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Full Length Article

Perinatal nicotine exposure increases obesity susceptibility by peripheral leptin resistance in adult female rat offspring

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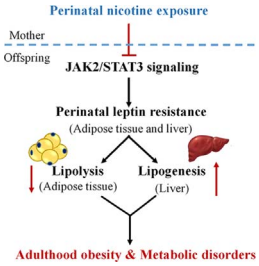
GRAPHICAL ABSTRACT



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ABSTRACT

Maternal nicotine (NIC) exposure causes overweight, hyperleptinemia and metabolic disorders in adult offspring. Our study aims to explore the underlying mechanism of perinatal NIC exposure increases obesity susceptibility in adult female rat offspring. In our model, we found that adult NIC-exposed females presented higher body weight and subcutaneous and visceral fat mass, as well as larger adipocytes, while no change was found in food intake. Serum profile showed a higher serum glucose, insulin and leptin levels in NIC-exposed females. In adipose tissue and liver, the leptin signaling pathway was blocked at 26 weeks, presented lower Janus tyrosine kinase 2 and signal transducer and activator of transcription 3 gene expression, higher suppressor of cytokine signaling 3 gene expression (in adipose tissue) and lower leptin receptors gene expression (in liver), indicating that peripheral leptin resistance occurred in NIC-exposed adult females. In female rats, the expression of lipolysis genes was affected dominantly in adipose tissue, but lipogenesis genes was affected in liver. Furthermore, the glucose and insulin tolerance tests showed a delayed glucose clearance and a higher area under the curve in NIC-

Abbreviations: NIC, nicotine; JAK2, janus tyrosine kinase; STAT3, signal transducer and activator of transcription 3; SOCS3, suppressor of cytokine signaling 3; OB-R, leptin receptors; GD, gestational day; isSWAT, interscapular subcutaneous white adipose tissue; igSWAT, inguinal subcutaneous white adipose tissue; gWAT, gonadal white adipose tissue; pWAT, perirenal white adipose tissue; mWAT, mesenteric white adipose tissue; CT, computed tomography; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NEFA, non-esterified fatty acid; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of beta cell function; IPGTT, intraperitoneal glucose tolerance test; ITT, insulin tolerance test; PPARα, peroxisome proliferator-activated receptor α; SREBP1c, sterol regulatory element binding protein 1c; PGC1α, peroxisome proliferator-activated receptor-γ coactivator 1α; FAS, fatty acid synthase; ACC, acetyl-CoA carboxylase; ATGL, adipose triglyceride lipase; HSL, hormone sensitive lipase; 36B4, acidic ribosomal phosphoprotein P0; HE, hematoxylin/eosin

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exposed females. Therefore, perinatal NIC exposure programed female rats for adipocyte hypertrophy and obesity in adult life, through the leptin resistance in peripheral tissue.

1. Introduction

The worldwide prevalence of obesity has increased dramatically (Mourtakos et al., 2015). Obesity is a multifactorial disorder. In addition to genetic factors, epigenetic environmental factors, such as cigarette smoke, are also risk factors for the development of obesity. Many epidemiological studies have demonstrated that maternal smoking during pregnancy or lactation can contribute to child and teenage obesity, hypertension and type 2 diabetes (de Jonge et al., 2013; Harris et al., 2013; Ino et al., 2012; Jaddoe et al., 2014; Wang et al., 2014). However, the mechanism of maternal nicotine-exposure-induced obesity has not been clearly elucidated. Obesity is manifested by excessive accretion of white adipose tissue. Adipose tissue is now acknowledged as an endocrine organ, which can secrete many adipokines to maintain the balance of adipocyte proliferation, lipogenesis, and lipolysis (Rasouli and Kern, 2008). Leptin, an adipocyte-secreted hormone, mediated by the leptin receptors (OB-R) to inhibit food intake and stimulate energetic utilization by specific hypothalamic signals, acts as a regulator of body weight homeostasis (Friedman and Halaas, 1998). Except for its central actions, leptin also has many peripheral actions that are involved in regulating lipogenesis and lipolysis in some peripheral tissues, such as adipose tissue, liver and skeletal muscle (Carter et al., 2013). Recent research has demonstrated that leptin can also increase insulin sensitivity and regulate glucose metabolism (Burgos-Ramos et al., 2015). Under physiological conditions, leptin acts through OB-R to initiate tyrosine phosphorylation by Janus tyrosine kinase 2 (JAK2). Activated JAK2 recruits and phosphorylates signal transducer and activator of transcription 3 (STAT3). Finally, phosphorylated STAT3 guides the leptin signal to the nucleus, stimulating gene transcription. The transcription of suppressor of cytokine signaling 3 (SOCS3), which acts as a negative feedback inhibitor of the leptin signaling pathway, can be stimulated by the JAK2/STAT3 pathway (Bjorbaek and Kahn, 2004). In obesity, leptin resistance is related to a decreased OB-R, JAK2 and STAT3 expression and to increased SOCS3 expression in the hypothalamus (de Oliveira et al., 2010; Ornellas et al., 2016). However, the action of leptin is not only at the hypothalamic level, but it also has effects in peripheral tissues, such as white adipose tissue, liver, muscles, thyroid and immune system (Bjorbaek and Kahn, 2004; Fruhbeck and Gomez-Ambrosi, 2001; Imajo et al., 2012; Santos-Silva et al., 2010).

