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Neural integration of satiation and food reward: Role of GLP-1 and Orexin pathways

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Abstract

Central nervous system control of food intake involves detecting, integrating and responding to diverse internal and external signals. For maintenance of energy homeostasis, the brain uses long-term signals of metabolic status and short-term signals related to the nutrient content of individual meals. Feeding is also clearly influenced by hedonic, reward-related factors: palatability, motivation, and learned associations and cues that predict the availability of food. Different neural circuits have been proposed to mediate these homeostatic and hedonic aspects of eating. This review describes research on neural pathways that appear to be involved in both, integrating gastrointestinal satiation signaling with food reward. First, the glucagon-like peptide 1 projections from the nucleus of the solitary tract to the nucleus accumbens and ventral tegmental area are discussed as a mechanism through which meal-related gut signals may influence palatability, motivation for food, and meal size. Second, the orexin projection from lateral hypothalamus to the nucleus of the solitary tract and area postrema is discussed as a mechanism through which cues that predict rewarding food may act to increase motivation for food and also to suppress satiation. Additional potential integrative sites and pathways are also briefly discussed. Based on these findings, it is suggested that the brain circuitry involved in energy homeostasis and the circuitry mediating food reward are, in fact, overlapping and far less distinct than previously considered.

1. Introduction

Despite considerable progress over the past several decades, the biological factors that control how much we eat and what kinds of foods we choose to eat have not been fully elucidated. Central nervous system control of feeding behavior is clearly complex. Each decision to start or stop eating is influenced by sensory, cognitive and emotional variables, long-term signals of metabolic status and fuel storage, and short-term signals related to the nutrient content of individual meals. For many years, research in this area focused primarily on the maintenance of energy homeostasis: a balance of energy intake with expenditure such that circulating and stored fuels remain at relatively constant levels [1]. However, it is clear

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that central mediation of reward, including factors such as palatability of food, motivation to obtain food, and learned associations and cues that predict the availability of food, strongly influences feeding behavior [2]. As a result, it has become common to see discussions of “homeostatic eating” for maintenance of energy balance vs. “hedonic eating” for food reward in the absence of or beyond homeostatic need (e.g., [3, 4]. At face value, this homeostatic/hedonic distinction is appealing. Most if not all of us have at one point or another chosen to eat palatable food in the absence of hunger, providing intuitive support for this dichotomy. Stemming in part from this conceptual distinction, current widely accepted models for brain control of feeding essentially describe two distinct neural systems, one homeostatic and one hedonic. These two systems are often discussed as operating in opposition to one another, with the homeostatic system providing negative feedback on eating and the hedonic system driving food intake, and overeating is seen as the result of the hedonic system “overriding” the homeostatic system [5, 6]. I suggest that with further examination, this homeostatic/hedonic dichotomy is misleading. First, it is difficult to cleanly place any individual bout of eating into one or the other of these categories. Second, and perhaps more importantly, there is evidence for overlap and interaction between brain areas commonly considered to be part of the homeostatic system and those considered part of the hedonic system, to the extent that it is inaccurate to continue to describe them as distinct systems. Below is a brief summary of some of the key features of the separate homeostatic/hedonic systems perspective, followed by evidence for a more integrated view.

