Int. J. Devl Neuroscience 42 (2015) 76–79

Contents lists available at ScienceDirect

International Journal of Developmental Neuroscience

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

Short communication

The effects of prenatal undernutrition and postnatal high-fat diet on hypothalamic *Kiss1* mRNA and serum leptin levels

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ARTICLE INFO

Article history:
Received 4 February 2015
Received in revised form 21 February 2015
Accepted 3 March 2015
Available online 5 March 2015

Keywords:
Kisspeptin
Kiss1
Leptin
IUGR
High-fat diet

ABSTRACT

Prenatal undernutrition and postnatal overnutrition increase the risk of some metabolic disorders in adulthood, and hypothalamic leptin resistance makes an important contribution to these effects. Leptin plays important roles in the maintenance of reproductive function, and its actions might be partially mediated by kisspeptin, which is a potent positive regulator of gonadotropin-releasing hormone. In this study, the effects of prenatal undernutrition and postnatal overnutrition on reproductive parameters and sexual maturation during the peripubertal period were evaluated. Rats subjected to prenatal undernutrition (IUGR) and fed a postnatal high-fat diet (HFD) ($n = 7$) exhibited 40% higher serum leptin levels and 30% lower hypothalamic Kiss1 (the gene encoding kisspeptin) mRNA levels than those subjected to prenatal undernutrition (IUGR) and fed a normal diet ($n = 7$). No such HFD-induced postnatal alterations were observed in the rats fed a normal diet during the prenatal period (control) ($n = 7$ per group). Although the consumption of the HFD did not affect the serum luteinizing hormone levels or body weight of the IUGR or control rats, it did promote vaginal opening in both groups (evaluated in 14 rats per group). These findings indicate that hypothalamic leptin resistance might occur in IUGR-HFD rats, but these changes do not influence downstream effectors of the reproductive endocrinological system. They also suggest that the relationships between nutritional conditions, body weight, reproductive factors, and sexual maturation are complex.

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1. Introduction

It has been reported that prenatal undernutrition and postnatal overnutrition increase the risk of some metabolic and psychological disorders in adulthood, and such effects are referred to as developmental origins of health and disease (DoHAD) (Godfrey and Barker, 2000). Hypothalamic resistance to leptin, which is a potent energy regulator derived from adipose tissue, is considered to play a major role in DoHAD (Yura et al., 2005). In prenatally undernourished animals, some hypothalamic factors already exhibit leptin resistance in the pre-pubertal period (Delahaye et al., 2008).

Leptin also plays important roles in the maintenance of reproductive function. Leptin-deficient animals display markedly suppressed fertility in adulthood (Barash et al., 1996). On the other hand, leptin plays a permissive, rather than an active, role in sexual maturation and the onset of puberty (Kaplowitz, 2008). Several studies have shown that leptin increases the activity of kisspeptin, which is a potent positive regulator of gonadotropin-releasing hormone (GnRH) encoded by the *Kiss1* gene; however, these findings are disputed (True et al., 2011).

Recently, it has been reported that overnutrition affects reproductive functions; however, the effects of overnutrition differ between the immature period and adulthood. In pre-pubertal rodents, the consumption of a high-fat diet (HFD) increases leptin and hypothalamic *Kiss1* mRNA levels and GnRH activity, and advances the onset of puberty, indicating that overnutrition promotes sexual maturation (Li et al., 2012). On the other hand,

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http://dx.doi.org/10.1016/j.ijdevneu.2015.03.001
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although the consumption of a HFD was found to increase the serum leptin levels of adult rodents, also decreased their hypothalamic *Kiss1* mRNA and kisspeptin levels, indicating that overnutrition might induce leptin resistance in kisspeptin neurons (Quennell et al., 2011). It is supposed that the difference in the duration of the HFD consumption period (around 10 days in the pre-pubertal study and around 14 weeks in the adult study) was one of the causes of the discrepancies between the abovementioned studies.

Although prenatally undernourished rats exhibit central leptin resistance during the pre-pubertal period regardless of whether they are exposed to overnutrition, their reproductive functions have not been evaluated. We hypothesized that the hypothalamic kisspeptin expression of prenatally undernourished rats that consumed a HFD during the postnatal period would exhibit leptin resistance and that this would have adverse effects on pubertal onset. In the present study, the effects of prenatal undernutrition and the postnatal consumption of a HFD on puberty, serum leptin levels, and the hypothalamic expression levels of the leptin receptor and *Kiss1* and its receptor were evaluated. In addition, the hypothalamic expression of RFamide-related peptide (RFRP), an inhibitor of GnRH, and its receptor were also assessed because a recent study suggested that leptin is involved in the regulation of RFRP expression (Poiling et al., 2014).

2. Materials and methods

2.1. Animals

Pregnant Sprague–Dawley rats were purchased (Charles River Japan, Inc., Tokyo, Japan) and housed individually. The animal rooms were maintained under controlled lighting (14 h light, 10 h dark cycle) and temperature (24 °C) conditions. All animal experiments were conducted in accordance with the ethical standards of the institutional Animal Care and Use Committee of the University of Tokushima.

