Physiology & Behavior 187 (2018) 97–107

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/physbeh

Considering sex differences in the cognitive controls of feeding

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ARTICLE INFO

Keywords:
Sex differences
Learning
Energy regulation
Obesity
Estrogen

ABSTRACT

Women are disproportionately affected by obesity, and obesity increases women's risk of developing dementia more so than men. Remarkably little is known about how females make decisions about when and how much to eat. Research in animal models with males supports a framework in which previous experiences with external food cues and internal physiological energy states, and the ability to retrieve memories of the consequences of eating, determines subsequent food intake. Additional evidence indicates that consumption of a high-fat, high-sugar diet interferes with hippocampal-dependent mnemonic processes that operate to suppress eating, such as in situations of satiety. Recent findings also indicate that weakening this form of hippocampal-dependent inhibitory control may also extend to other forms of learning and memory, perpetuating a vicious cycle of increased Western diet intake, hippocampal dysfunction, and further impairments in the suppression of appetitive behavior that may ultimately disrupt other types of memorial interference resolution. How these basic learning and memory processes operate in females to guide food intake has received little attention. Ovarian hormones appear to protect females from obesity and metabolic impairments, as well as modulate learning and memory processes, but little is known about how these hormones modulate learned appetitive behavior. Even less is known about how a sex-specific environmental factor – widespread hormonal contraceptive use – affects associative learning and the regulation of food intake. Extending learned models of food intake to females will require considerably investigation at many levels (e.g., reproductive status, hormonal compound, parity). This work could yield critical insights into the etiology of obesity, and its concomitant cognitive impairment, for both sexes.

1. Introduction

The regulation of food intake and body weight depends critically on the ability of the brain to detect, monitor, and integrate metabolic, hormonal, and neural signals from the periphery that provide information about the body's energy needs and the status of its energy stores [147,151]. In addition, it is now widely recognized that the decision to eat or refrain from eating also depends on information about the availability of food, the type of food that is available (e.g., is it low-fat, gluten-free, Kosher), the effort needed to acquire it, and knowledge about the likely consequences of eating (e.g., will it satisfy me, will it make me fat). The information comes from our past experiences with food and eating, our evaluations of those experiences, and our expectancies about the likely outcomes of food-seeking (i.e., appetitive) and eating behaviors [62,144]. In addition, we can attempt to suppress appetitive and eating behaviors, even when the urge to eat is strong, by actively inhibiting thoughts [33,54,111] or by avoiding or shifting our attention away from cues in the environment that remind us about food and the pleasures of eating [63]. In other words, in addition to metabolic and hormonal mechanisms, energy regulation depends on the operation of cognitive processes involved in remembering and retrieving past experiences with food and eating, with the development of expectations about the likely outcomes eating and appetitive behaviors, and on the ability to control and inhibit those behaviors.

Moreover, disorders of both energy regulation and cognitive functioning appear to be intertwined. Much evidence from human and nonhuman animal models has accumulated indicating that intake of obesity-promoting diets that are high in saturated fats and sugar (i.e., Western diet) can lead to learning and memory impairments and signs of pathophysiology in brain substrates underlying cognition [5,10,45]. Conversely, a number of findings suggest that excess energy intake and weight gain may be a consequence of interference with the cognitive controls of eating (for review see Yeomans [148]). This pattern of findings is consistent with what has been termed a vicious-cycle of obesity and cognitive decline [33,58]. According to this hypothesis based on rat models, eating a Western diet high in saturated fats and sugars gives rise to disturbances in learning and memory processes that contribute to the inhibitory control of eating. A consequence of this

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https://doi.org/10.1016/j.physbeh.2017.11.023
Received 15 August 2017; Received in revised form 17 November 2017; Accepted 20 November 2017
Available online 22 November 2017
0031-9384/

reduced inhibitory control is increasing intake (i.e., overeating) of Western diet and further deterioration of inhibitory cognitive functioning. The hippocampus, a brain structure long implicated as a crucial substrate for learning and memory (e.g., Squire [128]), has received increasing research attention for its role in the control of eating and appetitive behavior [73,130,132]. However, this work has largely been conducted with male rodents. The role of the hippocampus and learning and memory processes in the control of energy intake and body weight in females has received little attention.

There are many reasons why it is important to fill this gap in knowledge. Women have a greater incidence of obesity [103], and are at greater risk for developing Alzheimer's disease and other forms of dementia, two disorders that are known to harm the hippocampus. Recent reviews have detailed links among sex, the development of Alzheimer's disease [84], and obesity [101]. Furthermore, estrogens are potent regulators of food intake, metabolic homeostasis, and adipose tissue distribution ([105]; also see Clegg et al., this issue). Animal models are clear that estrogens have anorexigenic and anti-obesogenic actions. Yet, despite the protection that estradiol should be affording, premenopausal women are as susceptible to obesity as men [103]. In addition, the cluster of risk factors that define the metabolic syndrome (i.e., abdominal obesity, hypertension, elevated fasting plasma glucose, high serum triglycerides, low high-density lipoprotein (HDL) levels) has reportedly increased most in young women in the 20–39 age range (NHANES from 1988–1994 to 1999–2006; [161]). Another sex-specific variable that has largely been neglected are the short- and longer-term effects of hormonal contraceptives on female energy regulation and cognitive functioning. It is possible that these contraceptives, which the majority of women in the United States use or have used [21], may diminish the protections normally afforded to the brain by estrogens.

