available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

The basolateral amygdala mediates the effects of cues associated with meal interruption on feeding behavior

Ezequiel M. Galarce, Michael A. McDannald, Peter C. Holland*

Johns Hopkins University, USA

ARTICLE INFO

Article history:
Accepted 10 February 2010
Available online 19 February 2010

Keywords:
Amygdala
Conditioning
Cue-potentiated feeding
Scarcity
Bingeing

ABSTRACT

Considerable evidence shows that environmental cues that signal food delivery when rats are food-deprived can substantially potentiate feeding later when rats are food-sated. Similarly, cues associated with meal interruption, food removal or impending food scarcity may also induce increased eating. For example, after learning the association between a discrete "interruption" stimulus and the unexpected termination of food trials, sated rats show enhanced food consumption when exposed to that stimulus. In Experiment 1, unlike sham-lesioned controls, rats with bilateral excitotoxic lesions of the basolateral amygdala (BLA) failed to display such cue-potentiated feeding. In Experiment 2, potentiation of feeding by an interruption signal was found to be food-specific. That is, a stimulus that signaled interruption of trials with one food but not trials with a second food later only facilitated consumption of the first food. These studies extend our knowledge of the psychological and neural processes underlying cue-induced feeding. Understanding these mechanisms may contribute our understanding of the etiology and treatment of binge eating disorders.

1. Introduction

During the last three decades, obesity rates have doubled for adults and tripled for children (e.g., CDC, 2009). Over 72 million people in the United States are now obese. The increasing prevalence of obesity has serious health implications, for example, augmenting the risk of Type II diabetes, cardiovascular diseases, hypertension, joint disorders and some forms of cancer. Additionally, obesity has an exorbitant monetary cost. It has been estimated that the total yearly costs of obesity in the Unites States are approximately $117 billion per year (CDC, 2009). Thus, understanding the etiology of obesity is of the utmost importance.

Prolonged binge eating may lead to obesity (Yanovski, 1993, 2003), and binge episodes can compromise compliance to weight control treatments in obese patients. Although there has been considerable research on metabolic and pharmacological contributions to overeating, there has been less investigation of the role of environmental triggers in binge-like behaviors. Environmental cues play a key part in the initiation, maintenance and termination of feeding behaviors. For example, sights and smells of palatable food can induce eating, regardless of hunger state. Interestingly, cues that signal the absence or removal of food, such as cues for dieting in adolescents and adults, or for prohibition or removal of palatable of food items in children, can also lead to increased eating (e.g. Herman et al., 1983; Herman and Polivy, 1990; Polivy and Herman, 1985, 2002, 2006). Better characterization of the environmental, psychological and neurobiological mechanisms underlying the influence of external triggers on eating is

* *Corresponding author*. Dana Farber Cancer Institute, 44 Binney Street LW 601, Boston, MA 02115, USA.
E-mail addresses: ezequiel_galarce@dfci.harvard.edu (E.M. Galarce), mmcda001@umaryland.edu (M.A. McDannald), pch@jhu.edu (P.C. Holland).

0006-8993/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2010.02.042

essential to progress in developing therapies for eating disorders. The research described in this article examined the role of the basolateral amygdala (BLA) in the control of feeding initiated by environmental cues that signal meal interruption in rats.

Normal food-sated rats are prompted to eat by presentation of a cue that had been previously associated with food while the rats were food-deprived (Holland et al., 2002; Holland and Gallagher, 2003; Petrovich et al., 2002; Petrovich et al., 2005; Petrovich et al., 2007a; Weingarten, 1983, 1985; Weingarten and Martin, 1989; Zamble, 1973). This cue-induced feeding by food-sated rats can be substantial (e.g., as much as 7 g of food in a 10-minute test; Petrovich et al., 2007b), and can come under strong phasic control by discrete auditory or visual cues, waxing and waning precisely with the repeated initiation and termination of those cues (e.g., Galarce et al., 2007). Thus, this example of cue-dependent overriding of satiety cues shares characteristics of binge eating (Herman and Polivy, 1990; Sobik et al., 2005).