Four pregnant rats were fed ad libitum during pregnancy. Another four pregnant rats received 50% of the daily food intake of the fed ad lib group from day 14 of pregnancy. After delivery, all dams were allowed ad libitum access to feed (normal diet was supplied to both groups). The day of delivery was defined as postnatal day 0. On postnatal day 2, female pups were selected, and litter size was adjusted to 12–14 per dam. On postnatal day 20, the pups were weaned and housed 6–8 per cage. Just after weaning, the pups from the normally nourished dams (control) and undernourished dams (IUGR) were sub-divided into two groups. One group was supplied with a normal diet (ND), and the other was given a high-fat diet (HFD) (HFD-60; Oriental Yeast Co. Ltd., Tokyo, Japan) (506.2 kcal/100 g) in which 60% of the provided calories were derived from lard-based fat. Namely, the pups were separated into the control-ND, control-HFD, IUGR-ND, and IUGR-HFD groups ($n = 14$ per group).

2.2. Effect of postnatal high-fat diet on vaginal opening, serum and hypothalamic reproductive factors in IUGR and control rats

Vaginal opening was checked daily from postnatal day 28 to 32 in all rats. On day 33, all rats were weighed, and seven rats were randomly selected from each group, and brain and blood samples were collected after the rats had been decapitated under sevoflurane anesthesia. The rats' serum leptin and luteinizing hormone (LH) levels were measured using radioimmunoassay kits, as shown previously (Iwasa et al., 2014a,b). In addition, hypothalamic explants were dissected, total RNA was isolated from them, and cDNA was synthesized, as described previously (Iwasa et al., 2014c,d). Real-time PCR analysis was performed using the StepOnePlus™ real-time PCR system (PE Applied Biosystems, Foster City, CA, USA) and SYBR green in order to quantify the relative mRNA expression levels of *OBRb*, *Kiss1*, *Kiss1r*, *RFRP*, *GPR147*, and *GnRH*. All expression levels were normalized to the mRNA expression level of GAPDH. The primer sequences and PCR conditions were selected

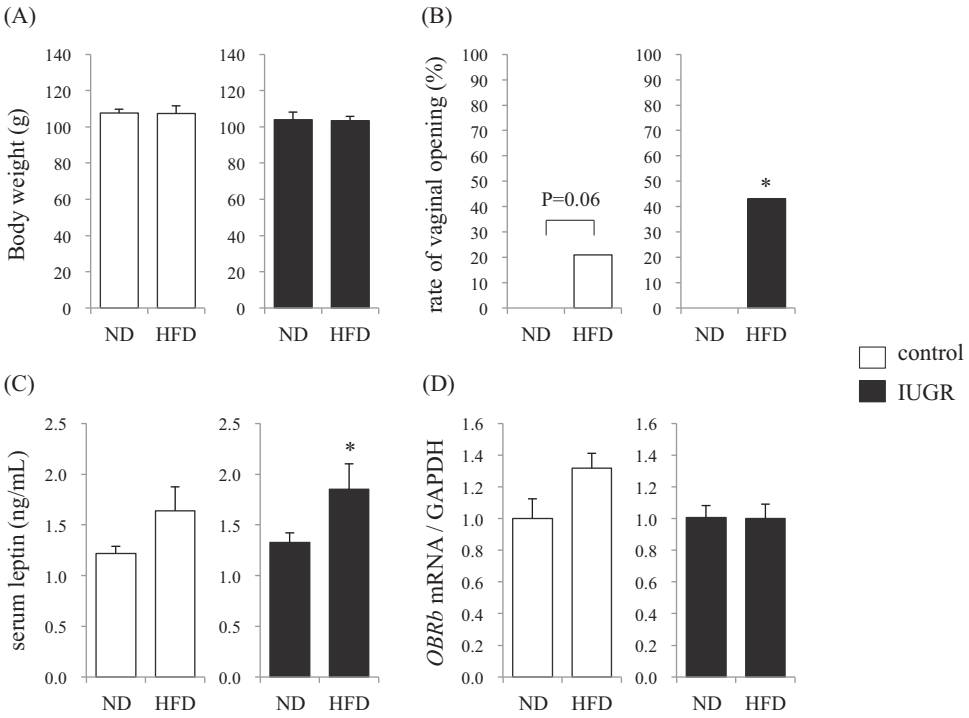

Fig. 1. Body weight ($n = 14$ per group) (A), vaginal opening frequencies ($n = 14$ per group) (B), and serum leptin ($n = 7$ per group) (C) and hypothalamic OBRb mRNA levels ($n = 7$ per group) (D) of control (□) and IUGR (■) rats fed a normal diet (ND) or a high-fat diet (HFD) at postnatal day 32 (vaginal opening) or 33 (body weight and leptin and OBRb levels). Data are expressed as mean ± SE values. *$P < 0.05$ vs. ND rats in the corresponding group.

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