Korean Journal of Fetal Medicine
Vol. 5 No. 2 June 2009

Fetal Programming: Gender-specific programmed plasma lipid dysregulation in low birth weight infant

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Abstract

The 'fetal origins' hypothesis proposes that alterations in fetal nutrition and endocrine status result in developmental adaptations that permanently change structure, physiology and metabolism, thereby predisposing to cardiovascular, metabolic and endocrine disease in adult life. In fetal life the tissues and organs of the body go through that are called 'critical' period of development. These may coincide with periods of rapid cell division. In common with other living creatures, human beings are 'plastic' in their early life, and are moulded by the environment. Although the growth of a fetus in influenced by its genes, studies in humans and animals suggest that it is usually limited by the environment, in particular the nutrients and oxygen received from the mother. There are many possible evolutionary advantages in the body remaining plastic during development, rather than having its development driven only by genetic instructions acquired at conception.

'Programming' describes the process whereby a stimulus or insult during a critical period of development has lasting or lifelong effects. Experimental studies in animals have documented many examples of fetal programming, with recent studies showing that alterations in maternal nutrition can have long-term effects on the offspring. These programmed changes may be the origins of adult diseases, including cardiovascular disease, obesity, and diabetes. Studies in humans and animals convincingly demonstrate that environmental perturbations in utero may permanently change organ structure and metabolism and/or alter homeostatic regulatory mechanisms among the offspring. Rats whose mothers had been fed a diet with a low ratio of protein to energy during pregnancy exhibited a permanently altered balance between hepatic glucose production and utilization; control rats fed the same diet during post-natal life had no alterations in hepatic glucose metabolism. Other notable long-term effects of alterations in maternal nutrition include changes in cholesterol metabolism, insulin secretion and renal development.

The rapid rise in incidence of metabolic syndrome in children and adolescents is well recognized. Metabolic syndrome is associated with a cluster of disorders, namely, obesity, insulin resistance, hypertension, and lipid abnormalities. It further causes severe pathologic changes in various organs, particularly the liver, where it is known to play an important role in the development of "fatty liver" (ie. fat accumulation within the liver).

Although the causes of the metabolic syndrome are manifold and complex, there is increasing evidence that intrauterine growth restricted (IUGR) newborn infants have an increased risk of the development of metabolic syndrome. In particular, low birth weight has been reported to be associated with an atherogenic lipid profile. This may be mediated, in part, through altered organ growth that results in permanent changes in structure, metabolism, and/or homeostatic regulatory systems.

Hepatic lipogenic transcription factor and lipid enzymes play a dey role in modulating lipid metabolism and plasma lipid concentrations. In particular, sterol regulatory element-binding proteins (SREBPs), which are a family of membrane-bound transcription factors, regulate cholesterol and fatty acid homeostasis. SREBP-1c specifically regulates hepatic liogenesis; its activation results in the induction of genes for enzymes that are involved in the biosynthesis of fatty acids and triglycerides. Lipogenic fatty acid synthase (FAS) is the key enzyme of de novo fatty acid synthesis; its expression is stimulated by insulin and glucose, whereas lipolytic lipoprotein lipase (LPL) is the rate-limiting enzyme in triglyceride hydrolysis. Hepatic LPL normally is expressed during the fetal and neonatal periods in the rat, and little or none is present in adult livers of humans and rats. Notably, starvation increases both the messenger RNA (mRNA) expression and activity of LPL in neonatal rats.

As lipid homeostasis is regulated primarily by the liver, we hypothesized that hepatic structure and lipid content of IUGR offspring would reflect a primary lipid dysfunction. We determined the hepatic lobule size, lipid content and expression of SREBP-1c and its downstream target, FAS. We further investigated changes in lipolytic enzyme, LPL and elucidated whether these changes were gender specific.

Objective

Intrauterine growth restriciton demonstrates increased risk of adult metabolic syndrome. The associated hyperlipidemia results from obesity or programmed metabolic abnormalities. Becuase lipid homeostasis is regulated by the liver, we hypothesized that hepatic structure and lipid content in intrauterine growth restriction would reflect a primary lipid dysfunction.

Study design

From 10 days to term gestation, control pregnant rats received ad libitum diet: study rats were 25% food-restricted (FR). All dams received ad libitum diet throughout lactation. At 3 weeks of age, hepatic lobule size and lipid profile of the pups were determined.

Results

At 3 weeks of age, body and liver weights of the pups were comparable with controls, although with reduced hepatic lobule size. FR males had increased hepatic triglyceride and cholesterol content with elevated sterol regulatory element-binding protein-1c, fatty acid synthase, and lipoprotein lipase expression; FR females exhibited decreased hepatic cholesterol levels. Plasma lipid levels were unchanged in FR males and females.

Conclusion

Developmental programming results in sex-dependent altered lipid metabolism with increased risk in males.