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Cord blood irisin at the extremes of fetal growth

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ABSTRACT

Background/aims. Irisin, a novel myokine with antiobesity properties, drives brown-fat-like conversion of white adipose tissue, thus increasing energy expenditure and improving glucose tolerance. We aimed to investigate circulating irisin concentrations in large-for-gestational-age (LGA) and intrauterine-growth-restricted (IUGR) fetuses, both associated with metabolic dysregulation and long-term susceptibility to obesity and metabolic syndrome development.

Methods. Plasma irisin and insulin concentrations were determined by ELISA and IRMA, respectively, in 80 mixed arteriovenous cord blood samples from LGA (n = 30), IUGR (n = 30) and appropriate-for-gestational-age (AGA, n = 20) singleton full-term pregnancies. Fetuses were classified as LGA, IUGR or AGA, based on customized birth-weight standards adjusted for significant determinants of fetal growth.

Results. Fetal irisin concentrations were lower in IUGR cases than AGA controls (p = 0.031). Cord blood irisin concentrations were similar in LGA and AGA groups and positively correlated with birth-weight, as well as customized centiles (r = 0.245, p = 0.029 and r = 0.247, p = 0.027, respectively). Insulin concentrations were higher in LGA, compared to AGA fetuses (p = 0.036). In the LGA group, fetal irisin concentrations positively correlated with fetal insulin concentrations (r = 0.374, p = 0.042).

Conclusions. Impaired skeletal muscle metabolism in IUGR fetuses may account for their irisin deficiency, which may be part of the fetal programming process, leading to increased susceptibility to later metabolic syndrome development. Furthermore, irisin down-regulation may predispose IUGR infants to hypothermia at birth, by inducing less "browning" of their adipose tissue and consequently less non-shivering thermogenesis. Irisin upregulation with increasing birth-weight may contribute to a slower fat gain during early infancy ("catch-down"), by promoting higher total energy expenditure. The positive correlation between irisin and insulin in the LGA group may reflect a counterbalance of the documented hyperinsulinemia, which is partly responsible for the excessive fat deposition in the LGA fetus.

Abbreviations: IUGR, intrauterine growth restriction; LGA, large for gestational age; AGA, appropriate for gestational age; WAT, white adipose tissue; BAT, brown adipose tissue; UCP-1, uncoupling protein 1; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; BMI, body mass index.

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1. Introduction

Fetal growth disturbances, i.e. intrauterine growth restriction (IUGR) and fetal macrosomia, although usually caused by different pathologic conditions, are both associated with alterations in fetal adipose tissue development, permanent changes in the regulation of hormonal functions and a high tendency of individuals to develop obesity and related metabolic disorders later in life [1,2]. IUGR fetuses present with a disproportionate reduction in fat mass, as compared with lean mass [3,4], as well as with reduced growth and impaired development of skeletal muscle [3,5]. Furthermore, IUGR neonates display enhanced insulin sensitivity at birth, followed by accelerated postnatal growth and subsequent emergence of insulin resistance [6]. On the other hand, large for gestational age (LGA) infants present with increased adiposity and reduced insulin sensitivity at birth, followed by higher rates of obesity and cardiometabolic diseases later in life [7,8].

Irisin is a recently identified exercise-induced myokine, which triggers the conversion of white adipose tissue (WAT) to brown-like adipose tissue (BAT), leading to increased energy expenditure and, subsequently to improved tissue metabolic profile, by promoting weight loss, improved glucose tolerance, and insulin sensitization [9,10]. Recent research suggests that irisin acts through upregulation of uncoupling protein 1 (UCP-1) – which is expressed by BAT adipocytes – and induces release of chemical energy as heat, thus, protecting against hypothermia and obesity [9–12]. In this respect, irisin has recently attracted a lot of interest as a potential new target for the treatment of obesity and its associated disorders, since data suggest that irisin induces "browning" of WAT and BAT thermogenesis [13–16]. However, data regarding irisin in the perinatal period are scarce and regulation of circulating irisin in cord blood of well-characterized IUGR and LGA pregnancies has not been, to the best of our knowledge, assessed so far.

