Behavioural Brain Research 312 (2016) 219–230

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Western diet and the weakening of the interoceptive stimulus control of appetitive behavior

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HIGHLIGHTS

- Rats learn to use deprivation states as discriminative cues for sucrose.
- When trained in compound, food cues do not overshadow energy state cues for appetitive control.
- Western diet intake impairs the ability to use food deprivation cues.
- Hippocampal lesions reduce sensitivity to the interoceptive satiety cue CCK.

ARTICLE INFO

Article history:
Received 4 September 2015
Received in revised form 8 June 2016
Accepted 10 June 2016
Available online 14 June 2016

Keywords:
Externality
Obesity
Hippocampus
Satiety
Learning
Memory

ABSTRACT

In obesogenic environments food-related external cues are thought to overwhelm internal cues that normally regulate energy intake. We investigated how this shift from external to internal stimulus control might occur. Experiment 1 showed that rats could use stimuli arising from 0 and 4 h food deprivation to predict sucrose delivery. Experiment 2 then examined (a) the ability of these deprivation cues to compete with external cues and (b) how consuming a Western-style diet (WD) affects that competition. Rats were trained to use both their deprivation cues and external cues as compound discriminative stimuli. Half of the rats were then placed on WD while the others remained on chow, and external cues were removed to assess learning about deprivation state cues. When tested with external cues removed, chow-fed rats continued to discriminate using only deprivation cues, while WD-fed rats did not. The WD-fed group performed similarly to control groups trained with a noncontingent relationship between deprivation cues and sucrose reinforcement. Previous studies provided evidence that discrimination based on interoceptive deprivation cues depends on the hippocampus and that WD intake could interfere with hippocampal functioning. A third experiment assessed the effects of neurotoxic hippocampal lesions on weight gain and on sensitivity to the appetite-suppressing effects of the satiety hormone cholecystokinin (CCK). Relative to controls, hippocampal-lesioned rats gained more weight and showed reduced sensitivity to a 1.0 ug but not 2.0 or 4.0 ug CCK doses. These findings suggest that WD intake reduces utilization of interoceptive energy state signals to regulate appetitive behavior via a mechanism that involves the hippocampus.

1. Introduction

A longstanding idea is that the regulation of energy intake and body weight depends on the integrative control by external food-related cues in the environment and physiological signals arising from the internal milieu. In fact, according to several accounts, the ability of such environmental food cues to evoke appetitive and consummatory responding is held in check by interoceptive satiety signals that inhibit those behaviors (e.g., [1–3]). It is not surprising that, within this framework, excess intake and body weight gain have often been seen as a consequence of a reduction in the control of feeding by internal cues relative to that by external cues [4,5].

A similar idea is expressed in Woods's model of energy regulation [6]. This model proposes that in humans and other animals, meal initiation depends almost exclusively on the presence of

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http://dx.doi.org/10.1016/j.bbr.2016.06.020
0166-4328/

environmental food cues, whereas meals are terminated, and presumably new intake is suppressed, by the emergence of interoceptive satiety cues. Thus, energy dysregulation leading to obesity can be seen as a failure of interoceptive satiety cues to adequately counter response evocation by food cues in the environment. That is, increased sensitivity to external food-related stimuli by obese compared to lean people may be based on insensitivity to internal signals that normally suppress the ability of external cues to evoke appetitive and consummatory responses.

Most of the world's obese and overweight populations live in Western and Westernized societies in which environmental cues associated with highly-palatable, energy-dense foods and beverages are ubiquitous [7]. This combination of heightened sensitivity to food cues and the creation of an "obesogenic" environment where contact with these cues is almost unavoidable may have produced a calamitous "perfect storm" in the current obesity pandemic. The so-called "Western diet" is widely popular in these places and contains high levels of saturated fats and processed sugars [8,9]. Intake of the Western diet is not only associated with excess energy intake and obesity, but also with increased incidence of brain pathology and cognitive dysfunction [10].

A variety of evidence shows that consuming a Western-style diet can impair the performance of rodents and humans on learning and memory problems that depend on the functional integrity of the hippocampus [11–15]. Other studies in our laboratory and elsewhere have demonstrated that the ability to use interoceptive food deprivation and hydrational stimuli to solve discrimination problems is also dependent on the hippocampus [16–19]. In contrast, there is little evidence that the hippocampus is required to learn about simple nonspatial discriminative stimuli [20,21]. Considered together, this set of findings is consistent with the idea that a WD-induced interference with hippocampal function could diminish appetitive control by interoceptive relative to exteroceptive cues. In other words, such a loss of hippocampal function could promote overeating based on a weakened ability to use interoceptive satiety signals to counter response evocation by food and food-related external cues.

