Physiology & Behavior 180 (2017) 78–90

Contents lists available at ScienceDirect

Physiology & Behavior

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

Cognitive impairment and gene expression alterations in a rodent model of binge eating disorder

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ARTICLE INFO

Keywords:
Binge eating
High fat
Cognition
Bdnf
TrkB
Serotonin receptor

ABSTRACT

Binge eating disorder (BED) is defined as recurrent, distressing over-consumption of palatable food (PF) in a short time period. Clinical studies suggest that individuals with BED may have impairments in cognitive processes, executive functioning, impulse control, and decision-making, which may play a role in sustaining binge eating behavior. These clinical reports, however, are limited and often conflicting. In this study, we used a limited access rat model of binge-like behavior in order to further explore the effects of binge eating on cognition. In binge eating prone (BEP) rats, we found novel object recognition (NOR) as well as Barnes maze reversal learning (BM-RL) deficits. Aberrant gene expression of brain derived neurotrophic factor (*Bdnf*) and tropomyosin receptor kinase B (*TrkB*) in the hippocampus (HPC)-prefrontal cortex (PFC) network was observed in BEP rats. Additionally, the NOR deficits were correlated with reductions in the expression of *TrkB* and insulin receptor (*Ir*) in the CA3 region of the hippocampus. Furthermore, up-regulation of serotonin-2C (*5-HT$_{2C}$*) receptors in the orbitoprefrontal cortex (OFC) was associated with BM-RL deficit. Finally, in the nucleus accumbens (NAc), we found decreased dopamine receptor 2 (*Drd2*) expression among BEP rats. Taken together, these data suggest that binge eating vegetable shortening may induce contextual and reversal learning deficits which may be mediated, at least in part, by the altered expression of genes in the CA3-OFC-NAc neural network.

1. Introduction

Binge eating disorder (BED) involves intermittent, distressful over consumption of palatable food (PF) in brief periods of time, and this behavior, unlike bulimia or anorexia nervosa, is often not accompanied with compensatory behaviors [1]. According to DSM-V, binge episodes should be associated with at least three of the following criteria: (1) eating more rapidly than normal, (2) eating when not physically hungry, (3) eating until uncomfortably full, (4) eating alone because of shame, and (5) feeling depressed, guilty, or disgusted with oneself after overeating [1]. Factors that can influence binge eating episodes are thought to include environmental and physiological stress, dietary restraint, and intermittent exposure to energy-rich palatable food [2]. Many animal models of binge eating disorder have successfully employed these factors to mimic characteristics of human binge eating [3–7]. Regarding the food content of binges, clinical data suggests that binge eating disorder patients consume significantly more energy from fats than proteins during a binge meal [8,9]. In a rodent model of BED, higher intermittent intake of highly PF, rich in fats and sugar, was found to predict binge eating behavior independent of body weight gain or obesity [10].

On a global scale, excessive consumption of highly palatable, and high fat (HF) foods is a major public health concern. On an individual basis, controlling ones' consumption of these foods, given their overwhelming presence in modern western diets and innate physiological drives to consume energy-rich foods, requires intact cognitive processes including response inhibition, goal-directed learning, behavioral flexibility, attention, working memory, or decision-making [11]. Clinical data suggests that high fat intake in all age groups negatively correlates with memory, cognitive flexibility, or executive functioning [12–14]. There is abundant evidence linking high fat diet (HFD) exposure to cognitive decline in the animal models [15–18]. Interestingly, even short-term exposure to HFD (< 20 days) in the rodent has been shown to significantly impair performance on spatial working memory and object recognition tasks [19,20].

Despite clear evidence from both human and rodent studies linking high fat diet to cognitive impairments, our current understanding of cognitive impairments in BED is very limited. Behavioral disinhibition or loss of control over eating, is mainly regulated by prefrontal cortex, and post treatment relapses occur commonly in BED patients [21,22],

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http://dx.doi.org/10.1016/j.physbeh.2017.08.004
Received 3 May 2017; Received in revised form 10 August 2017; Accepted 11 August 2017
Available online 15 August 2017
0031-9384/

suggesting that some other facets of BED such as its cognitive implications need to be taken into consideration in developing effective treatment strategies. In one study, BED patients performed more poorly on a battery of neuropsychological tests for cognitive flexibility, attention, decision-making, as well as visuospatial recognition and recall memory when compared to patients with anorexia nervosa and healthy controls [23]. In another study of patients with known neurodegenerative diseases, those with co-morbid binge eating disorder had greater atrophy in right-sided orbitofrontal-insular-striatal circuit and were more likely to be diagnosed with frontotemporal dementia [24]. While BED commonly occurs in normal-weight individuals, obese individuals with BED have significantly higher rates of dietary disinhibition, psychiatric comorbidities, and cognitive dysfunction [25–27] as well as higher rates of metabolic disorder and increased inflammatory markers [28]. In one study involving body weight matched overweight women, those with BED had greater risk taking behavior, reduced utilization of feedback processing, impaired decision-making and cognitive flexibility [29]. However, another study in morbidly obese individuals with or without BED found no differences in several cognitive tests [30]. Despite these sometimes conflicting findings from human studies, there are no published reports to our knowledge that have assessed the effects of binge eating on cognitive performance and the expression of genes underlying cognition in an animal model.