Nicotine (NIC) can distribute in placental tissue, amniotic fluid, fetal blood, and breast milk (Luck et al., 1985), possibly acting as an endocrine disruptor and an obesogen factor, significantly effecting the future development of the offspring (Grun and Blumberg, 2006; Tabb and Blumberg, 2006). Our research has previously demonstrated that prenatal and lactation NIC exposure induced deleterious effects on glucose homeostasis, lipogenesis and lipid metabolism in both mothers and pups and increased obesity susceptibility in male adult offspring (Fan et al., 2016a, 2016b). Additionally, the occurrence of obesity is often accompanied by leptin resistance, and other studies have indicated that NIC can lead to central leptin resistance by against the JAK2/STAT3 pathway in the hypothalamus (de Oliveira et al., 2010). However, whether prenatal and lactation NIC exposure have effects on peripheral leptin resistance and adipocyte hypertrophy that induce obesity has not been clearly elucidated. Therefore, we hypothesize that prenatal and lactation NIC exposure induce leptin resistance, which is important for the programming effects on lipogenesis and lipolysis in peripheral tissues, promoting the development of obesity in adult offspring. The aim of our research was to enhance the understanding of adipose dysfunction in our model by evaluating the leptin signaling in adipose tissue at three different stages of offspring life (4, 12, and 26 weeks of age).

2. Materials and methods

2.1. Animals

Pathogen-free Wistar rats 200–240 g (female) and 260–300 g (male) were supplied by the Experimental Center of Hubei Medical Scientific Academy (No. 2008-0005, Hubei, China). Rats were kept in a temperature-controlled room (22–24 °C), with 12 h light-dark cycles, and with free access to food and water. A schema of the experimental protocol is shown in Fig. 1. After one week of acclimation, virgin female rats were caged with male rats in the proportion of 2:1 overnight. The day when spermatozoa were found in the vaginal smears was defined as gestational day (GD) 0. In this study, the animal experiments were performed in the Center for Animal Experiment of Wuhan University, which has been accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. All animal experiment procedures were in accordance with the Guidelines for the Care and Use of Laboratory Animals of the Chinese Animal Welfare Committee.

2.2. Model of maternal nicotine exposure during pregnancy and lactation

After mating, each pregnant rat was randomly assigned to an NIC or a control group and placed in an individual cage with free access to food and water until 28 days of lactation (Fan et al., 2016b; Gray et al., 2000; Ostadalova and Babicky, 2012). In the NIC group, pregnant rats or dams were subcutaneously administered 1.0 mg/kg NIC (Sigma Chemical Co., MO, USA) twice per day from GD 9 to the end of lactation, and the control group was administered with the same volume of vehicle saline. In general, the pregnant rats produced 12–16 pups. We only used litters in which the pups of each gender were no fewer than 6. All litters (NIC, n = 8; control, n = 8) were adjusted to 12 pups (6 males and 6 females) at postnatal day 1 to avoid the influence of the litter size. After weaning, NIC and control pups were fed with a

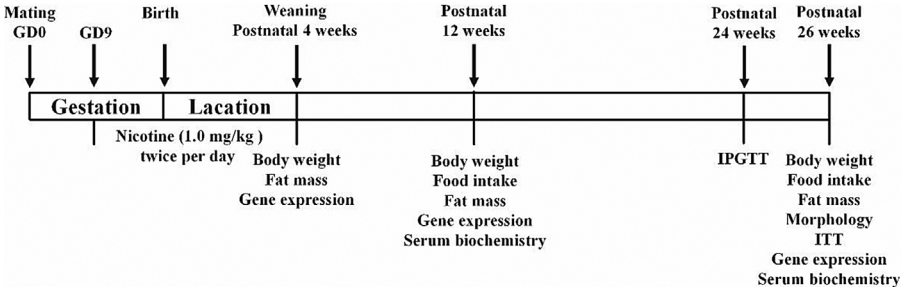

Fig. 1. Schema of experimental protocol.