Physiology & Behavior 130 (2014) 99–107

Contents lists available at ScienceDirect

Physiology & Behavior

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

Effects of energy status and diet on *Bdnf* expression in the ventromedial hypothalamus of male and female rats

Xian Liu [a], Zheng Zhu [b,c], Manu Kalyani [b], James M. Janik [a,b], Haifei Shi [a,b,*]

[a] Cell, Molecular, and Structural Biology, Miami University, OH, United States
[b] Physiology and Neuroscience, Department of Biology, Miami University, OH, United States
[c] Department of Statistics, Miami University, OH, United States

HIGHLIGHTS

- Sex differences existed in VMH *Bdnf* expression in response to a high-fat diet and changes of energy status.
- VMH *Bdnf* expression was down-regulated by dietary intervention in male rats.
- VMH *Bdnf* expression was stable in female rats under dietary disruption.

ARTICLE INFO

Article history:
Received 16 December 2013
Received in revised form 4 March 2014
Accepted 26 March 2014
Available online 4 April 2014

Keywords:
Dietary intervention
Glucose
Leptin
Estradiol
High-fat diet

ABSTRACT

Sex differences exist in the regulation of energy homeostasis in response to calorie scarcity or excess. Brain-derived neurotrophic factor (BDNF) is one of the anorexigenic neuropeptides regulating energy homeostasis. Expression of *Bdnf* mRNA in the ventromedial nucleus of the hypothalamus (VMH) is closely associated with energy and reproductive status. We hypothesized that *Bdnf* expression in the VMH was differentially regulated by altered energy balance in male and female rats. Using dietary intervention, including fasting-induced negative energy status and high-fat diet (HFD) feeding-induced positive energy status, along with low-fat diet (LFD) feeding and HFD pair-feeding (HFD-PF), effects of diets and changes in energy status on VMH *Bdnf* expression were compared between male and female rats. Fasted males but not females had lower VMH *Bdnf* expression than their fed counterparts following 24-hour fasting, suggesting that fasted males reduced *Bdnf* expression to drive hyperphagia and body weight gain. Male HFD obese and HFD-PF non-obese rats had similarly reduced expression of *Bdnf* compared with LFD males, indicating that dampened *Bdnf* expression was associated with feeding a diet high in fat instead of increased adiposity. Decreased BDNF signaling during HFD feeding would increase a drive to eat and may contribute to diet-induced obesity in males. In contrast, VMH *Bdnf* expression was stably maintained in females when energy homeostasis was disturbed. These results suggest sex-distinct regulation of central *Bdnf* expression by diet and energy status.

© 2014 Elsevier Inc. All rights reserved.

1. Introduction

Energy homeostasis is regulated by a complex neuroendocrine system involving many central and peripheral signals. Neuronal signals in the hypothalamus and circulating hormones produced by peripheral endocrine and exocrine cells cooperatively control feeding and energy expenditure to ensure the presence of sufficient energy stores during periods of food scarcity and/or to avoid obesity during periods of food abundance [1]. Sex differences exist in the regulation of energy balance in response to calorie scarcity or excess, due to the different roles played by males and females in survival of the species. Specifically males are more responsible for hunting and gathering, while females are responsible for gestation, lactation and care-giving, and both must maintain energy homeostasis to support the survival and development of themselves as well as their offspring [2].

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and plays an important role in the development, differentiation, growth, and maintenance of the nervous system. BDNF is also an anorexigenic signal. *Bdnf* mRNA is expressed at high levels in the ventromedial nucleus of the hypothalamus (VMH) [3,4], an area associated with feeding and metabolism, and lesion of the VMH leads to hyperphagia and obesity in a variety of species, including humans [5]. The VMH is also a target for BDNF to regulate energy balance [6]

Abbreviations: BDNF, brain-derived neurotrophic factor; HFD, high-fat diet; HFD-PF, high-fat diet pair-feeding; LFD, low-fat diet; VMH, ventromedial nucleus of the hypothalamus.

* Corresponding author at: Department of Biology, Miami University, 700 E. High St., Oxford, OH 45056, United States. Tel.: +1 513 529 3162; fax: +1 513 529 6900.
E-mail address: shih@miamioh.edu (H. Shi).

http://dx.doi.org/10.1016/j.physbeh.2014.03.028
0031-9384/© 2014 Elsevier Inc. All rights reserved.

and glucose homeostasis [7]. Central administration of BDNF attenuates hyperglycemia and improves glucose metabolism in an insulin-deficient diabetic model [7], and also potently decreases caloric intake [8–10], with estrous female rats responding to a lower dose of BDNF than males [8]. VMH *Bdnf* expression increases following the estradiol peak in female rats [8]. *Bdnf* deficient mice display hyperphagia, hyperglycemia, and obesity [11–14]. *Bdnf* expression in the VMH is regulated by alterations of energy status [15,16] and nutrient-related signals, such as leptin [17] and glucose [18]. Leptin activates neurons within the VMH [19], and stimulates *Bdnf* expression and increases BDNF protein concentration in the VMH [17]. Systemic or central administration of glucose induces *Bdnf* mRNA expression only in the VMH [18]. Additionally, high blood glucose levels inhibit VMH *Bdnf* expression in rodents [16] and inhibit BDNF release into the circulation from the CNS in humans [20].

The mechanisms involved in obesity development have been investigated using a rodent model of high-fat diet (HFD)-induced obesity that produces hyperphagia and hyperleptinemia similar to human obesity. While previous studies have demonstrated that BDNF is involved in obesity development in genetic rodent models [11,13,15] and in chronic 14-week HFD feeding-induced obesity [16], no study has examined the role of BDNF at an early stage of obesity development using an acute HFD feeding model. As with many key regulators of energy balance, most previous rodent studies investigating hypothalamic *Bdnf* gene expression have been conducted exclusively in male rodents. Few studies have investigated sex differences in the regulation of hypothalamic *Bdnf* expression.

