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Review

Forebrain networks and the control of feeding by environmental learned cues

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HIGHLIGHTS

- Food cues stimulate feeding in sated states (cue induced feeding model).
- Cue feeding circuitry: amygdala–prefrontal cortex–hippocampus–lateral hypothalamus
- Fear cues inhibit feeding in hungry states (fear induced anorexia model).
- Fear cue-induced feeding cessation depends on the central nucleus of the amygdala.

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ABSTRACT

The motivation to eat is driven by a complex sum of physiological and non-physiological influences computed by the brain. Physiological signals that inform the brain about energy and nutrient needs are the primary drivers, but environmental signals unrelated to energy balance also control appetite and eating. The two components could act in concert to support the homeostatic regulation of food intake. Often, however, environmental influences rival physiological control and stimulate eating irrespective of satiety, or inhibit eating irrespective of hunger. If persistent, such maladaptive challenges to the physiological system could lead to dysregulated eating and ultimately to eating disorders. Nevertheless, the brain mechanisms underlying environmental contribution in the control of food intake are poorly understood. This paper provides an overview in recent advances in deciphering the critical brain systems using rodent models for environmental control by learned cues. These models use associative learning to compete with the physiological control, and in one preparation food cues stimulate a meal despite satiety, while in another preparation fear cues stop a meal despite hunger. Thus far, four forebrain regions have been identified as part of the essential cue induced feeding circuitry. These are telencephalic areas critical for associative learning, memory encoding, and decision making, the amygdala, hippocampus and prefrontal cortex and the lateral hypothalamus, which functions to integrate feeding, reward, and motivation. This circuitry also engages two orexigenic peptides, ghrelin and orexin. A parallel amygdalar circuitry supports fear cue cessation of feeding. These findings illuminate the brain mechanisms underlying environmental control of food intake and might be also relevant to aspects of human appetite and maladaptive overeating and undereating.

Contents

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1. Introduction

Hunger drives appetite and eating, while satiety halts them. But, we also eat when not hungry and we cease eating when not sated. That is, the motivation to eat is not only controlled by the basic energy and nutrient needs, but also by other factors that are not directly related to energy homeostasis. Food consumption is regulated by internal, physiological signals from the body (e.g., deficit signals, hormones, circadian rhythm), as well as by external, environmental signals (i.e., sensory, reward, experiential, cognitive, emotional, social) [1–10]. Both physiological and environmental drivers therefore influence how much is consumed in a meal, and which one prevails ultimately depends on their strengths and the state and susceptibility (genetic background and prior experience) of the individual. Nevertheless, the stronger the non-physiological influences are, the harder it is for the homeostatic regulatory system to maintain constancy.

In the contemporary, developed world the environmental contribution to the control of food intake is becoming increasingly more powerful, and as such has an impact on eating dysregulation. Environmental influences are believed to promote overeating and susceptibility to weight gain at least in some individuals, and as such ultimately contribute to the rise in obesity in Western and other developed countries [3,5,11–14]. Environmental and social factors also enhance vulnerability to anorexia nervosa and other eating disorders [15–18]. Deciphering how the contemporary environment (and lifestyle) challenges our physiological systems and why fewer and fewer of us remain resilient to such challenges, are among the most difficult questions puzzling diverse fields of inquiry—from physiology, medicine and neuroscience, social and clinical psychology, to economy and public health and policy.

One of the fundamental questions is how the environmental influences are integrated with the physiological regulatory control and the brain mechanisms that orchestrate it. The focus of this review is on recent advancements in our understanding of the critical neural networks that support one form of non-physiological control of food intake—the control of feeding by environmental learned cues. Learned cues are initially arbitrary cues from the environment that gain the ability to control feeding through associations with rewarding or punishing events. Food predictive cues can stimulate eating despite satiety, while fear cues can inhibit eating despite hunger.

These preparations have therefore provided a framework for analyses of the brain mechanisms underlying the motivation to eat controlled not by hunger, but by environmental cues. The focus has been on the forebrain networks and this paper provides an overview of the findings that the amygdala, prefrontal cortex, hippocampus and lateral hypothalamus form a system that is an essential, minimal circuitry.

Rats have typically been used in these studies because the rat is an established model for mammalian brain structure and function [19], and the behaviors of interest are conserved across mammalian species and highly relevant to humans. Notably, recent work has extended these preparations to mice [20–22], which provides a promising avenue for future work with genetic mice models in identifying the critical molecular substrates. The findings from rodent studies are therefore relevant to our understanding of the fundamental principles of mammalian brain function in regulation of feeding behavior, as well as to understanding aspects of human eating and dysregulation.

2. The control of feeding by environmental learned cues

Towards a long-term aim to decipher the brain mechanisms underlying environmental (non-physiological) motivation to eat, we and others have been designing behavioral preparations suitable for brain imaging and manipulations. The basis for these paradigms is associative learning. Through Pavlovian conditioning procedures rats are trained to associate an initially neutral cue from the environment with a biologically significant event (i.e., an event that is rewarding or aversive). Then, these learned, predictive cues are used to induce motivational states that oppose the existing physiological drive.

In one set of preparations rats are repeatedly presented with a cue (tone or contextual conditioned stimulus, CS) immediately prior to food delivery (unconditioned stimulus, US). Through these associations the CS becomes a signal for the food US, and as such gains the capability to stimulate feeding even in sated states. In another set of preparations rats are repeatedly presented with a CS immediately prior to delivery of mild, electric foot shocks (US). Through these associations the CS becomes a signal for the shocks (US) and as such a "fear cue", which inhibits feeding even in hungry states.

It is beyond the scope of this paper to review other aspects of Pavlovian appetitive conditioning, or studies in which associative learning supports instrumental actions towards food (for recent review on these topics see Holland & Petrovich [89]). That includes important work on formation of preferences or aversions to foods and their cues based on taste and post-ingestive effects (for reviews see [23–26]). Similarly notable is the work on reward processes and hedonic aspects of food consumption, including formation of habits through associative processes (e.g., [27–29]).

2.1. Cue induced feeding

The cue induced feeding phenomenon was originally shown about three decades ago, first in rats and then in humans [30–32] (for recent reviews see [33,34]. In these preparations, a cue that signals food can stimulate eating despite satiety based on its prior association with food consumption when an organism was hungry. Discrete cues (e.g., tone, light) have been typically used in these preparations, however recent studies have demonstrated that the environment in which food is consumed (feeding context) can also stimulate subsequent intake in sated rats on its own (i.e., without any discrete cues) [35,36]. Through a few pairings with food consumption the feeding environment was shown to acquire the ability to later motivate eating, and it did so in a highly selective manner (see Section 2.1.1) [35,36]. Thus, both discrete and contextual cues associated with prior food consumption could later modulate intake demonstrating that cue induced feeding is not bound to the type of stimuli used, but rather it is a fundamental result of learning. These findings are in agreement with a study in mice [20] and a study