By contrast, rats with lesions of the basolateral amygdala or disconnections of BLA and the lateral hypothalamus fail to show such potentiated eating (Holland et al., 2002; Holland and Gallagher, 2003; Petrovich et al., 2002). This observation is consistent with the widely-recognized role for the BLA in various forms of emotional learning related to food. For example, in rats with BLA lesions, Pavlovian cues for food fail to acquire the ability to reinforce new Pavlovian or instrumental learning in second-order conditioning (Hatfield et al., 1996) or conditioned reinforcement tasks (Everitt and Robbins, 1992). Similarly, rats with BLA lesions are unable to access updated information about reward value to alter previously-acquired learned responses from those rewards. In devaluation experiments (see Pickens and Holland (2004), for a review) normal rats and monkeys will spontaneously reduce responding to previously-established cues for food, after the value of a food reinforcer is reduced by either satiety or pairing with illness (Hatfield et al., 1996; Johnson et al., 2009; Malkova et al., 1997). Furthermore, rats with BLA lesions fail to show Pavlovian-instrumental transfer when multiple food reinforcers are used (Corbit and Balleine, 2005). That is, when previously-trained Pavlovian cues for a specific reinforcer are presented while rats are performing an instrumental response to earn that same reinforcer, the instrumental response rates are enhanced in normal rats, but not in rats with BLA lesions.

Interestingly, potentiation of feeding seems to be specific to the food signaled by the potentiating cue (Fedoroff et al., 2003), consistent with suggestions that the BLA is critical to the integration of sensory and motivational information (e.g., Corbit and Balleine, 2005). For example, Petrovich et al. (2007a, b) found that when sated rats were placed in a context previously associated with the delivery of flavored food pellets, they consumed more of the pellets that had been previously presented in that context, but not of either novel or familiar pellets of a different flavor. Likewise, Delamater and Holland (2008) and Galarce et al. (2007) presented food-deprived rats with pairings of two different auditory cues with two distinctive food reinforcers (sucrose and maltodextrin). After satiation on chow, rats were given access to each of the reinforcers in separate sessions, in which one or the other auditory cue was presented. Consumption was enhanced when the presented cue had signaled the available food, but not when it had signaled the other food.

Some studies have shown that uncertainty about food availability can also have orexigenic properties (e.g. Herman et al., 1983; Herman and Polivy, 1990; Polivy and Herman, 1985, 2002, 2006). Recently, Galarce and Holland (2009) found that cues that signaled interruption of a meal also potentiated feeding later when rats were sated. In those studies, food delivery occurred randomly during presentations of one auditory cue (CS+), but when another auditory "interruption signal" (IS) cue was presented at random times during the first cue, both that cue and food delivery was canceled. Subsequently, the IS was found to potentiate feeding of satiated rats.

Experiment 1 was designed to begin a neural analysis of IS-induced feeding. Because previous experiments showed that feeding induced by IS and CS+ share common characteristics, such as phasic stimulus control (Galarce and Holland, 2009), and the BLA is important to CS+ induced feeding, we sought to describe the role of the BLA in IS-induced feeding. If BLA plays a role in IS-induced feeding, then, given BLA's role in integrating sensory and motivational information, it is likely that this type of cue, like a CS+, also controls feeding in food-specific manner. Thus, Experiment 2 was designed to determine whether control of food consumption by an IS is food-specific.

2. Results

2.1. *Experiment 1*

Experiment 1 was designed to determine the role of the BLA on IS-induced feeding. First, all animals underwent bilateral BLA infusions of N-methyl-D-aspartate (BLA-lesioned group) or PBS vehicle (sham group). Two weeks later, all rats were food-deprived to 85% of their ad-lib weights. During the first stage of Pavlovian training, rats learned to associate presentation of an auditory stimulus (CS+) with sucrose (US). Later in training, CS+ trials were interrupted by another cue (IS). After IS presentation, the CS+ was terminated and no more food was delivered until the following trial. After one week of ad-lib access to lab chow, three consumption tests evaluated the influence of CS+, no cue, or IS presentations on US intake.

Of the 11 BLA-lesioned rats, 2 were excluded because their lesions covered less than 75% of BLA. The 9 remaining rats had 91±3% bilateral BLA damage, which included lateral, basal and accessory basal nuclei. Most lesions spared CeA, and damage to that region was minimal when observed (2.7±0.5%). Some animals showed ventricular enlargement at the caudal portion of the lesions. No rat manifested recovery complications after surgical procedures. At the end of the recovery period, there was no significant difference between the weights of the BLA-lesioned (433±6 g) and sham-lesioned (441±4 g) rats ($F(1,13)=1.10$, $p=0.313$). Fig. 1 shows a photomicrograph of representative BLA (a) lesion and (b) sham brains, and Fig. 2 illustrates the extents of BLA lesions for all 9 animals used in this experiment.

2.1.1. *Pavlovian conditioning — Phase I*

Training was evaluated with a 3-way ANOVA which included group (sham or BLA), session and period (CS+ or ITIs). All rats,