The present case–control study was based on the hypothesis that cord blood irisin concentrations may differ between IUGR and LGA cases, compared with appropriate for gestational age (AGA) controls, since the former present with alterations in the development of fetal adipose tissue and skeletal muscle, metabolic dysregulation and increased susceptibility to later development of obesity and related metabolic disorders [1,2]. Therefore, this study aimed to evaluate and compare cord blood irisin and insulin concentrations in IUGR, LGA versus AGA infants and investigate the association of the above concentrations with a variety of perinatal variables.

2. Materials and Methods

The study was conducted according to the Declaration of Helsinki. The Ethics Committee of our University Hospital approved the study protocol. Participating mothers provided signed informed consent before enrolment. The study population was partly previously described [17]. Briefly, eighty parturients giving consecutively birth either to 30 asymmetric IUGR (birth-weight ≤ 7th customized centile), 30 LGA (birth-weight ≥ 90th customized centile) and 20 AGA full-term singleton infants were prospectively recruited for this case–control study. The Gestation Related Optimal Weight (GROW) computer-generated program was used to calculate the customized centile for each pregnancy [18]. Significant determinants of birth-weight (maternal height and booking weight, ethnicity, parity, gestational age and gender) were entered to adjust the normal birth-weight centile limits [18].

Possible causes of IUGR were maternal smoking >10 cigarettes/day (n = 9), thrombophilia under thromboprophylaxis with heparin (n = 7), caffeine consumption (n = 6), pregnancy-induced hypertension (n = 3) treated with orally administered antihypertensives, hypothyroidism under supplementation therapy (n = 2), gestational diabetes mellitus treated with diet (n = 1), preeclampsia treated with intravenous hydralazine (n = 1), and arterial hypertension treated with orally administered antihypertensives (n = 1).

Umbilical artery blood flow patterns and resistance indices (RI: maximal systolic velocity–maximal diastolic velocity/maximal systolic velocity) were recorded. An increased umbilical artery RI outside the normal range signified a pathologic flow pattern [19]. In all IUGR pregnancies blood flow was impaired, reflected by an increased umbilical artery RI [19]. However, no absent end-diastolic flow in the umbilical arteries was documented.

Amniotic fluid and placental weight were reduced in all IUGR cases [20,21]. Maternal gestational diabetes was recorded in 5 LGA pregnancies, all treated with diet. In the AGA group, mothers were healthy non-smokers and placentas were normal in appearance and weight [21].

All women were supplemented with iron, folic acid and calcium. Eight out of 30 mothers with IUGR offspring and 13 out of 30 mothers with LGA offspring were overweight/obese, while in the AGA group, 3 out of 20 mothers were overweight and 17 out of 30 mothers had normal weight [22].

Pregnancies with chromosomal aberrations, fetal malformations, congenital or acquired infections and genetic syndromes were excluded. One- and five-minute Apgar scores were ≥8 in all neonates.

Clinical characteristics of participating mothers and infants of each group are shown in Table 1.

Mixed arteriovenous cord blood samples were collected in pyrogen-free tubes from the doubly clamped umbilical cords at birth, reflecting the fetal state. Blood samples were transferred within 20 minutes of sampling in the laboratory into special containers on ice and were immediately centrifuged. The supernatant plasma was separated into two equal aliquots and immediately stored in a deep freezer (−80 °C) for less than 6 months until assay.

Following the above strict sample collection and maintenance criteria and according to irisin ELISA manufacturers' guidelines, treatment of samples with protease inhibitor (Aprotinin) can be omitted from the procedure without any problems.

The determination of plasma irisin concentrations was performed by ELISA (Phoenix Pharmaceuticals, Karlsruhe, Germany). The minimum detectable concentration, intraassay and interassay coefficients of variation were 11 ng/ml, 4–6% and 8–10%, respectively.

This specific ELISA kit has been validated by previous recent studies [23–25]. The antibodies used have been