2. The distinct systems perspective

The homeostatic system for food intake control is primarily a negative feedback system based on the detection and integration of adiposity and satiation, and satiety signals (Figure 1A). Adiposity signals such as the hormones leptin and insulin, are released in direct proportion to body fat mass [7]. Leptin and insulin bind to receptors in hypothalamic nuclei including the arcuate (ARC), paraventricular nucleus (PVN), and ventromedial nucleus (VMN), as well as the hindbrain nucleus of the solitary tract (NTS), and activate neuropeptide mediators that reduce food intake (e.g., proopiomelanocortin neurons in the ARC) while suppressing others that promote feeding (e.g., agouti-related peptide and neuropeptide Y neurons in the ARC) [8]. Signals arising from the gastrointestinal tract in response to incoming nutrients during a meal (e.g., gastric distention and the intestinal hormone cholecystokinin (CCK)) suppress food intake [9, 10]. Satiation signals are within-meal signals that lead to meal termination, while satiety signals influence post-meal behavior, suppressing the initiation the next meal [9, 11]. Some satiation and satiety signals act directly in the CNS but many are transmitted to the brain via the vagus nerve, which synapses in the NTS and area postrema (AP), two nuclei widely considered to mediate satiation and satiety [9, 12, 13]. Leptin, insulin and their central effectors are thought to affect feeding in part by modulating the hindbrain response to satiation signals, through downstream projections from hypothalamus or direct action in caudal brainstem [14]. Thus, homeostatic eating, or cessation of eating, is seen as the result of hypothalamic and hindbrain nuclei interacting to control satiation and satiety.

As currently described, hedonic control of eating involves a number of distinct brain regions (Figure 1B). The mesolimbic dopamine pathway from the ventral tegmental area (VTA) to

the nucleus accumbens (NAc) has been most well studied in the context of drug addiction, but is also known to play a role in food reward [2, 15]. In addition to dopamine transmission, there is a clear contribution of opioid receptors in these and other connected nuclei [16, 17]. Neurons from VTA and NAc project to the medial prefrontal cortex (mPFC), and other NAc outputs include GABAergic projections to ventral pallidum (VP) and the lateral hypothalamic area (LH). Reciprocal connections among most of these regions (and others) exist, as well, and manipulations of activity in these areas affect food palatability and motivation to perform operant responses to obtain food [18].

In the “distinct systems” view, this hedonic system is coordinated with the homeostatic system largely through the influence of adiposity signals. Leptin and insulin are thought to affect food reward-related behaviors via their receptors in VTA [19]. For example, knockdown of leptin receptor expression in VTA increases sucrose self-administration by rats on a progressive ratio (PR) schedule of reinforcement, for which the rat must make an increasing number of operant responses to obtain each successive reinforcement [20]. In contrast, leptin receptor knockdown in the hypothalamus affects total food intake and body weight with no effect on food reward-related measures [20]. This dissociation has been taken as evidence supporting the independence of the homeostatic and hedonic systems. In addition to coordination through leptin and insulin, some authors include the LH as a node of convergence between homeostatic and hedonic systems [21].

3. A more integrated perspective

The details of the “distinct systems” view described above are supported by a great deal of research, but this model is incomplete. In fact, as has been pointed out previously [13, 22], there exist monosynaptic links between nuclei traditionally placed in the homeostatic system and those placed in the hedonic system. Thus, coordination between these homeostatic and hedonic pathways goes beyond the fact that leptin and insulin can act within each. Here, I focus on recent data from my laboratory and others on some of these direct links, in particular: 1) glucagon-like peptide 1 (GLP-1) neurons in the NTS that project to mesolimbic reward-related brain regions; and 2) orexin neurons in the LH that project to the NTS and AP (Figure 1C).

3.1 GLP-1 Projection to NAc and VTA

GLP-1 is produced by a relatively small population of neurons in the caudal NTS [23], and these cells have been hypothesized to play a role in the control of food intake since it was first shown that icv injection of GLP-1 potently suppresses feeding [24]. GLP-1 is also released by the intestine, and peripheral GLP-1R influence food intake [25]. The peptide can readily cross the blood-brain barrier [26], but because it is rapidly degraded by dipeptidyl peptidase 4 (half life <2 min), it is unlikely that sufficient amounts of intestine-derived active GLP-1 reach CNS receptors to influence feeding through action in brain [27]. Behavioral data support this suggestion. Blockade of central GLP-1R via icv injection of the GLP-1R antagonist Exendin (9-39) (Ex9) has no impact on the anorexic effect of GLP-1 injected intraperitoneally (IP) [25]. Thus, the endogenous source of ligand for central GLP-1R is thought to be neuronal, though it is likely peripherally administered degradation-resistant GLP-1R agonists enter the brain and exert some of their effects on feeding at CNS

