Developmental programming of adult obesity and cardiovascular disease in rodents by maternal nutrition imbalance\textsuperscript{1–4}

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ABSTRACT

Studies on fetal undernutrition have generated the hypothesis that fetal programming corresponds to an attempt of the fetus to adapt to adverse conditions encountered in utero. These adaptations would be beneficial if these conditions prevail later in life, but they become detrimental in the case of normal or plentiful nutrition and favor the appearance of the metabolic syndrome. In this article, the discussion is limited to the developmental programming of obesity and cardiovascular disorders caused by an early mismatched nutrition, particularly intrauterine growth retardation followed by postnatal catch-up growth. Selected data in human are reviewed before evoking some mechanisms revealed or suggested by experiments in rodents. A variety of physiologic mechanisms are implicated in obesity programming, 2 of which are detailed. In some, but not all observations, hyperphagia resulting from perturbed development of the hypothalamic circuitry devoted to appetite regulation may contribute to obesity. Another contribution may be the developmental changes in the population of fat cell precursors in adipose tissue. Even if the link between obesity and cardiovascular disease is well established, alteration of blood pressure regulation may appear independently of obesity. A loss of diurnal variation in heart rate and blood pressure in adulthood has resulted from maternal undernutrition followed by postnatal overnutrition. Further research should clarify the effect of mismatched early nutrition on the development of brain centers regulating energy intake, energy expenditure, and circadian rhythms. \textit{Am J Clin Nutr} doi: 10.3945/ajcn.110.001651.

INTRODUCTION

Studies of fetal undernutrition have generated the hypothesis that fetal programming corresponds to an attempt by the fetus to adapt to adverse conditions encountered in utero, ie, the thrifty phenotype (1). If such adverse conditions prevail later in life, these adaptations would be beneficial, but they become detrimental in cases of normal or plentiful nutrition (1–4). A consequence is to favor the appearance of the so-called metabolic syndrome with markers such as central obesity, hypertension, and insulin resistance, culminating in overt obesity, type 2 diabetes, and cardiovascular disease. In this article, we limit the discussion to the developmental programming of obesity and cardiovascular disorders caused by an early mismatched nutrition, particularly intrauterine growth retardation followed by postnatal catch-up growth.

Selected data in humans will be reviewed, but to reveal mechanisms underlying the developmental programming animal models have been developed. Among the frequently used models of nutritional insults are calorie restriction, protein restriction, uterine artery ligation, and, more recently, maternal obesity (reviewed in references 5–7). Although data from other species—such as the guinea pig, sheep, and monkey—are more easily extrapolated to humans, rodents remain the main model and, because of space constraints, we focused on this model. The purpose of the chapter is not to provide an exhaustive review, but to selectively comment on some aspects related to data that we collected in this domain.

DEVELOPMENTAL PROGRAMMING OF OBESITY

Evidence of the developmental programming of obesity from epidemiologic data

The relation between birth weight and obesity measured at childhood or adulthood is generally positive. Heavier infants have higher body mass indexes (BMIs) as adults. However, studies have reported a J- or U-shaped link between birth weight and adult BMI, which indicates a higher propensity for obesity in infants with low and high birth weights (reviewed in 8–10). Even when small infants tended to have lower BMIs in adult life, they were found to feature a more central pattern of fat distribution, reduced lean mass, and higher body fat (11, 12). Obviously, birth weight is a crude indicator that neglects many confounding factors, among which is postnatal growth. A comparison of the Dutch and Leningrad famines exemplifies the possible importance of the mismatch between fetal and postnatal nutrition. Exposure to a reduced nutrient supply in the first trimester of pregnancy, which occurred during the Dutch winter famine in November 1944–April 1945, resulted in obesity and a more truncal and abdominal fat distribution in adult male progeny (13). In contrast, no such consequence was observed in the Leningrad famines. November 1944–April 1945, resulted in obesity and a more truncal and abdominal fat distribution in adult male progeny (13). In contrast, no such consequence was observed in the Leningrad famines

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Evidence of the developmental programming of obesity from animal studies