The purpose of this paper is to consider the influence of sex on the cognitive controls of energy regulation. This review will be guided by our previously developed model of the learned controls of intake. We will begin by summarizing the associative relationships described by the model. We then examine what is known about sex differences in the learning and memory processes relevant to the model and in the brain substrates of those processes with emphasis on the hippocampus. The paper will conclude with a discussion of how differences in sex hormones may impact both body weight regulation and cognitive functioning. As part of this discussion, we will present a case that research on energy regulation, cognitive functioning, and their interrelationships should consider the effects of widely-used hormonal contraceptives to increase the generality of their findings with respect to human females.

2. An integrative model of the physiological and cognitive controls of energy intake

Food-related environmental cues gain the power to evoke appetitive behaviors that anticipate the occurrence of rewarding postingestive outcomes [70]. This anticipatory response evocation can be accomplished to the extent that such environmental stimuli excite or retrieve the memories of their associated rewarding postingestive outcomes [16]. The stronger is the excitement of those memories, the greater the strength of the appetitive response. However, it has been increasingly recognized that the strength of memory retrieval is also subject to inhibitory learning processes that antagonize or weaken the ability of environmental cues to excite reward memories. This type of inhibitory learning occurs when the memory of a reward is retrieved but the actual reward does not occur [139]. For example, with respect to eating and appetitive behavior, environmental food cues are typically followed by rewarding postingestive stimulation at the outset of a meal, whereas those same cues may be followed by nonrewarding or even aversive postingestive consequences if eating continues after the need for food has been met. Based on longstanding principles of Pavlovian conditioning, inhibitory associations are formed when environmental cues retrieve the memory of postingestive rewards under conditions in which those rewarding postingestive outcomes are not forthcoming [113]. As a result the ability of an environmental cue to excite the memory of rewarding postingestive stimulation will be countered to the extent that those cues are embedded concurrently in inhibitory associations that antagonize the excitement of reward memories (Bouton [14]).

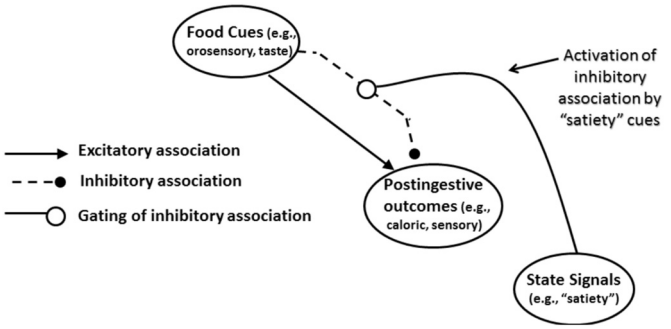

Fig. 1. Mechanisms underlying the learned control of intake by external food cues, memories of postingestive outcomes, and energy state signals. Adapted from [35,156].

Within this framework, the decision to eat or refrain from eating is determined by the degree to which the inhibitory association can block or weaken the retrieval of reward memories. When the inhibitory association is strongly activated, the ability of food cues to excite reward memories will be reduced and feeding behavior will be suppressed. When the inhibitory association is weak, food cues will more strongly excite the memories of rewarding postingestive stimulation which will, in turn, evoke appetitive and eating behavior more strongly. From this perspective, a key question is what determines the degree to which the inhibitory association is activated. We have proposed previously that interoceptive physiological satiety states suppress appetitive and eating behavior by signaling that food cues will not be followed postingestive reward. In other words, this energy state information activates the inhibitory association to suppress feeding [35] (see Fig. 1).

According to this model, three fundamental learning and memory processes are involved with the regulation of energy intake: (1) the formation of excitatory associations between environmental food cues and rewarding postingestive outcomes; (2) the formation of inhibitory associations between environmental food cues and rewarding postingestive outcomes; (3) the modulation of the strength of the inhibitory associations by satiety signals. The next section of this paper will briefly review relevant findings about sex differences in each of these processes as a means of understanding differences in energy and body weight regulation.

3. Sex differences in learning and memory

3.1. Simple cue-reward excitatory learning

In simple learning situations, an excitatory association is formed between two events when one event (a conditioned stimulus (CS) or a response) predicts the occurrence of another event (an unconditioned stimulus (US)). A typical demonstration of simple Pavlovian learning in the laboratory might involve training rodents with a brief auditory or visual CS which signals the subsequent availability of a biologically-relevant US such as food or drugs. As a consequence of exposure to this predictive relationship, the CS comes to elicit a behavior change or conditioned response (e.g., salivation, approaching the place where food is delivered) in anticipation of the presentation of the US. This type of behavior change is one example of simple cue-reward learning (see [113]). Evidence from rodent models indicates that the excitatory CS→US associations formed during simple-cue-reward learning may be stronger and more persistent in females than males. This phenomenon is most established with research on drugs of abuse, in which female