CNS Spectrums

www.cambridge.org/cns

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

Rodrigo B. Mansur[1,2,3], Joshua D. Di Vincenzo[1], Sebastian Badulescu[1,2], Hartej Gill[1,3], Aniqa Tabassum[1,2], Cristian Llach López[1,2], Joshua D. Rosenblat[1,2,3] and Roger S. McIntyre[2]

[1]Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada; [2]Department of Psychiatry, University of Toronto, Toronto, ON, Canada and [3]Institute of Medical Science, University of Toronto, Toronto, ON, Canada

Perspective

Cite this article: Mansur RB, Di Vincenzo JD, Badulescu S, Gill H, Tabassum A, López CL, Rosenblat JD, and McIntyre RS (2025). Are glucagon-like peptide-1 receptor agonists anti-consummatory drugs? *CNS Spectrums* https://doi.org/10.1017/S109285292400244X

Received: 18 July 2024
Accepted: 02 December 2024

Keywords:
glucagon-like peptide-1; glucagon-like peptide-1 receptor agonists; behavior; reward; metabolism

Corresponding author:
Rodrigo B. Mansur;
Email: rodrigo.mansur@uhn.ca

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

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,

https://doi.org/10.1017/S109285292400244X Published online by Cambridge University Press

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

https://doi.org/10.1017/S109285292400244X Published online by Cambridge University Press

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.

Author contribution. Writing – review & editing: R.S.M., A.T., J.D.R., C.L.L., H.G., J.D.V., S.B.; Conceptualization: R.B.M.; Methodology: R.B.M.; Project administration: R.B.M.; Writing – original draft: R.B.M.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process. No generative AI and AI-assisted technologies were used in the preparation of this manuscript.

Disclosures. RBM has received research grant support from the CIHR, the PSI Foundation, and the Baszucki Brain Research Fund and an Academic Scholars Award, Department of Psychiatry, University of Toronto.

CDL has received the support of a fellowship from" la Caixa" Foundation (ID 100010434). The fellowship code is "LCF/BQ/EU22/11930062". CDL has also received CME-related honoraria, or consulting fees from CASEN Recordati, Organon, Lundbeck, and the Academy for Continuing Medical Education (Akademijazakme), with no financial or other conflicts of interest relevant to the subject of this article.'

JDR has received research grant support from the Canadian Institute of Health Research (CIHR), Physician Services, Inc. (PSI) Foundation, Labatt Brain Health Network, Brain and Cognition Discovery Foundation (BCDF), Canadian Cancer Society, Canadian Psychiatric Association, Academic Scholars Award, American Psychiatric Association, American Society of Psychopharmacology, University of Toronto, University Health Network Center for Mental Health, Joseph M. West Family Memorial Fund, and Timeposters Fellowship and industry funding for speaker/consultation/research fees from iGan, Boehringer Ingelheim, Janssen, Allergan, Lundbeck, Sunovion, Braxia Health, Braxia Scientific Corp., and COMPASS.

RSM has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals,Viatris, Abbvie, Atai Life Sciences. Dr. Roger McIntyre is a CEO of Braxia Scientific Corp.

References

1. Yao H, Zhang A, Li D, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. *BMJ.* 2024; **384**: e076410.
2. Ansari HUH, Qazi SU, Sajid F, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists on body weight and cardiometabolic parameters in individuals with obesity and without diabetes: a systematic review and meta-analysis. *Endocr Pract.* 2024; **30**(2): 160–71.
3. Alkhezi OS, Alahmed AA, Alfayez OM, Alzuman OA, Almutairi AR, Almohammed OA. Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: a network meta-analysis of randomized clinical trials. *Obes Rev.* 2023; **24**(3): e13543.
4. Mahase E. GLP-1 agonist shortage will last until end of 2024, government warns. *BMJ.* 2024; **384**: q28.
5. Friedrichsen M, Breitschaft A, Tadayon S, Wizert A, Skovgaard D. The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. *Diabetes Obes Metab.* 2021; **23**(3): 754–62.
6. Gibbons C, Blundell J, Tetens Hoff S, Dahl K, Bauer R, Baekdal T. Effects of oral semaglutide on energy intake, food preference, appetite, control of eating and body weight in subjects with type 2 diabetes. *Diabetes Obes Metab* 2021; **23**(2): 581–8.