receptors [28]. GLP-1 neurons express c-Fos in response to nutrients and meal-related signals such as gastric distention, and are directly activated by vagal afferent stimulation [29-31]. A physiologic role for neuronal GLP-1 has been supported by experiments showing that either pharmacologic blockade of GLP-1 receptors (GLP-1R) or siRNA-mediated knock-down of NTS GLP-1 expression increases food intake and body weight [32, 33]. NTS GLP-1 neurons project throughout the brain to many areas typically considered to play a role in energy homeostasis, including the ARC, PVN, and LH, but these cells also project to nuclei associated with reward and motivation such as the VTA and the NAc [34-37].

Until recently, hypothalamic nuclei have been the most widely studied sites of action for GLP-1's effects on feeding. The PVN was the only identified site into which injection of low doses (subthreshold for effect when delivered to the ventricle) of GLP-1 reduced food intake [38, 39], and it was also reported that intra-LH injection of a ventricle-subthreshold dose of the GLP-1R antagonist Ex9 increases food intake [40]. Over the past few years, however, our laboratory and others have reported evidence for GLP-1 action in the reward-related regions described above (see [41] for a recent review of this topic). We focused on the projection to the NAc core subregion (NAcC), confirming its existence through combined retrograde tracing and immunohistochemistry [36]. Alhadeff and colleagues [37] also provided anatomical evidence of a NTS GLP-1 neuronal projection to NAcC as well as to the shell subregion of the NAc (NAcSh). By administering doses of GLP-1 to the NAcC or NAc shell (NAcSh) that are subthreshold for effect when delivered to the nearby lateral ventricle, we determined that the NAcC is a sensitive site for GLP-1R stimulation to reduce chow intake for up to 24-h after injection, whereas NAcSh injections were not effective in our hands [36]. Others have shown that the degradation resistant GLP-1R agonist, Exendin 4 (Ex4) suppresses high-fat food and sucrose intake when injected into the NAcC, and has a smaller but significant effect to suppress high-fat food intake when administered to the NAcSh [37], suggesting that the NAcC may be the more sensitive site for GLP-1 effects on feeding. We have focused on the NAcC, based on our initial findings, and have observed that ventricle-subthreshold doses of Ex9 directly delivered into the NAcC increase intake of chow, sweetened condensed milk, and sucrose solutions [36, 42]. Alhadeff and colleagues also reported that NAcC injection of Ex9 increases high fat food intake, with no effect of intra-NAcSh administration [37]. These data strongly suggest that endogenous GLP-1R stimulation within NAcC plays a role in food intake control. Because central GLP-1 has been implicated in the anorexic response to illness and nauseating stimuli such as LiCl [43-45], it was important to evaluate whether NAcC GLP-1 might reduce feeding by causing malaise or viscerosensory distress. To that end, we demonstrated that NAcC GLP-1 treatment does not support conditioned taste aversion [36], and two other labs have shown that it does not induce pica [37, 46]. Together, our data supports the idea that the GLP-1 projection to NAcC is involved in the physiologic control of food intake.

The NAc is well known for its role known in reward-motivated behavior, in general, and manipulations directed at the NAc can affect food intake in this way [2]. Therefore, the data on GLP-1 action in NAc naturally raised the question of whether GLP-1R at this site also influence motivation for food. In support of this possibility, Dickson and colleagues [46] have reported that intra-NAcSh injection of the Ex4 reduces operant responding for sucrose on a PR schedule. Effects of GLP-1R blockade on motivation have not been reported in the

literature, so it is not clear whether there is a physiologic role for NAc GLP-1R in motivation for food or if the effects of GLP-1R stimulation to suppress motivation are purely pharmacologic in nature.

