Editorial Focus. Developmental programming of sex-dependent alterations in lipid metabolism: a role for long-term, sex-specific alterations in LDL-receptor expression. Focus on “Developmental programming of lipid metabolism and aortic vascular function in C57BL/6 mice: a novel study suggesting an involvement of LDL-receptor”

Barbara T. Alexander
Department of Physiology, University of Mississippi Medical Center, Jackson, Mississippi

THE NOBEL PRIZE in physiology or medicine was awarded to Brown and Goldstein in 1985 for their discovery of the low-density lipoprotein (LDL) receptor and its importance in the regulation of cholesterol metabolism (2). Cholesterol, an essential component of the mammalian cell membrane, is transported within the circulation by a class of particles called lipoproteins. In humans, the most abundant cholesterol-containing lipoprotein, LDL, is removed from the blood primarily via hepatic LDL-receptor-mediated endocytosis (2). Numerous experimental studies demonstrate the important role of hepatic LDL-receptors in the regulation of cholesterol homeostasis and protection against the development of atherosclerosis. For example, as a result of LDL-receptor suppression in inbred strains of mice, diets rich in saturated fatty acids supplemented with cholesterol increase plasma LDL-cholesterol levels (11). Overexpression of hepatic LDL-receptors prevents the increase in plasma LDL-cholesterol in mice fed a high-fat, high-cholesterol diet (12); LDL-receptor-deficient mice have a marked increase in plasma LDL-cholesterol (7) and develop atherosclerosis when fed a high-fat, high-cholesterol diet (8). These types of studies in experimental animal models clearly demonstrate the critical role for the LDL-receptor in cholesterol metabolism and the development of atherosclerosis.

It is well established that undernutrition during fetal life is an important determinant of adult cardiovascular health; however, exposure to overnutrition or excess fat during fetal life is also linked to an increase in cardiovascular risk via alterations in lipid metabolism (3, 6) and vascular dysfunction (6). Chechi et al. (4) demonstrate that the developmental programming of lipid metabolism in response to fetal undernutrition (4) is sex specific, and that sex-specific developmental programming of altered gene expression persists into adult life. Sex differences are observed in the fetal response to under- and overnutrition. Female offspring demonstrate a greater sensitivity to developmental programming of lipid metabolism in response to fetal overnutrition (9), whereas male offspring demonstrate a greater sensitivity to developmental programming of lipid metabolism in response to fetal undernutrition (5). Chechi et al. (4) demonstrate that alterations in adult vascular function were observed in both male and female offspring exposed to fetal overnutrition. However, the increase in plasma LDL-cholesterol levels associated with the reduction in hepatic LDL-receptor gene expression was observed only in female offspring, and these alterations were present in adulthood (4). Thus, this study suggests that developmental programming of lipid metabolism in response to fetal overnutrition may be mediated via a sex-specific, long-term alteration in gene expression of the hepatic LDL-receptor. Although plasma

![Diagram](http://www.ajpregu.org)

**Maternal diet rich in saturated fatty acids**

**Fetal life**

- **Male:**
  - Adulthood
  - Changes in gene expression?
  - LDL receptor expression
  - Plasma triglycerides
  - Plasma LDL-cholesterol
  - Vascular dysfunction

- **Female:**
  - Adulthood
  - Changes in gene expression?
  - LDL receptor expression
  - Plasma triglycerides
  - Plasma LDL-cholesterol
  - Vascular dysfunction

![Fig. 1.](http://www.ajpregu.org)

Fig. 1. Developmental programming leads to sex-specific alterations in lipid metabolism. Long-term sex-specific developmental programming of altered LDL-receptor expression may be a potential mechanism mediating alterations in lipid metabolism in female offspring exposed to a maternal diet rich in saturated fatty acids.

Address for reprint requests and other correspondence: B. T. Alexander, Dept. of Physiology, Univ. of Mississippi Medical Center, 2500 North State St., Jackson, MS 39216-4505 (e-mail: balexander@physiology.umsmed.edu).
LDL-cholesterol levels and expression of the LDL-receptor were not altered in male offspring in this study, an increase in plasma triglyceride levels were observed in male, but not female offspring (4). A complete analysis of genes critical to lipid metabolism remains to be determined; however, these findings indicate that programming of vascular dysfunction in this model occurs through sex-specific pathways (Fig. 1).

It is clear that developmental programming of lipid metabolism in response to fetal undernutrition is also associated with sex-specific alterations in gene expression of factors critical to cholesterol and lipid homeostasis (5). In a rat model of undernutrition, Choi et al. (5) report that a marked increase in expression of the hepatic Sterol Regulatory Element Binding Protein (SREBP), a transcription factor critical to the activation of the gene for the LDL-receptor, is associated with an increase in hepatic cholesterol content at weaning in male offspring. Additionally, a marked increase in hepatic lipolytic lipoprotein lipase (LPL), the rate-limiting enzyme in triglyceride hydrolysis, and an increase in hepatic triglyceride content is also observed in these male offspring (5). To the contrary, female offspring in this rat model of undernutrition exhibit a decrease in hepatic cholesterol, but no alteration in hepatic triglyceride content, hepatic SREBP, or hepatic LPL gene expression at weaning (5). Whether these sex-specific alterations in gene expression continue into adulthood is unknown. However, together the study by Chechi et al. (6) and the recent report from Choi et al. (5) suggest that nutritional insults during fetal development can result in sex-dependent programming of lipid metabolism mediated by alterations in genes critical to the maintenance of lipid homeostasis. These studies also highlight the sex- and insult-specific nature of developmental influences. The mechanism(s) by which gene expression is altered by developmental programming has not yet been clearly elucidated, but may involve epigenetic modification (1), warrants further investigation, and illustrates the importance of research into the mechanisms linking fetal life and an increased risk for cardiovascular disease.

**REFERENCES**


**GRANTS**

B. T. Anderson is supported by National Institutes of Health Grants HL-074927, HL-51971, and MD-002725.