Even if evidence for adult obesity in animal models of fetal malnutrition is not readily clear, there is now a general consensus that the mismatch between fetal undernutrition and the postnatal normal food supply predisposes to adult obesity, which may require a high energy intake to be revealed. Rodent studies of calorie restriction ranging from moderate (50% calorie reduction) to severe (70% calorie reduction) showed low birth weight in the offspring (19, 20). Pups that experienced a 50% calorie restriction during gestation, nursed by normally fed dams, showed rapid catch-up growth that persisted in adulthood and a greater fat mass than observed in nonrestricted pups (20). Severely restricted pups nursed by adequately fed dams showed hyperphagia, amplified by postweaning hypercaloric diet, which lead to hyperinsulinemia, hyperleptinemia, hypertension, and obesity in adulthood (21). In rats, offspring exposed to protein restriction during gestation and lactation did not show a higher propensity to develop obesity, even when challenged with a high-fat, high-sucrose postweaning diet (22, 23). However, as shown in 2 independent studies, limiting the restriction period to gestation and then providing normal nutrition induced increased weight gain in the offspring (24, 25). In coordinated experiments (26), we found that protein restriction (8% instead of 20%) or calorie restriction (50%) during gestation led to growth retardation at birth. If malnutrition was prolonged throughout lactation, adult body weight was permanently reduced. However, if growth-retarded offspring were overfed during the suckling period to induce a rapid catch-up growth, they became heavier than the normally fed rats and even more so after intraterine calorie restriction. Consumption of a high-calorie diet after weaning amplified these effects, and offspring that underwent catch-up growth became more obese than did control rats. This was associated with hyperglycemia, hyperinsulinemia, glucose intolerance, insulin resistance, and adipocyte hypertrophy. Consistent with this, nutrition manipulation during the suckling period only, by rearing in small litters (27) or by feeding a high-carbohydrate milk formula in the immediate postnatal life of rat pups (28), also led to an increased risk of developing obesity at an adult age.

We reproduced the same model of mismatch between fetal (protein restriction) and postnatal (overfeeding during lactation) environments in mice (29). At weaning, male mice were fed laboratory feed pellets alone or supplemented with a hypercaloric diet to induce obesity. At 9 mo, nutritionally mismatched offspring featured increased relative fat mass, hyperglycemia, hypercholesterolemia, and hyperleptinemia. Using a microarray designed to study the expression of genes involved in adipose tissue differentiation/function, we showed that the expression profile of several genes was dependent on the maternal diet, namely those encoding several lipogenic enzymes and growth factors, which may increase their susceptibility to overweight when challenged after weaning with a hypercaloric diet (29).

Similarly, when different schemes of successive under-, over-, or normal nutrition were applied during gestation, lactation, and a young adult age, only undernutrition during gestation followed by overnutrition during lactation and normal diet thereafter were able to induce glucose intolerance and obesity at older ages (30).

The programming of obesity may result from programming hyperphagia, changes in the cellular composition of adipose tissue, lower energy expenditure, and/or modification of neurohormonal factors, as reviewed in (6, 31). We shall focus here on the first 2 mechanisms. Hyperphagia is often cited as a major mechanism leading to obesity induced by maternal malnutrition (32–34). The hypothalamic arcuate nucleus (ARC) is considered to be the main site of appetite regulation. Neurons within the ARC express leptin and insulin receptors. Many regulatory neuropeptides interplay in this mechanism. Two populations of cells in the ARC are first-order neurons: those expressing the anorexigenic proopiomelanocortin and cocaine and amphetamine-regulated transcript and those expressing the orexigenic neuropeptide Y and agouti-related protein (32, 33). Elevated concentrations of leptin or insulin, which indicate the fed state, act to increase proopiomelanocortin/cocaine and amphetamine-regulated transcript expression and concomitantly reduce neuropeptide Y/agouti-related protein concentrations. These neurons project to downstream nuclei, where additional information from other higher cortical centers is integrated. In addition to the ARC, the brainstem receives information from the gastrointestinal afferents and also contains leptin and insulin receptors as well as glucose-sensing cells (33, 35). The suckling period in altricial species, such as rodents, has been identified as a critical time window for the development of hyperphagia, because hypothalamic nuclei continue to differentiate until postnatal day 20 (33). Postnatal overfeeding by reduction of litter size at birth (36) is associated with increased food intake in adult offspring, as is also the case in the progeny of overfed or obese dam (37, 38) or after growth restriction in utero followed by suckling normal dams (19, 20, 39). A central role for leptin in developmental programming of hypothalamic nuclei has been shown. The leptin surge during lactation occurred earlier in undernourished mouse pups, which was associated with hyperphagia and obesity in adulthood (40). Normal pups that receive exogenous leptin to mimic this premature surge have greater weight gains when fed a high-fat diet. In contrast, subcutaneous administration of leptin postnatally to offspring of underfed rats reversed hyperphagia and obesity in adulthood (41). Treatment of dams with leptin during gestation also prevented a diet-induced increase in the obesity risk (42). Thus, leptin concentrations during pregnancy and lactation can affect the development of energy balance regulatory systems in the offspring (43). In addition to leptin, the ghrelin orexigenic response seems to be programmed by gestational nutrient restriction. Offspring from dams restricted during gestation but not during lactation presented more ghrelin-excited neurons in the hypothalamic ARC and ventromedial nuclei (44).
However, obesity resulting from early food manipulation is not always attributable to hyperphagia. In our rat (26) and mouse (29) models of fetal protein or calorie restriction and subsequent catch-up, no evidence of deregulation of energy intake was observed after weaning because all groups ate the same quantity of food, both with a diet of normal feed pellets and a hypercaloric diet. Despite similar food intakes, the nutritionally mismatched progeny had higher leptin mRNA and protein expressions in adipose tissue and increased leptin circulating concentrations, which suggests leptin resistance (26, 29).

