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Insulin-like Growth Factor 1 Mediates Adrenal Development Dysfunction in Offspring Rats Induced by Prenatal Food Restriction

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Background. Our previous study demonstrated that prenatal food restriction (PFR) could induce the dysfunction of the hypothalamic−pituitary−adrenal axis and glucocorticoid-related glucose and lipid metabolic alterations in adult offspring rats.

Aim of the study. To investigate the intrauterine programming mechanism of adrenal dysfunction in the PFR offspring rats.

Methods. From gestational days (GDs) 11−20, pregnant Wistar rats were fed a restricted diet (50% of the daily food intake of control rats, 60 g/kg·d). Some were executed at GD20, while the others survived to full-term delivery; all pups were fed a high-fat diet (HFD) after weaning. The serum corticosterone concentration, expression level of adrenal steroidal synthetase, and insulin-like growth factor 1 (IGF1) signaling pathway were tested.

Results. We confirmed that the fetal body weight of the PFR group was lower than that of the control group, and the mRNA expression of adrenal steroidogenic acute regulatory protein, cytochrome P450 cholesterol side chain cleavage, 3β-hydroxysteroid dehydrogenase, and steroid 11β-hydroxylase (P450c11) were decreased in the PFR fetal rats. The maternal and fetal serum corticosterone levels were significantly increased in the PFR groups. Furthermore, the expression of the adrenal IGF1 signaling pathway (including IGF1, IGF1R, and Akt1) was suppressed. However, after a post-weaning HFD, the body weight gain rates and serum corticosterone levels were elevated, and the expression of adrenal steroid 21-hydroxylase and P450c11, as well as the IGF1 signaling pathway, were significantly increased in the PFR group.

Conclusions. These results showed that a higher level of circulation corticosterone by PFR *in utero* inhibited adrenal IGF1 signaling and steroidogenesis, whereas post-weaning HFD induced adrenal steroidogenesis by an enhanced IGF1 signaling.

Key Words: Prenatal food restriction, Adrenal gland, Steroidal synthetase system, Insulin-like growth factor 1 signaling pathway.

Introduction

Intrauterine growth retardation (IUGR) refers to an impaired growth potential, which is caused by various factors and defined as a developing baby weighing 10% (or 2 standard deviations) less than the mean body weight of other babies at the same gestational age (1). The prevalence of IUGR is approximately 2.5% in Europe and America, but is as high as 10% in China (2). IUGR can cause fetal distress, neonatal asphyxia, and perinatal death. It can also have chronic detrimental consequences on physical and intellectual development, and renders the child susceptible to adult chronic diseases, such as metabolic syndrome and neuropsychiatric disorders (3,4). Prenatal

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food restriction (PFR) is one of the most common causes of IUGR during pregnancy, which can result in developmental problems in the endocrine system (5).

As one of the vital neuroendocrine axes, the hypothalamic−pituitary−adrenal (HPA) axis plays a critical role in the physiological development of all mammals (6), and the dysfunction of the HPA axis may elevate the risk of adult chronic diseases (7). As a terminal effector in the HPA axis, the adrenal gland is in charge of the synthesis of several steroid hormones (8). *In utero,* basal glucocorticoid (cortisol in humans and corticosterone in rodents) plays a significant role in the maintenance of pregnancy and fetal development, which determines the maturation of pre- and postnatal organs (9−11). A previous study suggested that PFR could lead to an enhanced sensitivity of the HPA axis (12). Our animal experiments demonstrated that PFR-induced IUGR exhibited low basal activity, and enhanced sensitivity of the HPA axis to chronic stress, as well as peripheral glucocorticoid-related glucose and lipid metabolism (13). However, the effect of PFR on adrenal functional development has not been reported.