https://doi.org/10.1017/S109285292400244X Published online by Cambridge University Press

7. Heise T, DeVries JH, Urva S, et al. Tirzepatide reduces appetite, energy intake, and fat mass in people with type 2 diabetes. *Diabetes Care.* 2023; **46**(5): 998–1004.
8. Shoemaker AH, Silver HJ, Buchowski M, et al. Energy balance in hypothalamic obesity in response to treatment with a once-weekly GLP-1 receptor agonist. *Int J Obes (Lond).* 2022; **46**(3): 623–9.
9. Klausen MK, Thomsen M, Wortwein G, Fink-Jensen A. The role of glucagon-like peptide 1 (GLP-1) in addictive disorders. *Br J Pharmacol.* 2022; **179**(4): 625–41.
10. Arillotta D, Floresta G, Guirguis A, et al. GLP-1 receptor agonists and related mental health issues; insights from a range of social media platforms using a mixed-methods approach. *Brain Sci.* 2023; **13**(11).
11. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. *Circulation.* 2012; **126**(1): 126–32.
12. Maciel MG, Beserra BTS, Oliveira FCB, et al. The effect of glucagon-like peptide 1 and glucagon-like peptide 1 receptor agonists on energy expenditure: a systematic review and meta-analysis. *Diabetes Res Clin Pract.* 2018; **142**: 222–35.
13. Jalleh R, Pham H, Marathe CS, et al. Acute effects of lixisenatide on energy intake in healthy subjects and patients with type 2 diabetes: relationship to gastric emptying and intragastric distribution. *Nutrients.* 2020; **12**(7).
14. Pinelli NR, Jantz A, Smith Z, et al. Effect of administration time of exenatide on satiety responses, blood glucose, and adverse events in healthy volunteers. *J Clin Pharmacol.* 2011; **51**(2): 165–72.
15. Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes Obes Metab.* 2017; **19**(9): 1242–51.
16. Wharton S, Batterham RL, Bhatta M, et al. Two-year effect of semaglutide 2.4 mg on control of eating in adults with overweight/obesity: STEP 5. *Obesity (Silver Spring).* 2023; **31**(3): 703–15.
17. Farr OM, Sofopoulos M, Tsoukas MA, et al. GLP-1 receptors exist in the parietal cortex, hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomised, placebo-controlled trial. *Diabetologia.* 2016; **59**(5): 954–65.
18. van Bloemendaal L, Veltman DJ, Ten Kulve JS, et al. Brain reward-system activation in response to anticipation and consumption of palatable food is altered by glucagon-like peptide-1 receptor activation in humans. *Diabetes Obes Metab.* 2015; **17**(9): 878–86.
19. Coppin G, Munoz Tord D, Pool ER, et al. A randomized controlled trial investigating the effect of liraglutide on self-reported liking and neural responses to food stimuli in participants with obesity. *Int J Obes (Lond).* 2023; **47**(12): 1224–31.
20. Quddos F, Hubshman Z, Tegge A, et al. Semaglutide and tirzepatide reduce alcohol consumption in individuals with obesity. *Sci Rep* 2023; **13**(1): 20998.
21. Probst L, Monnerat S, Vogt DR, et al. Effects of dulaglutide on alcohol consumption during smoking cessation. *JCI Insight.* 2023; **8**(22).
22. Lengsfeld S, Burkard T, Meienberg A, et al. Effect of dulaglutide in promoting abstinence during smoking cessation: a single-centre, randomized, double-blind, placebo-controlled, parallel group trial. *EClinicalMedicine.* 2023; **57**: 101865.
23. Klausen MK, Jensen ME, Moller M, et al. Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. *JCI Insight.* 2022; **7**(19).
24. Angarita GA, Matuskey D, Pittman B, et al. Testing the effects of the GLP-1 receptor agonist exenatide on cocaine self-administration and subjective responses in humans with cocaine use disorder. *Drug Alcohol Depend.* 2021; **221**: 108614.
25. Hanssen R, Kretschmer AC, Rigoux L, et al. GLP-1 and hunger modulate incentive motivation depending on insulin sensitivity in humans. *Mol Metab* 2021; **45**: 101163.
26. Hanssen R, Rigoux L, Kuzmanovic B, et al. Liraglutide restores impaired associative learning in individuals with obesity. *Nat Metab.* 2023; **5**(8): 1352–63.
27. Muller TD, Finan B, Bloom SR, et al. Glucagon-like peptide 1 (GLP-1). *Mol Metab.* 2019; **30**: 72–130.
28. Trapp S, Brierley DI. Brain GLP-1 and the regulation of food intake: GLP-1 action in the brain and its implications for GLP-1 receptor agonists in obesity treatment. *Br J Pharmacol.* 2022; **179**(4): 557–70.