Obesity results from an expansion of fat mass due to either adipocyte hypertrophy by lipid accumulation or an exaggerated number of adipocytes in the more severe form of hyperplastic obesity. Adipose tissue development begins in utero and continues in postnatal life with periods of rebounds in fat mass deposition occurring at different times according to species. Fat cells derive from mesenchymal precursors (preadipocytes), which proliferate and differentiate by expressing a succession of markers, including transcription factors, matricial proteins, and lipogenic enzymes. These precursors exist in adipose tissue along life.

In rats fed a highly palatable diet during the suckling period, adipocytes showed hypertrophy (45), whereas rats overfed during the same period by reducing the litter size showed hyperplasia of adipose tissue (46). Offspring of diet-induced obese dams showed increased fat mass with larger adipocytes at an adult age (37). In the progeny of mice underfed during gestation and overfed during lactation, mean adipocyte diameter was increased, although cell numbers did not differ, when examined at 3 and 6 wk of age. These findings suggested that catch-up fat is primarily associated with lipogenesis rather than with adipogenesis in this murine model (47). However, we observed a biphasic curve of adipocyte size in mice grown restricted during gestation and overfed during lactation, with a peak of hypertrophied adipocytes and a second peak of small adipocytes that might suggest the commitment of a new population of precursors (29). Therefore, we hypothesized that nutritional manipulation in early life could program the capacity for proliferation and/or differentiation of fat cell precursors. In rats, in a first series of experiments, a stromal-vascular fraction of perigenital fat depot from fetuses, neonates, and weanling offspring of protein-restricted dams was cultured in vitro. No changes in preadipocyte proliferation and differentiation were detected (48). As stated above, these animals showed a permanent reduction in body weight compared with the controls, even when challenged after weaning with a cafeteria diet (26). However, when similar experiments were performed in 28-d-old offspring of protein-restricted (LP) dams that were overfed during suckling, a clear effect was noted (49). At late stages of preadipocyte differentiation in the culture, no difference was observed in lipid accumulation or in the activity of lipogenic enzymes, but mRNA expression of leptin was enhanced in LP cells. At early stages of culture, higher DNA and protein contents accompanied by a higher rate of proliferation were measured in LP adipocytes, which was accompanied by an increased mRNA expression of cyclin D1. However, the expression of 2 early markers of differentiation—peroxisome proliferator-activated receptor-γ and steroyl regulatory element binding protein 1c—was significantly reduced (49). Prenatal growth restriction followed by rapid catch-up growth appears to be associated with a higher rate for proliferation in preadipocytes, which may contribute to the higher obesity observed later in life in these animals. Similar findings were reported, which showed that visceral preadipocytes from fetal protein–restricted rats have an increased proliferation rate under standard culture conditions but a reduced growth rate under poor serum conditions (50). However, in these experiments, no catch-up growth was induced after fetal malnutrition, and the preadipocytes were taken at 130 d of age when the rats presented visceral obesity and insulin resistance (51).