While external food cues in the obesogenic environment are often described as overwhelming the internal biological controls of intake, the mechanisms that underlie this phenomenon remain to be specified. The purpose of the present paper is to investigate the possibility that the weakening of internal relative to external stimulus control of appetitive behavior is a consequence of a Western diet-induced impairment in the ability to discriminate between interoceptive energy state signals.

Previous research in our laboratory has shown that rats can use the interoceptive stimulus consequences of different levels of food deprivation as discriminative cues for the delivery of either mild shock (e.g., [16,22]) or sucrose pellets [23]. Evidence for this learning has been obtained after as few as three reinforced trials [17], and discriminative control generalizes from cues produced by food deprivation and satiation to hormonal manipulations such as exogenous administration of ghrelin [23], cholecystokinin-octapeptide (CCK-8) [24,25], and leptin [25] that are known to promote or suppress feeding behavior. Experiment 1 expanded on these earlier studies by employing levels of food deprivation and satiation more comparable to what rats would experience as part of their normal meal patterning (i.e., 0 and 4 h food deprivation) (e.g., [26]). Experiment 2 investigated (a) how cues arising from low levels of food deprivation control appetitive behavior in compound with discrete external cues, and (b) how consuming a Western diet affects discriminative control by food deprivation cues in the presence and absence of external stimuli. Experiment 3 compared rats with selective ibotenate lesions of the hippocampus and intact controls with respect to post-surgical body weight and sensitivity to the intake-suppressing effects CCK-8. CCK-8 has long been considered to be a hormonal satiety signal based on findings that the release of endogenous CCK from the intestine after eating is correlated with suppression of food intake, administration of exogenous CCK reduces food intake, and administration of CCK antagonists increases food intake (for review [27]). Further, studies of deprivation discrimination learning have shown that exogenous CCK produces interoceptive stimuli that generalize to cues arising from 0 h food deprivation [24,25].

2. Methods

2.1. Apparatus

All training and testing sessions were conducted in 8 identical conditioning chambers constructed of aluminum end walls and Plexiglas sidewalls, measuring 59.7 × 34.3 × 26.35 cm (Lafayette Instruments). The floors of the chamber consisted of stainless steel metal rods measuring 0.48 cm in diameter and 1.07 cm apart. The auditory stimulus was a tone (1500 Hz, 74–76 db, Sonalert, Lafayette Instruments). The light conditioned stimulus measured 2.4 cm in diameter and was located 5 cm to the left of and 6 cm above the recessed food magazine. A computer-operated infrared monitoring system located in the recessed food magazine was used to record food magazine entries. Reinforcers were 45 mg sucrose pellets (Research Diets, P.J. Noyes Company Inc., Lancaster, N.H.).

2.2. Experiment 1: learning to use food deprivation states as discriminative cues for sucrose

2.2.1. Subjects

The subjects were 16 naïve male Sprague-Dawley rats (Harlan), weighing 250–300 g upon arrival. Rats were individually housed in exhaust ventilated plastic tub cages (Optirat). The colony room was maintained on a 10:14 h light:dark cycle with lights on at 1330 h. All rats were maintained on standard laboratory rodent chow (LabDiet, Formula 5001), which has a caloric density of 3.0 kcal/g (approximately 13% kcal from fat, 56% kcal from carbohydrates). All rats were maintained on ad libitum water throughout the experiment. All procedures for the care and treatment of the rats in this experiment were approved by the American University Institutional Animal Care and Use Committee.

2.2.2. Behavioral training

After acclimating to the colony room for approximately two weeks, the rats were assigned to one of two training groups (n = 8) matched on body weight. All rats were then placed on a daily alternating schedule of 0 h and 4 h food deprivation throughout the remainder of the study. Rats were given 24 h access to ad lib chow on 0 h days and deprived for 4 h prior to training on 4 h days. All rats were placed in the apparatus for 6 min training sessions. Rats in Group 0+ were reinforced under 0 h deprivation (~24 h ad libitum access to food), but not reinforced under 4 h deprivation, while Group 4+ received the opposite contingency. When training sessions occurred under the rewarded deprivation, the feeder activated and dispensed five 45 mg sucrose pellets into the food magazine 4 min after the start of the session. When sessions occurred under the nonrewarded deprivation state, the pellet dispensers operated, but pellets were not dispensed into the food cup. Rats remained in the chambers for 2 additional minutes following pellet dispenser activation before being returned to their home cages. Throughout the experiment, the 4 min period that ended with feeder activation was further subdivided into twenty-four 10 s intervals. The percent of these intervals during which the infrared photobeam inside the food magazine was broken (i.e., percent beam breaks) was the index of appetitive behavior throughout the experiment. Training sessions were conducted at 1330 h but