29. Brierley DI, Holt MK, Singh A, et al. Central and peripheral GLP-1 systems independently suppress eating. *Nat Metab.* 2021; **3**(2): 258–73.
30. Williams DL. The diverse effects of brain glucagon-like peptide 1 receptors on ingestive behaviour. *Br J Pharmacol.* 2022; **179**(4): 571–83.
31. Nauck MA, Meier JJ. Incretin hormones: their role in health and disease. *Diabetes Obes Metab.* 2018; **20** Suppl 1: 5–21.
32. Holst JJ, Deacon CF. Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. *Diabetologia.* 2005; **48**(4): 612–5.
33. Holt MK, Richards JE, Cook DR, et al. Preproglucagon neurons in the nucleus of the solitary tract are the main source of brain GLP-1, mediate stress-induced hypophagia, and limit unusually large intakes of food. *Diabetes.* 2019; **68**(1): 21–33.
34. Zheng H, Stornetta RL, Agassandian K, Rinaman L. Glutamatergic phenotype of glucagon-like peptide 1 neurons in the caudal nucleus of the solitary tract in rats. *Brain Struct Funct.* 2015; **220**(5): 3011–22.
35. Alvarez E, Martinez MD, Roncero I, et al. The expression of GLP-1 receptor mRNA and protein allows the effect of GLP-1 on glucose metabolism in the human hypothalamus and brainstem. *J Neurochem.* 2005; **92**(4): 798–806.
36. Usdin TB, Mezey E, Button DC, Brownstein MJ, Bonner TI. Gastric inhibitory polypeptide receptor, a member of the secretin-vasoactive intestinal peptide receptor family, is widely distributed in peripheral organs and the brain. *Endocrinology.* 1993; **133**(6): 2861–70.
37. Nyberg J, Anderson MF, Meister B, et al. Glucose-dependent insulinotropic polypeptide is expressed in adult hippocampus and induces progenitor cell proliferation. *J Neurosci.* 2005; **25**(7): 1816–25.
38. Alhadeff AL, Rupprecht LE, Hayes MR. GLP-1 neurons in the nucleus of the solitary tract project directly to the ventral tegmental area and nucleus accumbens to control for food intake. *Endocrinology.* 2012; **153**(2): 647–58.
39. Boer GA, Hay DL, Tups A. Obesity pharmacotherapy: incretin action in the central nervous system. *Trends Pharmacol Sci.* 2023; **44**(1): 50–63.
40. Brierley DI, de Lartigue G. Reappraising the role of the vagus nerve in GLP-1-mediated regulation of eating. *Br J Pharmacol.* 2022; **179**(4): 584–99.
41. Krieger JP. Intestinal glucagon-like peptide-1 effects on food intake: Physiological relevance and emerging mechanisms. *Peptides.* 2020; **131**: 170342.
42. Verdich C, Flint A, Gutzwiller JP, et al. A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. *J Clin Endocrinol Metab.* 2001; **86**(9): 4382–9.
43. Salameh TS, Rhea EM, Talbot K, Banks WA. Brain uptake pharmacokinetics of incretin receptor agonists showing promise as Alzheimer's and Parkinson's disease therapeutics. *Biochem Pharmacol.* 2020; **180**: 114187.
44. Rhea EM, Babin A, Thomas P, et al. Brain uptake pharmacokinetics of albiglutide, dulaglutide, tirzepatide, and DA5-CH in the search for new treatments of Alzheimer's and Parkinson's diseases. *Tissue Barriers.* 2023: 2292461.
45. Gabery S, Salinas CG, Paulsen SJ, et al. Semaglutide lowers body weight in rodents via distributed neural pathways. *JCI Insight.* 2020; **5**(6).
46. Petrovich GD. Feeding behavior survival circuit: anticipation & competition. *Curr Opin Behav Sci.* 2018; **24**: 137–42.
47. Guerrero-Hreins E, Goldstone AP, Brown RM, Sumithran P. The therapeutic potential of GLP-1 analogues for stress-related eating and role of GLP-1 in stress, emotion and mood: a review. *Prog Neuropsychopharmacol Biol Psychiatry.* 2021; **110**: 110303.
48. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev.* 2013; **14**(1): 2–18.
49. Sorensen G, Caine SB, Thomsen M. Effects of the GLP-1 agonist exendin-4 on intravenous ethanol self-administration in mice. *Alcohol Clin Exp Res.* 2016; **40**(10): 2247–52.
50. Jensen ME, Galli A, Thomsen M, et al. Glucagon-like peptide-1 receptor regulation of basal dopamine transporter activity is species-dependent. *Neurochem Int.* 2020; **138**: 104772.
51. Athauda D, Maclagan K, Skene SS, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2017; **390**(10103): 1664–75.
52. Erbil D, Eren CY, Demirel C, Kucuker MU, Solaroglu I, Eser HY. GLP-1's role in neuroprotection: a systematic review. *Brain Inj.* 2019; **33**(6): 734–819.