NAc-targeted manipulations can also affect feeding by changing food palatability. This has been evaluated for the NAcSh using the well-validated taste reactivity approach [47]. We hypothesized that NAcC GLP-1R may suppress intake in part by reducing palatability. In a series of experiments, we evaluated this hypothesis by blocking NAcC GLP-1R with Ex9 in rats licking for sucrose solutions [42]. Analysis of licking microstructure can provide an indication of drug effects on palatability, and this is indeed what we observed for intra-NAcC Ex9 treatment. Initial rate of licking, burst size, and burst duration are all associated with palatability of the test solution, each increasing with increasing sucrose concentration [48]. When rats were licking for either 0.1M or 0.25M sucrose, we saw increased rates of licking, burst size and burst duration early, but not late, during meals. These data suggest that blockade of NAcC GLP-1R enhances palatability of these sucrose solutions, effectively causing the rats to treat a given concentration of sucrose as though it is sweeter, and this supports the idea that endogenous GLP-1 action at this site reduces food palatability.

The NAc has not traditionally been considered a mediator of post-ingestive negative feedback signals arising from the gastrointestinal tract, but the fact that GLP-1 neurons can be activated by these signals raises the possibility that NAcC GLP-1R contribute to satiation or satiety. We have found that endogenous activation of GLP-1R in NAcC reduces meal size, with no effect on meal frequency or satiety ratio, when rats are consuming sweetened condensed milk or sucrose [42]. In another experiment, we directly assessed NAcC GLP-1R mediation of gastrointestinal nutrient-induced satiation by infusing 40% sucrose intragastrically during the first few minutes of a meal. The intragastric nutrient infusion strongly suppresses meal size, but pre-treatment with a subthreshold dose of Ex9 injected into the NAcC significantly attenuated that intragastric nutrient effect. Analysis of licking microstructure revealed that intra-NAcC Ex9 prevented the nutrient-induced reduction in meal size by reversing nutrient-induced reductions in burst size and duration early in the meal [42]. This suggests that at least part of the response to gut nutrients is mediated through endogenous stimulation of GLP-R in NAcC, and that the behavioral effect of this stimulation is to reduce palatability.

NTS GLP-1 neurons also project monosynaptically to the VTA [37], so this is another pathway through which these cells may influence food reward. Injection of Ex4 into the VTA suppresses intake of chow [46] and high-fat food [37, 49], and also reduces operant responding for sucrose reinforcement on a PR schedule [46]. The feeding-suppressive effect of intra-VTA Ex4 is primarily mediated by a reduction in meal size, and not meal number [49]. Within the VTA, Ex4 injection increases tyrosine hydroxylase levels, and bath application of Ex4 to slices increases AMPA-mediated excitatory post-synaptic currents in VTA dopamine neurons [49], raising the possibility that the observed effects on food intake and motivation are at least in part mediated by these VTA dopamine cells. Blockade of VTA GLP-1R has been shown to increase high fat food intake [37], so there is a physiologic role for these receptors in feeding control. However, this has not yet been demonstrated for effects of VTA GLP-1R on motivation or other aspects of food reward.

3.2. Orexin projection to the hindbrain

While the GLP-1 projections to reward-related brain areas may provide a route through which gastrointestinal nutrient detection can reduce food reward, we propose that the orexin projection to the hindbrain is a mechanism for the inverse. We suggest that the orexin projection to dorsomedial hindbrain is a mechanism by which highly rewarding food reduces satiation and increases motivation to obtain food.

Orexin-A and orexin-B, also known as hypocretins 1 and 2, are the cleavage products of prepro-orexin [50]. There are also multiple orexin receptors, OX1R and OX2R, with differing affinities for the two peptides [51]. Our laboratory has focused on orexin-A action at the OX1R because orexin-A increases feeding while orexin-B treatment does not [52], and OX1R-specific antagonist treatment reduces feeding with no sign of malaise [53]. Orexin neurons in the LH and perifornical area (PFA) of the hypothalamus project to many feeding-relevant brain regions [54], and OX1R are expressed in many nuclei known to influence feeding [55, 56]. LH orexin cells are activated by environmental cues that predict highly rewarding food stimuli, and 3rd-icv orexin-A not only increases food intake but also increases operant responding for palatable food on a PR schedule [57]. Conversely, peripheral injection of the selective OX1R antagonist SB334867 reduces PR responding for palatable food reinforcement [57-59]. The orexin projection to the VTA, in particular, has been suggested to play a role in palatable food intake. For example, high-fat food intake can be potently stimulated by injection of the μ -opioid receptor agonist DAMGO into the NAc, and this effect can be blocked by OX1R antagonist directed at the VTA [60]. OX1R in the paraventricular thalamus may also play a role, because shRNA-mediated knockdown of OX1R in this region has been shown to reduce high-fat food intake under some circumstances [61].

