Prenatal nutritional programming of central obesity and the metabolic syndrome: role of adipose tissue glucocorticoid metabolism

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Central obesity, with respect to its continuously growing frequency and the severity of its complications, is now becoming a major public health concern. Central obesity is part of the metabolic syndrome, which associates insulin resistance, high blood pressure, and dyslipidemia, leading to increased prevalence of coronary artery disease and diabetes mellitus. The aetiology of central obesity is not well understood. Apart from genetic or environmental factors, such as increased food intake and sedentary life style, there is evidence that the environment during the perinatal period plays an important role in programming the regulation of metabolic axes in adulthood. Developmental plasticity is an important mechanism by which a growing organism can adapt to its environment to maximize its chances of survival. However, such alteration could result in permanent changes in physiological axes and subsequent predispositions to pathology in adulthood (22).

A number of epidemiological studies have revealed a strong inverse relationship between birth weight and the risk of developing the metabolic syndrome in adulthood. These epidemiological observations have led Hales and Barker to propose the “Thrifty Phenotype Hypothesis” (10). This hypothesis suggests that, in response to undernutrition, a fetus will selectively distribute nutrients to preserve brain growth at the expense of other organs such as liver, pancreas, and muscle, and it will program its metabolic regulations. However, these adaptations will be detrimental to health in adulthood, with increased prevalence of type 2 diabetes mellitus and coronary heart disease. The mechanisms underlying the association between in utero growth retardation and the appearance of the metabolic syndrome are not completely understood. However, it is known that individuals with in utero growth retardation who experience improved postnatal nutrition, with a subsequent catch-up growth, are at higher risk for disease in adulthood (7). Such compensatory catch-up growth is associated, as soon as 5 years of age, with increased visceral adipose tissue mass and later on with insulin resistance (18). A resetting of the hypothalamo-pituitary-adrenal (HPA) axis has also been proposed to participate in the pathophysiology of obesity and the metabolic syndrome associated with intrauterine growth retardation (20). Indeed, cortisol was implicated as a pathophysiological mediator of central obesity because an excess of glucocorticoids, when associated with hyperinsulinism, favors an increase in lipogenesis and a decrease of lipolysis at a visceral level, together with a stimulation of hepatic neoglucogenesis and an inhibition of peripheral glucose utilization (5). Alterations in the HPA axis have been described in human obesity in general and in rodent models of obesity. They involve several phenomena such as a hyperactivity of the central command of ACTH secretion secondary to an increased exposure or sensitization to stress (24) or a decreased negative glucocorticoid feedback (11). Similarly, patients with low birth weight and cardiovascular risk factors have elevated basal and stimulated cortisol secretion (23), which appear early in life (21) and could be subsequent to an intrauterine programming of the HPA axis.

In addition, it is now established that the action of glucocorticoids in adipose tissue depends not only on the circulating concentrations of the hormone, but also on its prereceptor and receptor metabolism. As a consequence, changes in peripheral glucocorticoid signaling with increased visceral adipose tissue glucocorticoid receptor concentrations and local reactivation of circulating inert cortisone to cortisol driven by 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1), play a pivotal role in the pathophysiology of obesity (19, 25). Transgenic mice with adipocyte-targeted 11βHSD1 overexpression developed a visceral obesity that was exaggerated by a high-fat diet and exhibited high blood pressure, insulin-resistant diabetes, and hyperlipidemia (15, 16). 11βHSD1 knockout mouse presented with adipocyte insulin sensitizations and reduced high-fat feeding-induced body weight gain, visceral fat enlargement, and lipid alterations (17) and showed attenuated starvation-induced activation of hepatic glucose-6-phosphatase and pyruvatecarboxylase (PEPCK) and stress-induced hyperglycemia (13). Selective inhibition of 11βHSD1 decreased blood glucose concentrations in spontaneously hyperglycemic KKAβ, ob/ob, and db/db mice and circulating free fatty acids in ob/ob mice (1, 2). Obese patients have increased 11βHSD1 mRNA and activity in subcutaneous adipose tissue, which correlates with several features of the metabolic syndrome such as central adiposity, fasting glucose, insulin, and insulin resistance (12, 14). Taken together with the demonstration that visceral adipose tissue contributes substantially to the regeneration of cortisol (3), our findings that 11βHSD1 and hexose-6-phosphate dehydrogenase (H6PDH, the enzyme responsible for the synthesis of NADPH, the cofactor required for 11βHSD1 oxoreductase activity) mRNAs are increased in visceral adipose tissue of obese patients (Desbriere et al., unpublished observations) strongly suggest that alterations in splanchic cortisol production could contribute to visceral fat accumulation and hepatic insulin resistance of the metabolic syndrome. As a consequence, it is tempting to suggest that the nutritional alterations responsible for intrauterine growth retardation and postnatal catchup can program visceral adipose tissue glucocorticoid metabolism and its accompanying metabolic disturbances in adulthood.