https://doi.org/10.1017/S109285292400244X Published online by Cambridge University Press

53. Maskery MP, Holscher C, Jones SP, et al. Glucagon-like peptide-1 receptor agonists as neuroprotective agents for ischemic stroke: a systematic scoping review. *J Cereb Blood Flow Metab*. 2021; **41**(1): 14–30.
54. Kong F, Wu T, Dai J, et al. Glucagon-like peptide 1 (GLP-1) receptor agonists in experimental Alzheimer's disease models: a systematic review and meta-analysis of preclinical studies. *Front Pharmacol*. 2023; **14**: 1205207.
55. Wong CK, McLean BA, Baggio LL, et al. Central glucagon-like peptide 1 receptor activation inhibits Toll-like receptor agonist-induced inflammation. *Cell Metab*. 2024; **36**(1): 130–43 e5.
56. Chai S, Liu F, Yu S, Yang Z, Sun F. Cognitive protection of incretin-based therapies in patients with type 2 diabetes mellitus: a systematic review and meta-analysis based on clinical studies. *J Diab Investig*. 2023; **14**(7): 864–73.
57. Vadini F, Simeone PG, Boccatonda A, et al. Liraglutide improves memory in obese patients with prediabetes or early type 2 diabetes: a randomized, controlled study. *Int J Obes (Lond)*. 2020; **44**(6): 1254–63.
58. Li Q, Jia M, Yan Z, et al. Activation of glucagon-like peptide-1 receptor ameliorates cognitive decline in type 2 diabetes mellitus through a metabolism-independent pathway. *J Am Heart Assoc*. 2021; **10**(14): e020734.
59. Mansur RB, Ahmed J, Cha DS, et al. Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: a pilot, open-label study. *J Affect Disord*. 2017; **207**: 114–20.
60. Nilsson M, Gjedde A, Brock B, Gejl M, Rungby J. The effects of incretin hormones on cerebral glucose metabolism in health and disease. *Neuropharmacology*. 2018; **136**(Pt B): 243–50.
61. Gejl M, Gjedde A, Egefjord L, et al. In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. *Front Aging Neurosci*. 2016; **8**: 108.
62. Orquin JL, Kurzban R. A meta-analysis of blood glucose effects on human decision making. *Psychol Bull*. 2016; **142**(5): 546–67.
63. Wang XT, Huangfu G. Glucose-specific signaling effects on delay discounting in intertemporal choice. *Physiol Behav*. 2017; **169**: 195–201.
64. Koban L, Lee S, Schelski DS, et al. An fMRI-based brain marker of individual differences in delay discounting. *J Neurosci* 2023; **43**(9): 1600–13.
65. Pietrzak M, Yngve A, Hamilton JP, et al. Ghrelin decreases sensitivity to negative feedback and increases prediction-error related caudate activity in humans, a randomized controlled trial. *Neuropsychopharmacology*. 2024.
66. Pfabigan DM, Frogner ER, Schele E, et al. Ghrelin is related to lower brain reward activation during touch. *Psychophysiology*. 2024; **61**(2): e14443.
67. Pietrzak M, Yngve A, Hamilton JP, et al. A randomized controlled experimental medicine study of ghrelin in value-based decision making. *J Clin Invest*. 2023; **133**(12).
68. Schlogl H, Janssen L, Fasshauer M, et al. Reward processing during monetary incentive delay task after leptin substitution in lipodystrophy—an fMRI case series. *J Endocr Soc*. 2023; **7**(6): bvad052.