Insulin-like growth factor 1 (IGF1) is an important regulatory growth factor, which is involved in the proliferation, differentiation, and metabolism of adrenal cells at different developmental periods (14). Through phosphoinositide-3-kinase (PI3K) and serine/threonine kinase (Akt), adrenal IGF1 stimulates steroidogenic factor-1 (SF-1) and steroidal synthetases, including steroid 21-hydroxylase (P450c21) and steroid 11β-hydroxylase (P450c11) (15,16). The elevated IGF1 signaling can significantly stimulate the expression of adrenal steroidal synthetase (15), and knocking out the IGF1 receptor (IGF1R) leads to adrenal developmental retardation and dysfunction (17). ''Catch-up growth'' is described as a fetus undergoing growth acceleration when it is separated from intrauterine pathological factors resulting in growth retardation (18), which is caused by elevating the IGF1 level, and is related to susceptibility to various metabolic diseases (19). It has been reported that the augmentation of serum IGF1 may induce catch-up growth, which is shown in the IUGR fetus fed with a high-fat diet (HFD) (20). HFD has been proven to be correlated with hypertension, impaired glucose tolerance, insulin resistance, and type 2 diabetes (21,22). Hence, the IGF1 signaling system might act on the prenatal and postnatal adrenal dysfunction in IUGR rats.

High levels of glucocorticoid have been shown to inhibit the expression and secretion of IGF1 in various tissues and cells (23,24). Our previous studies found that high levels of blood corticosterone could inhibit adrenal IGF1 expression, and there is a programming effect between them in fetal rats of prenatal caffeine exposure (25). Hence, we speculated that the effect of PFR on adrenal steroidogenesis might be associated with circulatory corticosterone levels and adrenal IGF1 signaling alterations. In this study, based on our established IUGR rat model induced by PFR (13), the prenatal and postnatal blood corticosterone levels, adrenal IGF1 signaling pathway, and steroidal synthetase system expression were observed, in order to explore the underlying intrauterine mechanisms and possible pathophysiological significance.

Materials and Methods

Materials

Isoflurane was obtained from Baxter Healthcare Co. (Deerfield, IL, USA). An enzyme-linked immunosorbent assay (ELISA) kit for rat corticosterone was obtained from Assay-pro LLC. (Saint Charles, MO, USA). The Trizol reagent was purchased from Invitrogen Co. (Carlsbad, CA, USA). Reverse transcription and real-time quantitative polymerase chain reaction (RT-qPCR) kits were purchased from Takara Biotechnology Co., Ltd. (Dalian, China). Oligonucleotide primers for rat RT-qPCR genes (PAGE purification) were custom-synthesized by Sangon Biotech Co., Ltd. (Shanghai, China). Other chemicals and reagents were of analytical grade.

Animals and Treatment

Specific pathogen-free Wistar rats, females weighing 221 ± 16 g and males weighing 280 ± 17 g were obtained from the Experimental Center of Hubei Medical Scientific Academy (No. 2008−0005, Hubei, China). All experiments were performed in the Center for Animal Experiments of Wuhan University (Wuhan, China), which has been accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. The Committee on the Ethics of Animal Experiments of the Wuhan University School of Medicine approved the protocol (permit number: 201719). All experimental animal procedures were performed in accordance with the Guidelines for the Care and Use of Laboratory Animals of the Chinese Animal Welfare Committee.

Animals were kept under temperature-controlled conditions with a 12 h light/dark cycle and fed a standard chow diet and tap water *ad libitum*. After a one-week acclimation period, two females were mated with one male overnight. Mating was confirmed by the appearance of sperm in a vaginal smear the following day, which was designated as gestational day (GD) 0. The pregnant females were then kept individually. They were allowed food *ad libitum* or put on a restricted diet (50% of the daily food intake of control rats, 60 g/kg·d) from GD11. On GD20, to sacrifice animals with minimal suffering, pregnant rats were placed in a quiet preparation room beforehand and euthanized under isoflurane anesthesia within several minutes. Pregnant rats with a litter size from 8−14 qualified for this study. Fetal blood samples were collected, and the

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