Finally, although the neural mechanisms underlying cognitive impairment in BED are largely unknown, several studies have identified genes involved in the regulation of different learning and memory processes. Among the most robust findings is the observation that performance on object recognition and spatial learning and memory tasks depends on intact expression of brain derived neurotrophic factor (Bdnf) and its receptor tropomyosin receptor kinase B (TrkB) in the hippocampus (HPC) [31–34]. BDNF-TrkB binding contributes to the control of activity dependent synaptic regulation, long term potentiation, and neurogenesis, which are all critical for learning and memory formation [35]. Similar to the hippocampus, intact BDNF-TrkB expression in the prefrontal cortex (PFC) can regulate working memory, discrimination reversal learning as well as object recognition learning [36–40]. Furthermore, effects of high fat diet on disrupting both hippocampal and cortical bdnf and trkb expression have been reported in rodent models [38,40–42]. Hippocampus and PFC interact to synchronize contextual, spatial learning and memory retrieval with working memory, decision-making, and executive functions [43,44]. These executive functions mainly contributing to behavioral flexibility, reversal learning, and set-shifting are primarily regulated by adequate functioning of serotonergic and dopaminergic receptors signaling in the PFC and the striatum [45–51].

Though the effects of HFD and obesity on cognition have now been well studied and the underlying mechanisms are becoming more apparent, neuronal causes and consequences of BED are less understood and cannot be easily determined in human subjects. Therefore, several rodent models of BED have been developed. Some use food restriction and refeeding [3], while others employ various stressors at the end of food restriction-refeeding cycles to drive escalation in PF intake [4,52]. In this study, we employed a previously described limited access model of BED, which involves intermittent exposure to a fat source (vegetable shortening) to induce binge eating episodes [6]. This model was adopted as it remains independent of the impact that food restriction or stress may have on the behavior or the neurochemistry of animals. Rats in our study were further divided into binge eating prone (BEP) and binge eating resistant (BER) categories based on the differences in their fat intake, as seen in some of the previous studies [7,10], to further understand behavioral and neuronal aspects of these extreme phenotypes.

Thus, the objectives of this study were to employ the limited access rat model of BED to understand the cognitive deficits associated with binge eating shortening and to further explore the underlying neuronal mechanisms. We show differences between binge eating prone versus binge eating resistant and other control groups in fat intake, cognitive performances as well as changes in underlying patterns of neuronal gene expression. Our findings suggest that binge eating prone rats have impaired contextual and reversal learning, which may be related, at least in part, to the expression of tropomyosin receptor kinase B (*TrkB*) and insulin receptor (*Ir*) in the CA3 region of HPC and serotonin-2C (*5-HT$_{2C}$*), dopamine receptor 1 (*Drd1*) or dopamine receptor 4 (*Drd4*) in the orbitoprefrontal cortex (OFC). We also found decreases in dopamine receptor 2 (*Drd2*) in the nucleus accumbens (NAc) region of BEP rats, which closely correlated with the amounts of shortening intake during binge episodes. Together, these results indicate that binge eating shortening may be associated with cognitive impairments, and to the alterations in expression of genes in the CA3-OFC-NAc neural network. Whether these cognitive deficits are a consequence of the binge eating behavior, or are preexisting and contribute to the development of binge eating will be an important focus of future studies.

2. Methods

2.1. Animals

Forty-four male, young adult (50–55 PND at the beginning of the study) Sprague-Dawley rats (Harlan) were housed individually in tub cages in a temperature and humidity-controlled room under a 12:12 h light-dark schedule. Throughout the experiment, all rats had ad libitum access to water and standard laboratory rodent chow (2018 Teklad, Harlan, Frederick, MD; 3.1 kcal/g: fixed formula diet of 18.6% protein, 44.2% carbohydrate, and 6.2% fat). All rats were initially habituated to the laboratory environment for one week. All procedures were approved by the Institutional Animal Care and Use Committee at Johns Hopkins University.

2.2. Limited access model of binge eating disorder

Rats were divided into 3 experimental groups: intermittent access binge group (binge, n = 28), daily access group (DAILY, n = 8) and chow controls (CON, n = 8). All these groups were housed in the same room for a total of eight weeks of binge paradigm, during which each group was maintained on its respective diet schedule. In our study, we employed a previously described limited access model of binge paradigm [6], using pure hydrogenated fat vegetable shortening (Crisco® brand All-Vegetable Shortening, Procter and Gamble, Cincinnati, OH; percent of calories as fat: 100%; 9.2 kcal/g) as a source of high fat. Our paradigm was slightly modified from Corwin's limited access model such that, in our study, rats in the binge group were further divided into binge prone and resistant groups. The binge and DAILY groups were initially provided overnight shortening access to prevent neophobia during the study. Starting on PND 60, the binge group was given intermittent, restricted access to shortening on Monday, Wednesday and Friday (M/W/F) for 1 h each day. The DAILY group was given access to shortening every day for one hour each at the same time as the binge group. Both the groups received access to shortening two hours before onset of the dark cycle. Food intake and body weight of all the rats were monitored daily. CON rats received only chow diet throughout the eight weeks of this study. After the first four weeks of exposure to the binge paradigm, the binge group rats were further classified into binge eating prone (BEP), binge eating neutral (BEN), and binge eating resistant (BER) groups based on the amounts and consistency in the kilocalories (kcals) of shortening consumed. In previous studies of BEP/BER rat models, alternative PF sources as well as different statistical methods have been employed for classifying these phenotypes [7,10]. In our study, the statistical cut-off for the classification of BEP versus BER group was defined as above or below two times the standard error of the average shortening intake of all the rats across 4 weeks. After which the rats were ranked based on the amounts of shortening intake and the consistency in the intake for all the shortening access days (M/W/F)