69. Wang XT, Reed RN, Baugh LA, Fercho KA. Resource forecasting: differential effects of glucose taste and ingestion on delay discounting and self-control. *Appetite*. 2018; **121**: 101–10.
70. Wang XT, Dvorak RD. Sweet future: fluctuating blood glucose levels affect future discounting. *Psychol Sci*. 2010; **21**(2): 183–8.
71. Hsu TM, McCutcheon JE, Roitman MF. Parallels and overlap: the integration of homeostatic signals by mesolimbic dopamine neurons. *Front Psychiatry*. 2018; **9**: 410.
72. Blum K, Thanos PK, Gold MS. Dopamine and glucose, obesity, and reward deficiency syndrome. *Front Psychol*. 2014; **5**: 919.
73. Liu S, Borgland SL. Regulation of the mesolimbic dopamine circuit by feeding peptides. *Neuroscience*. 2015; **289**: 19–42.
74. Fernandes MF, Sharma S, Hryhorczuk C, Auguste S, Fulton S. Nutritional controls of food reward. *Can J Diab*. 2013; **37**(4): 260–8.
75. Perello M, Dickson SL. Ghrelin signalling on food reward: a salient link between the gut and the mesolimbic system. *J Neuroendocrinol*. 2015; **27**(6): 424–34.
76. Kennedy DO, Scholey AB. Glucose administration, heart rate and cognitive performance: effects of increasing mental effort. *Psychopharmacology (Berl)*. 2000; **149**(1): 63–71.
77. Scholey AB, Harper S, Kennedy DO. Cognitive demand and blood glucose. *Physiol Behav*. 2001; **73**(4): 585–92.
78. Beierholm U, Guitart-Masip M, Economides M, et al. Dopamine modulates reward-related vigor. *Neuropsychopharmacology*. 2013; **38**(8): 1495–503.
79. Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. A causal link between prediction errors, dopamine neurons and learning. *Nat Neurosci*. 2013; **16**(7): 966–73.
80. Hamid AA, Pettibone JR, Mabrouk OS, et al. Mesolimbic dopamine signals the value of work. *Nat Neurosci*. 2016; **19**(1): 117–26.
81. Eshel N, Touponse GC, Wang AR, et al. Striatal dopamine integrates cost, benefit, and motivation. *Neuron*. 2024; **112**(3): 500–14 e5.
82. Soutschek A, Jetter A, Tobler PN. Toward a unifying account of dopamine's role in cost-benefit decision making. *Biol Psychiatry Glob Open Sci*. 2023; **3**(2): 179–86.
83. Wang XT. Resource signaling via blood glucose in embodied decision making. *Front Psychol*. 2018; **9**: 1965.
84. Beeler JA, Mourra D. To do or not to do: dopamine, affordability and the economics of opportunity. *Front Integr Neurosci*. 2018; **12**: 6.
85. Gomez-Marin A, Ghazanfar AA. The life of behavior. *Neuron*. 2019; **104**(1): 25–36.
86. Eren-Yazicioglu CY, Yigit A, Dogruoz RE, Yapici-Eser H. Can GLP-1 be a target for reward system related disorders? A qualitative synthesis and systematic review analysis of studies on palatable food, Drugs of Abuse, and Alcohol. *Front Behav Neurosci*. 2020; **14**: 614884.
87. Badulescu S, Tabassum A, Le GH, et al. Glucagon-like peptide 1 agonist and effects on reward behaviour: a systematic review. *Physiol Behav*. 2024; **283**: 114622.
88. Eronen MI. The levels problem in psychopathology. *Psychol Med*. 2021; **51**(6): 927–33.
89. Chiel HJ, Beer RD. The brain has a body: adaptive behavior emerges from interactions of nervous system, body and environment. *Trends Neurosci*. 1997; **20**(12): 553–7.

https://doi.org/10.1017/S109285292400244X Published online by Cambridge University Press