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Research paper

A high fat diet-induced decrease in hippocampal newly-born neurons of male mice is exacerbated by mild psychological stress using a Communication Box

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ABSTRACT

Background: Obese persons have a higher incidence of depression than healthy-weight persons. Several studies indicated that the exposure to a high fat diet (HFD) results in a decrease in hippocampal neurogenesis, which leads to higher stress response and stress-induced depression. Although stress is a risk factor for obesity and depression, no studies to date have investigated the effect of stress on the hippocampal neurogenesis of HFD-induced obese animals. The aim of this study was to elucidate whether or not obese HFD-fed mice are vulnerable to stress-induced depression by investigating hippocampal neurogenesis.

Methods: Sixty-four male ICR mice (four weeks of age) were fed a control (N=24) or 45%HFD (N=40) for seven weeks. Of the HFD-fed group, twenty-four mice met the criteria for "diet-induced obesity". The animals were then exposed to three consecutive days of psychological stress using a Communication Box. Half were sacrificed to evaluate the physiological changes, and the other half were perfused to quantify hippocampal neuroblasts/immature neurons by the estimation of doublecortin-immunopositive cells.

Results: In the HF.D-fed mice, psychological stress resulted in increases in caloric intake and visceral adipose tissue and a significant decrease in doublecortin-positive cells in the dentate gyrus; however, no such differences were found in the control diet-fed group.

Limitations: Further study using other neurogenic markers to assess the stage-specific changes in hippocampal neurogenesis will be required

Conclusions: Our findings suggest that an HFD-induced decrease in hippocampal newly-born neurons leads to stress vulnerability, which may contribute to a high risk of stress-induced depression for obese persons.

1. Introduction

Obesity is one of the most common metabolic problems, and its prevalence has increased worldwide. Obesity is associated with a higher risk of lifestyle-related diseases, such as hypertension, diabetes mellitus, and dyslipidemia. Several epidemiological studies demonstrated that obesity is a risk factor for the development of depression (Dong et al., 2004; Hamer et al., 2012; Roberts et al., 2003; Simon et al., 2006; Zhao et al., 2011). A meta-analysis of longitudinal data from a study of Americans indicated that obesity increases the overall risk of the onset of depression by 55% (Luppino et al., 2010), which indicates the importance of establishing the pathophysiological mechanism underlying the onset of the depression of obese persons so that effective treatment strategies can be developed.

It is well known that physical and psychological stress negatively affect mood and emotional behavior that leads to the development of depression (Bartolomucci and Leopardi, 2009; de Kloet et al., 2005; McEwen, 2000). Accumulating evidence indicates that stress also contributes to the development of obesity (Björntorp, 2001; Block et al., 2009; Dallman, 2010; Patterson and Abizaid, 2013). Exposure to stress increases the consumption of energy-dense foods that include high fat ingredients, because eating such foods can produce feelings of comfort and alleviate transiently depressed mood and anxiety (Macht, 2008). Chronic stress leads to a persistent increase in the ingestion of calorie rich foods in an attempt to dampen signs of stress, which subsequently results in the excess fat accumulation (Finger et al., 2011, 2012; la Fleur et al., 2005; Maniam and Morris, 2010; Pecoraro et al., 2004). Thus, everyday life stress is a key predisposing risk factor for

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both obesity and depression.

Recently, it has been reported that neurogenesis in the hippocampus may be implicated in the link between obesity and mood disorders. Adult hippocampal neurogenesis in the subgranular zone (SGZ) of the dentate gyrus (DG) has been reported to be involved in the stress-related pathophysiology of depressive disorder and plays an important role in the action mechanism of antidepressants (Duman, 2004; Samuels and Hen, 2011; Santarelli et al., 2003; Schoenfeld and Gould, 2012). We previously found that hippocampal neurogenesis is increased by chronic administration of tandospirone, a clinically available 5-HT1A receptor partial agonist with anxiolytic and antidepressant effects, under stress and non-stress conditions (Mori et al., 2014; Murata et al., 2015). Many researchers have reported that neurogenesis in the hippocampal DG is decreased in rodents with a chronic intake of obesogenic diets, including a high fat diet (Boitard et al., 2012; Gault et al., 2015; Hamilton et al., 2011; Hwang et al., 2008; Klein et al., 2016; Park et al., 2010; Pathak et al., 2015; Rivera et al., 2013; Vinuesa et al., 2016; Yoo et al., 2011a, b, c, d, 2012, 2014). Of interest, recent data demonstrate that a decrease in hippocampal neurogenesis contributes to the dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis and the activation of a stress response (Dranovsky and Leonardo, 2012; Snyder et al., 2011). Thus, these findings suggested that a high fat diet-induced reduction of hippocampal neurogenesis may be related to the higher incidence of depressive disorder via the development of stress vulnerability in obese persons.

Of note, in order to clarify the impact of an obesity-induced reduction of hippocampal neurogenesis on the development of depression, study using stress exposure is necessary. However, no studies to date have investigated the changes in hippocampal neurogenesis of high fat diet-induced obese animals under stress conditions. The present study was conducted to elucidate whether or not obese mice are vulnerable to stress-induced depression. For this purpose, we utilized a Communication Box that is based on a pure psychological stress paradigm to investigate stress-induced changes in the hippocampal neurogenesis of high fat diet-induced obese mice.