We have recently demonstrated that in rats, changes in the perinatal nutritional status are able to program adult adipose
tissue glucocorticoid sensitivity. Indeed, overfeeding in the immediate postnatal period accelerated the maturation of the HPA axis and resulted in adulthood in a moderate overweight condition, metabolic disturbances comparable with those described in the metabolic syndrome, and increased adipose tissue glucocorticoid receptor (GR) and 11βHSD1 mRNAs (6). However, direct evidence that undernutrition during gestation can program adipose tissue glucocorticoid sensitivity and metabolism was lacking. In this issue of The American Journal of Physiology—Regulatory, Integrative, and Comparative Physiology, Gnanalingham and colleagues (9) present a study investigating in sheep the ontogeny and the nutritional programming of adipose tissue GR, 11βHSD1, 11βHSD2 (this 11βHSD isoform has exclusive dehydrogenase activity and catalyzes the conversion of cortisol into cortisone), and uncoupling protein (UCP)-2 (an inner mitochondrial protein regulating basal thermogenesis and expressed at high levels in macrophages) mRNAs. The authors have chosen to focus on perirenal adipose tissue because this fat compartment represents 80% of total fat stores up to the time of birth and because its weight increases exponentially from <1 g in the mid-gestational fetus up to 400 g in prepubertal adolescents. In normally fed animals, GR and 11βHSD1 mRNAs increased steadily from late gestation up to 6 months of age, whereas 11βHSD2 mRNA levels demonstrated opposite variations. UCP-2 mRNA concentrations increased up to 30 days of life and decreased thereafter. The developmental ontogeny of visceral adipose glucocorticoid sensitivity and metabolism is in contrast to other tissues such as the lung, in which GR and 11βHSD1 mRNA levels are maximal during late gestation and decline thereafter (8). Thus, the parallel increase in glucocorticoid sensitivity and in the growth of adipose tissue is in line with the known trophic effects of glucocorticoids. The ontogenical changes in UCP2 mRNA concentrations may reflect the transition from brown to white adipose tissue, which involves the proliferation and differentiation of preadipocytes, and/or an increased macrophage accumulation in adipose tissue, which is associated with enhanced fat deposition.

The authors next studied the effects of fetal undernutrition, obtained by early- to mid- (28–80 days) or late-(110–147 days) gestational maternal nutrient restriction (NR). After early- to mid-gestational NR, lamb adipose tissue GR, 11βHSD1, and UCP2 mRNAs were increased and 11βHSD2 mRNA was decreased; late-gestational NR had opposite effects. The above-mentioned results strongly suggest that the growth of adipose tissue during late gestation and the postnatal period is accompanied by increased sensitivity and local conversion of inactive to active glucocorticoids and that this phenomenon is partly dependent upon maternal food intake during gestation. As a consequence, they support the hypothesis that the nutritional programming of metabolic and hormonal axes involves changes in adipose tissue glucocorticoid sensitivity and metabolism. However, there was no effect of early- to mid- or late-gestational NR on whole body or adipose tissue weight, suggesting that, in this experimental model, changes in adipose tissue mass induced by alterations in local glucocorticoid sensitivity and metabolism may require the examination of offspring beyond 6 months of age. Alternatively, alterations in UCP2-induced energy dissipation could counteract changes in tissue accumulation subsequent to modifications in glucocorticoid sensitivity. This hypothesis suggests also that variations in adipose tissue glucocorticoid metabolism could be sufficient to induce metabolic alterations without any increase in fat mass. Additional experiments are clearly needed to answer these questions. The experimental model of maternal gestational NR is an interesting tool to perform such studies.

REFERENCES