In summary, findings in rodent models highlight the importance of the early growth trajectory in determining the appearance of obesity in adults. The mismatch between fetal undernutrition and overnutrition during lactation is particularly detrimental. A variety of physiologic mechanisms are implicated in this programming, and we cited 2 of them. In some, but not all, observations, hyperphagia resulting from the perturbed development of the hypothalamic circuitry devoted to appetite regulation may contribute to obesity. Another contribution may be the developmental changes in the population of fat cell precursors in adipose tissue.

DEVELOPMENTAL PROGRAMMING OF CARDIOVASCULAR DISEASE

Evidence of cardiovascular disease from epidemiologic data of developmental programming

Initial studies by Barker et al (52) identified an association between low birth weight and adult risk of coronary heart disease, hypertension, and diabetes. In subsequent years, other epidemiologic studies have focused on the link between low birth weight and adult cardiovascular disease risk (reviewed in references 53–56). In the Dutch famine cohort, a 3-fold increase in coronary heart disease was found in persons exposed to famine in early gestation, which was accompanied by a more atherogenic lipid profile, clotting changes, and more obesity (15). However, no evidence of an excess of hypertension was observed among those exposed in early gestation (57). The relation between birth weight and higher blood pressure in adulthood is indeed unclear. A meta-analysis of epidemiologic data provided little support for a significant link, which might be artifactual and confounded by uncontrolled factors (53). Nevertheless, more recently, the general consensus was reinforced that prenatal insults that adversely affect fetal growth result in an increased incidence of hypertension in adulthood (55, 56, 58). In addition, a possible programming of hypertension might begin in utero, but can also occur in postnatal life, and growth trajectories after low birth weight can differentially modulate cardiovascular morbidities (55).

Atherosclerosis has a long preclinical phase. Pathologic changes begin to develop in the arteries of children and young adults decades before the overt clinical manifestation of disease. Nutritional factors in utero, in infancy, and in childhood have been shown to be important in this process. In particular, maternal hypercholesterolemia, obesity, and diabetes affect lifetime cardiovascular disease risk (reviewed in references 56, 59).

Evidence of the developmental programming of hypertension from rodent studies

In rodents, there is some evidence of fetal programming of hypertension by maternal malnutrition or undernutrition. Severe maternal calorie restriction (30% of normal food intake) induced
an elevated systolic blood pressure in adult offspring at different ages (60). However, other studies using global food restriction failed to show a strong programming effect on the long-term control of arterial blood pressure (54). Langley-Evans and Jackson (61) initially showed that maternal protein restriction during pregnancy caused significant elevations in systolic blood pressure in rat offspring, and these findings were reproduced in many studies by the same investigators (reviewed in reference 62). However, results obtained in maternal low-protein rat models, but with a different diet source, failed to show major effects of offspring hypertension (22, 63, 64). Adult offspring of rat dams fed a diet rich in lard 10 d before and throughout pregnancy and lactation had elevated systolic and diastolic blood pressures measured by radiotelemetry (65). Similarly, offspring of diet-induced obese mice dams had higher blood pressures at night but not during the day (66). In recent experiments (67), we fed mice dams a low-protein diet during gestation and then catch-up growth was induced in pups during lactation by nursing with normal dams and reducing the litter size. After weaning, the rats were fed either a diet of normal feed pellets or an obesogenic diet. At 9 mo, blood pressure and heart rate were measured by telemetry and were found to increase independently by the early mismatched nutritional environment and by induced obesity. Moreover, as will be discussed later, we found impaired circadian rhythms in animals that were exposed in utero to an LP diet and then forced to achieve catch-up growth during lactation. Plasma corticosterone concentrations were elevated in these mice (67).

Several possible mechanisms were proposed to explain the programming of hypertension, one of which is the glucocorticoid transfer from mother to fetus (68). Treatment of pregnant rats with dexamethasone or with an inhibitor of 11β-hydroxysteroid dehydrogenase-type 2 resulted in elevated blood pressure in the progeny (69). On the other hand, treatment of low-protein fed dams with metyrapone, an inhibitor of maternal glucocorticoid synthesis, resulted in offspring that did not develop elevated blood pressure, whereas corticosterone treatment in these same dams restored the hypertensive effect of the diet (70). The mechanisms by which prenatal glucocorticoids induce adult hypertension are still not completely clear and are probably multifaceted, including overactivity of the renin-angiotensin system, sympathetic nervous system activation, abnormalities of renal development, and altered vasoactive response (reviewed in 54, 62).

