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Review

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

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HIGHLIGHTS

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

Contents

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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 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 (Fig. 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.

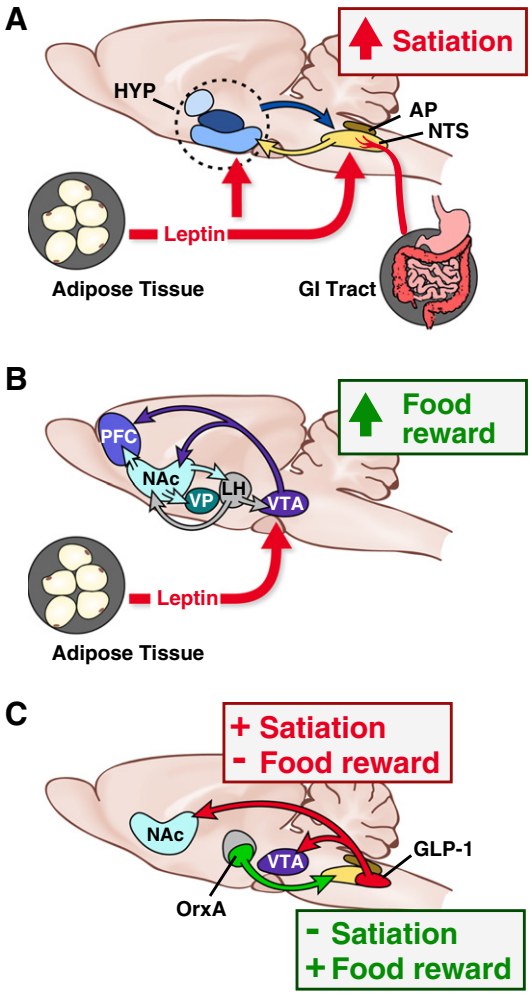

Fig. 1. (A) Simplified model of brain control of homeostatic eating. Leptin acts on hypothalamic (HYP) nuclei and the hindbrain NTS. Neurons within these nuclei and interactions between hypothalamus and hindbrain promote satiation. (B) Simplified model of brain control of hedonic eating. Leptin can act 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.

As currently described, hedonic control of eating involves a number of distinct brain regions (Fig. 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