The orexin neuron projection to the dorsal vagal complex (NTS, AP, and the dorsal motor nucleus of the vagus nerve) has been demonstrated by retrograde tracing and immunohistochemical studies [54, 62], and OX1R are expressed in these nuclei [55, 56]. We and others have shown that these hindbrain OX1R can increase eating through an effect on meal size. Orexin A increases meal size when delivered to the hindbrain via 4th-icv injection in rats licking for sucrose solutions [63] or consuming chow [64], and our evidence suggests that endogenous activation of hindbrain OX1R does the same, because meal size is reduced by 4th-icv injection of SB334867 [64]. Orexin-A is well known to affect physical activity and locomotor behavior, but we do not believe that the feeding effects of 4th-icv orexin-A are secondary to general changes in arousal or motor behavior because we have observed that doses of 4th-icv OrxA and SB334867 that affect meal size have no effects on spontaneous locomotor activity [64]. These data raised the possibility that OX1R stimulation in the hindbrain increase meal size by suppressing the effects of gastrointestinal satiation signals that act on NTS and AP neurons. In support of this idea, Zheng and colleagues [62] showed that gastric nutrient infusion activates hindbrain neurons in close proximity with orexin-A fibers, and we found that the same is true of the pancreas-derived satiation hormone amylin [64]. In a direct test of the hypothesis that hindbrain orexin-A blunts the effect of within-meal satiation signals, we showed that pre-treatment with a subthreshold dose of 4th-icv OrxA blocks the meal size reduction normally observed after amylin injection [64]. We

believe that OX1R in the NTS, specifically, play a role in these effects, because we have observed that direct injection of orexin-A or SB334867, at ventricle-subthreshold doses, influence food intake [65].

Based on the previous evidence that brain OX1R stimulation increases motivation for palatable food, we hypothesized that hindbrain OX1R may play a role food reward as well as in modulating satiation. In a recent study, we found that 4th-icv orexin-A injection robustly increased operant responding for sucrose reinforcement on a PR schedule, while hindbrain application of the OX1R antagonist significantly suppressed responding in this task [65]. We also examined the possible role of hindbrain OX1R in place preference conditioned by high-fat food, another way to examine food reward. In the conditioned place preference model, rats form a Pavlovian association between one side of a two-sided chamber and a high-fat food treat. After repeated pairings of one side with the food and the other side with no food, subjects are placed in the apparatus with the gate between sides opened, so they can explore and spend time in either side. Typically, rats show a strong preference for the high-fat food-paired side of the chamber in this post-training test, but we found that rats given 4th-icv injection of SB334867 prior to the preference test showed no preference for one side vs. the other [65]. Taken together, our data support the proposal that the orexin projection to the dorsomedial hindbrain serves as a pathway through which cues that predict rewarding food can increase motivation to obtain that food and decrease satiation when food is ingested to increase consumption.

3.3. Additional links

This review has focused on GLP-1 and orexin neurons because we have amassed a considerable amount of data on these pathways, but it is likely that there exist numerous links and overlap between brain areas traditionally considered homeostatic and those considered hedonic. Several suggestions of this already exist in the literature. For example, Kanoski and colleagues [66] have shown that leptin-sensitive neurons in the NTS influence motivation for palatable food and food-seeking behavior. Infusion of a ventricle-subthreshold dose of leptin into the medial NTS suppressed operant responding for sucrose and also reversed high-fat food-conditioned place preference. Like GLP-1 neurons, leptin-sensitive neurons in the NTS respond to meal-related gastrointestinal signals such as gastric distention [67], so these leptin-sensitive NTS cells may be serving to translate gastrointestinal feedback into changes in motivation for food. However, the NTS neurons responsible for these effects must be a non-GLP-1 population, because it has previously been established that in the rat, GLP-1 neurons do not respond to leptin [68]. This suggests that there are multiple NTS cell populations that can influence food reward.