This study aimed to investigate whether any sex difference exists in the energy status-associated change of *Bdnf* expression. We hypothesized that VMH *Bdnf* expression was differentially regulated by altered energy status in male and female rats. Using quantitative PCR on microdissected VMH tissue, responses of VMH *Bdnf* mRNA levels to variations of caloric density or quantity in male and female rats were examined. Food deprivation for 24 h produced an acute negative energy balance that corresponded to clinically relevant regimens as in glucose tolerance tests. HFD feeding for four days and four weeks produced an acute and a chronic positive energy status, respectively. Comparison between HFD feeding-induced acute and chronic positive energy status would determine if the difference in *Bdnf* expression is an early event that initiates long-term alteration in energy homeostasis leading to obesity development, *i.e.*, whether the difference in *Bdnf* expression is a cause or consequence of HFD-induced obesity. Furthermore, an energy-restricted HFD pair-feeding (HFD-PF) method was used so that rats on a standard rodent diet with low-fat content (LFD) and rats on a HFD were fed identical amounts of calories. This technique was used to determine whether difference in *Bdnf* expression would remain once body weight and adiposity of HFD and LFD rats were normalized, and thus would allow us to dissociate the effects of eating a diet that is high in fat from the effects of resulting obesity. Circulating estradiol, leptin, and glucose concentrations were also measured to indicate any association between peripheral reproductive- and nutrient-related signals and central *Bdnf* expression.

2. Methods

2.1. Animals and diets

Seventy male and seventy female Long-Evans rats (Harlan, Indianapolis, IN; n = 10 per group) were individually housed in separate rooms with controlled temperature (22–24 °C) and 12 h light–dark cycle (light on 0200 h–1400 h). To compare sex differences in VMH *Bdnf* mRNA levels which are dependent on energy status and adiposity [15,16], body fat-matched male rats at 8–10 weeks of age and female rats at 14–16 weeks of age were obtained. Ovarian cycles of female rats were determined by examining predominant cell types of vaginal cytology samples [8], and all female rats included were cycling normally throughout the current study. To be consistent, all female rats were analyzed in the estrus because estrogen levels of female rats fluctuate [21]. Rats were fed a LFD (Teklad, Madison, WI) and their body weights and caloric intake were monitored during acclimation. After acclimation, a HFD (D12451, Research Diets, Inc., New Brunswick, NJ) was provided to the HFD-fed groups. Each gram of LFD and HFD contains similar amounts of proteins (LFD: 0.243 g; HFD: 0.237 g) and carbohydrates (LFD: 0.402 g; HFD: 0.414 g), but different amounts of fat (LFD: 0.047 g; HFD: 0.236 g). Each gram of LFD provides 3.003 kcal, whereas each gram of HFD provides 4.728 kcal. All animal procedures were approved by the Institutional Animal Care and Use Committee of Miami University and were in accordance with the Guide for the Care and Use of Laboratory Animals.

2.2. Experimental design

2.2.1. Exp 1: 24-hour feeding or fasting

Twenty male and twenty female rats were assigned to either a feeding or a fasting group. Body weights and fat were measured when the feeding or fasting period was initiated and again 24 h later before rats were sacrificed. Female rats started the feeding or fasting regimen in proestrus and were sacrificed 24 h later during estrus.

2.2.2. Exp 2: 4-day LFD or HFD feeding

Twenty male and twenty female rats were assigned to either a LFD or a HFD group. Rats assigned to LFD groups remained on LFD, whereas rats assigned to HFD groups were placed on HFD for 4 days. Female rats started the HFD when in estrus and were sacrificed 4 days later when they were again in the estrous phase of the cycle.

2.2.3. Exp 3: 4-week LFD or HFD feeding

Thirty male and thirty female rats were assigned to one of the three groups, LFD, HFD, or HFD-PF. Rats in the LFD group remained on the LFD for the entire 4 weeks; rats assigned to the HFD groups had unlimited access to the HFD for 4 weeks; and rats assigned to HFD-PF groups were also placed on the HFD, but they were pair-fed so that they consumed the same number of calories as the same sex animals in the LFD group consumed. Female rats were sacrificed in the estrous phase after the 4-week feeding period. One study shows that mice exhibit anovulation 4 weeks after feeding a HFD containing 22% fat [22]. In another study, after feeding the same HFD as the current study for 6 weeks, 20% of diet-resistant rats and 80% of diet-induced obese rats fail to display regular estrous cycles [23]. Our unpublished observation indicates that female rats tend to have irregular ovarian cyclicity beginning the fifth week of HFD feeding. Thus, the current study was terminated after 4 weeks. HFD males and females gained more weight and fat than their same sex LFD groups, indicating that positive energy status was established 4 weeks after *ad libitum* HFD feeding.

2.3. Experimental procedures

2.3.1. Body weight, body composition, and caloric intake

Daily body weight and food intake were measured to the nearest 0.01 g. Food intake was calculated by the difference of weights of food hoppers over 24 h and corrected for spillage. Food intake data were then converted to calories to represent daily caloric intake. Cumulative caloric intake was calculated for the 4-day and 4-week feeding experiments. Weekly caloric totals were also determined for the 4-week regimen with intake determined 7 days/week for weeks 1–3 and for 6 days in the fourth week. An Echo MRI whole body composition analyzer (EchoMedical Systems, Houston, TX) was used to assess body fat mass in conscious rats before and after dietary intervention to provide longitudinal adiposity data for comparison.

Download English Version:

https://daneshyari.com/en/article/5924216

Download Persian Version:

https://daneshyari.com/article/5924216

Daneshyari.com