not limited to, insulin, leptin, and ghrelin, affect human behavior and decision-making, beyond food-related rewards.^{62–68} Importantly, in manipulation studies, the effects of glucose on motivated behavior seem to be a direct result of glucose ingestion, with the consequential elevation in blood glucose and counterregulatory hormonal response, rather than a hedonic or

perceptual process, as artificial sweeteners or glucose mouth rinses, had either none or opposite effects on decision making.^{69,70} Indeed, the mesolimbic pathway is known to be modulated by a variety of homeostatic signals.⁷¹ Replicated evidence indicates that oral glucose administration stimulates dopaminergic activity in the striatum.⁷² Furthermore, mesolimbic dopamine neurons also express receptors for insulin,⁷³ leptin,⁷⁴ and ghrelin.⁷⁵

The precise mechanisms whereby energy availability and its signals affect reward response remain unclear, but it has been suggested that more demanding behaviors and actions are thought to require greater energetic resources, and thus higher glucose availability and utilization.^{76,77} Circulating glucose and regulatory hormones also have a signaling function, as indicators of the body's "energy budget." Furthermore, recent work has highlighted the role of dopaminergic neurotransmission in the mesolimbic pathway in cost-benefit decision-making. Every action has an energetic cost, actual and/or opportunity. Dopamine signaling has traditionally been implicated in arousal, motivation, and psychomotor activation (that is incentive salience models), and reward learning/reinforcement (that is prediction error models).^{78–80} Recent work has suggested that dopamine can potentially signal relative value (that is the available reward for a certain cost of effort), thus integrating cost and benefit factors, which can then be employed for both learning and motivational functions.^{80–82} Conceptually, homeostatic input to striatal dopamine neurons can then serve as signals of the current and anticipated energy resources. Therefore, even complex behaviors can potentially be affected by each individual's internal energy milieu, and their perception of their energy environment.^{83,84}

Conclusions

Behavior has a context and a purpose.⁸⁵ The process of obtaining nutrients from the environment, as well as transforming and allocating those nutrients to build cellular structures and maintain the function of body tissues, is crucial for survival and reproduction. The central and peripheral GLP-1 systems are critical nodes of the energy homeostasis network, and as such, are expected to modulate behavior, potentially beyond its direct effects on feeding. Nonetheless, the intricacies of this system, vis-à-vis the subtle but physiologically meaningful differences in the roles of central and peripheral GLP-1, and the complexity of its relationship with other metabolic signals and the reward pathway, suggest that broad and indiscriminate anti-consummatory effects are unlikely. On the other hand, effects on specific behavioral domains in well-defined subpopulations are not only theoretically possible but are already well supported by accumulating preclinical and clinical studies. Within this context, pragmatic studies focusing on establishing the efficacy of GLP-1R agonists for alcohol and substance use disorders, or more broadly on conditions related to "reward dysfunction"^{86,87} are needed. Nonetheless, there is also a need for more mechanistically focused efforts, aimed at parsing the specific behavioral effects of GLP-1R agonists, considering its physiological and environmental determinants.

The study of GLP-1R agonists is also a tremendous opportunity to broaden our understanding of normal and dysfunctional behavior, particularly those related to neuropsychiatric conditions. Historically, psychopathology has primarily focused on describing and analyzing behavior at the psychological and neurocircuitry level,⁸⁸ often neglecting its physiological causal factors. But, as the literature on GLP-1R agonists highlights, the brain has a body.⁸⁹ A better

understanding of the brain-body connection, and appreciation for the role of whole-body physiology, can fundamentally reframe the conceptualization of behavior and provide novel insights for a deeper, more contextualized consideration of its related conditions.

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