PVN oxytocin neurons may serve as another link between homeostatic and hedonic systems, though one may argue that this would be less direct than others discussed here. Oxytocin neurons are activated by leptin and CCK and have been proposed to mediate at least some aspects of gastrointestinal nutrient-induced satiation [69]. These neurons also project to the VTA [70, 71], and we recently examined the role of this projection in control of sucrose intake. We found that intra-VTA oxytocin suppressed intake of 10% sucrose, and blockade of VTA oxytocin receptors with either of two different antagonists increased sucrose intake

[72]. Based on these data, we speculate that the oxytocin-to-VTA projection could be another mechanism through which gastrointestinal satiation signaling changes food reward, although additional research is clearly needed before this conclusion can be made for this oxytocin pathway.

4. Conclusions

This review describes evidence that NTS neurons, traditionally considered to reside firmly within the homeostatic system for feeding control, are capable of influencing both satiation and food reward. Likewise, brain areas such as the NAc and VTA, previously considered exclusively part of the hedonic system, not only influence food reward but also respond to nutrient-related gastrointestinal signals and contribute to meal size control. This sort of dual function has previously been discussed for the LH, as well [21], and it seems likely that further research will reveal the same of other brain regions that have historically been placed in one or the other category. This is not to suggest that all neurotransmitters and neuromodulators acting in these brain regions will affect both food reward and satiation or satiety. To the contrary, it is clear that some segregation of function exists. For example, in multiple studies, antagonism of dopamine D1 and D2 receptors in the NAc has been shown to reduce operant responding for food on a fixed or progressive ratio schedule, indicating a role for endogenous dopamine on motivation for food reward, but the same treatments fail to affect or even increase ad lib feeding [73, 74]. However, as described above, GLP-1 action in this same brain area plays a role in meal size control and the satiation response to gastrointestinal nutrients [42]. Thus, the contributions of the NAc as a whole cannot be defined as exclusively “hedonic,” as was previously the case. The same is true for other brain regions discussed here. While it remains possible, we cannot assume that a given neural circuit will play a role either in food reward or in satiation, but not both. For this reason, I propose that it is not useful to describe brain control of food intake in terms of distinct homeostatic and hedonic systems. Instead we should acknowledge that brain mediation of food reward, adiposity and satiation/satiety signaling is widely distributed with significant overlap.

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Highlights for: Williams, DL

Neural Integration of Satiety and Food Reward: Role of GLP-1 and Orexin pathways

- GLP-1 release in NAc and VTA influences meal size and food reward.
- Orexin action in hindbrain suppresses satiety and increases motivation for food.
- Satiety and food reward are influenced by some of the same neural pathways.

Figure 1.

(A) Simplified model of brain control of homeostatic eating. Leptin acts on hypothalamic (HYP) nuclei and the hindbrain NTS. Neurons within these nuclei and interactions between hypothalamus and hindbrain promote satiation. (B) Simplified model of brain control of hedonic eating. Leptin can act on the VTA, which sends projections to NAc. Output of the NAc includes mPFC, VP, and LH, and changes in activity within these nuclei can enhance or reduce the rewarding value of food. (C) This review focuses on 2 specific circuits that link the models described in (A) and (B). GLP-1 neurons of the NTS detect satiation signals from the GI tract and project to NAc and VTA, where GLP-1R activation promotes satiation and reduces food reward. Orexin-A neurons in the LH are activated by cues that predict highly rewarding food. These neurons project to NTS, where OX1R activation dampens satiation and enhances food reward.