2. Methods

2.1. Animals and diet

Male (four weeks of age) ICR mice (obtained from Kyudo Co. Ltd., Saga, Japan) were used in this study. They were housed in groups of four on a 12:12 h reversed light-dark cycle (light on 19:00) at a temperature of 22 ± 2 °C and a humidity of 55 ± 5% and were provided with food and water ad libitum. All procedures regarding animal care and use were carried out based on the regulations dictated by the Experimental Animal Care and Use Committee of Fukuoka University.

The mice were randomly assigned on arrival to one of two groups: a control diet group given CE-2 (CLEA Japan, Inc., Tokyo, Japan), which contains 12.6% of the total calories as fat (3.43 kcal/g) and another given a high fat diet (no. D12451; Research Diets, Inc., New Brunswick, NJ) that contained 45% of the total calories as fat (4.73 kcal/g). One week prior to the start of stress exposure, all mice were individually housed and continued the prescribed diet.

High fat diet-induced obesity was defined according to the criteria of Hariri and Thibault (2010). Briefly, high fat diet-fed rodents with at least 10% greater body weight than age-matched control rodents fed with standard chow were defined as obese. Of the 64 male ICR mice purchased, 24 were fed with CE-2 (control diet) for seven weeks to prepare them for inclusion in the “control diet-fed group”. Of the remaining 40 mice that were fed a 45% high fat diet for seven weeks, 24 fulfilling the criteria for high fat diet-induced obesity were included in the “high fat diet-fed group”.

2.2. Exposure to psychological stress using a Communication Box

A Communication Box (CBX-9M; Muromachi Kikai Co. Ltd., Tokyo, Japan) can be used to set intraspecies emotional stimuli. This apparatus is equipped with a grid floor composed of stainless steel rods. The box consists of nine compartments divided by transparent acrylic panels (Supplementary Fig. 1a). Plastic insulator plates were placed on the grid floors of four compartments other than the center and the four corners (Supplementary Fig. 1b). For the purpose of adaptation, a total of nine mice were introduced individually into each compartment 30 min prior to the start of stress exposure. Five of the nine were placed individually in foot-shock compartments (marked “FS” in Supplementary Fig. 1b) and received a 0.6 mA electric current of one second duration, delivered randomly an average of twice per min for 60 min, from a shock generator (CSG-001; Muromachi Kikai Co. Ltd., Tokyo, Japan). Four mice were placed individually in psychological stress compartments (marked “PS” in Supplementary Fig. 1b) that were covered with plastic insulator to prevent the animals from receiving the electric shock (Supplementary Fig. 1c). The psychologically-stressed mice received visual, auditory, and olfactory emotional stimuli (such as crying, jumping, and evacuation) from the mice receiving electric foot shock. Exposure to psychological stress induced by the Communication Box was given for 1 h (14:00–15:00) daily for three consecutive days, with minor modifications of the previous description by Li et al. (2005). Because the electric foot shock-induced emotional response was gradually diminished due to habituation to the painful stimuli, the mice receiving electric foot shock were changed every stress session. Only the mice exposed to psychological stress were included in our analysis. To control for the possible effects of the novel environment, sham-treated controls were placed in the insulator-covered compartment (marked “PS” in Supplementary Fig. 1b), similar to the above-described experimental procedure but with no electric stimuli.

2.3. Experimental procedures

All mice were fed with the control or high fat diet after arrival, then the mice of each diet group were randomly allocated to sham or psychological stress exposure. 1) *Control diet×sham* group (N=12) animals were fed the control diet for seven weeks after arrival and subjected to one hour sham exposure daily for three consecutive days. 2) *Control diet×STRESS* group (N=12) animals were fed the control diet for seven weeks after arrival and subjected to one hour psychological stress exposure daily for three consecutive days. 3) *High fat diet×sham* group (N=12) animals were fed the 45% high fat diet for seven weeks after arrival and subjected to one hour sham exposure daily for three consecutive days. 4) *High fat diet×STRESS* group (N=12) animals were fed the 45% high fat diet for seven weeks after arrival and subjected to one hour psychological stress exposure daily for three consecutive days. After the last stress session, half of the animals in each group (each N=6) were randomly assigned to either cohort 1 (physiological assessment) or cohort 2 (neurogenesis assessment). The experimental design is shown in Fig. 1.

2.4. Physiological assessment

For the mice in cohort 1, body weight and food intake were measured every day after the start of sham treatment or psychological stress exposure. Based on these data, body weight changes, food intake, caloric intake, and food efficiency were calculated daily for each of the three days under psychological stress exposure and for the seven days after the last stress session. The caloric intake (kcal) was calculated for each group by multiplying the food intake (gram) by the calories of each diet (3.43 kcal/g for control diet, 4.73 kcal/g for 45% high fat diet). Food efficiency was calculated using the following equation; [body weight gain (gram)/caloric intake (kcal)].