Adipocytes synthesize and release several factors that have been linked to blood pressure control, including adiponectin, leptin, angiotensin, perivascular relaxation factors, and resistin (reviewed in reference 71). Previous results obtained in our laboratory suggest that alterations due to early nutritional manipulations in the production of such adipokines by adipose tissue could also provide a mechanism for the development of cardiovascular disease (26, 29). Postnatal catch-up growth immediately after fetal malnutrition led to the misprogramming of adipokine expression in adult offspring fed normally from the time of weaning. The increased expression of plasminogen activator inhibitor 1 and angiotensinogen, the decreased expression of adiponectin, and the higher leptin mRNA and protein expression and leptin circulating concentrations observed in these offspring suggested that gene expression in adipose tissue could be programmed during early life and therefore favor the development of hypertension and cardiovascular disease (26, 29).

Telemetry experiments allowed the study of the diurnal variation of blood pressure and heart rate in the offspring of obese dams (37, 66, 72) and in progeny exposed in utero to LP diet and forced to achieve catch-up growth during lactation (67). In the latter, we noted a disappearance of circadian rhythmicity. It was postulated that the functional significance of the normal increase in blood pressure and heart rate during the active period, which is during the dark phase in rodents, is to allow the animals to meet the metabolic demands of increased activity (73).

A loss of circadian rhythm?

All living organisms are submitted to cyclic changes in the environment (seasons or light-dark cycles), and adaptations to such variations ensure that the organism anticipates environmental fluctuations and optimizes the relevant biological processes. Many body functions, such as temperature, eating, blood pressure, heart rate, and blood concentrations of glucose, lipids, insulin, adiponectin, leptin, and plasminogen activator inhibitor 1 exhibit diurnal variation (74, 75).

The control of circadian rhythm is complex and involves central and peripheral clocks in mammals. The central clock is influenced primarily by light and is located within the suprachiasmatic nucleus (SCN) in the brain. Peripheral clocks are located in many peripheral tissues as in the liver, kidneys, and heart (76, 77). Even if mechanisms linking the SCN and peripheral clocks are still poorly understood, they might involve circulating hormones (78). Interestingly, the rhythmic secretion and the ability to phase shift peripheral clocks make glucocorticoids possible candidates for the entrainment of peripheral oscillators (79). At the cellular level, the endogenous clock is controlled through positive and negative transcriptional and translational feedback loops that involve different genes known as bmal1, clock, per1, per2, per3, cry1, cry2, and rev-erb (80, 81).

In humans, blood pressure exhibits a circadian pattern with a nightly decrease. A loss of this nocturnal decrease in blood pressure is correlated with a higher risk of cardiovascular complications (reviewed in 82). However, other facets of the metabolic syndrome, such as type 2 diabetes or obesity, may be linked to the loss of the normal physiologic variation between day and night, which leads to continuous organ damage (82, 83).

Interestingly, using transgenic mice for different clock genes (bmal1−/−, clockmut, and nasp2mut) indicated abolition of the rhythms in cardiovascular function and in concentrations of sympathoadrenal hormones, such as norepinephrine and adrenaline (84). In addition, mutant mice with a disruption of the clock gene develop obesity and show altered feeding patterns and hormonal abnormalities, such as hyperleptinemia and hyperinsulinemia (85). Although the role of circadian clocks in the onset of obesity has just begun to be explored, some clues indicate that alterations in the diurnal variations within the adipocyte can potentiate the development of obesity through changes in metabolic and/or differentiation pathways under the control of circadian clocks. For example, C/EBP transcription factors, which are involved in the early differentiation of adipocyte, exhibit diurnal variation in mouse adipose tissue (77). Also, rev-erbα acts as a repressor of anti-adipogenic genes and therefore promotes differentiation and influences downstream differentiation factors, such as peroxisome proliferator–activated receptor-γ (86). The higher levels of rev-erbα during the light
shown that high-fat feeding in mice induced overweight ac-
explained by genetic and environmental factors. It has been
damage and to the development of metabolic dysfunctions.

A diurnal variation could be a mechanism that leads to organ
in circadian rhythm control and in the expression of genes after
translocase, fatty acid transport protein, fatty acyl-CoA synthe-
tase, and perilipin (87). These data tend to suggest that changes
involved in lipid metabolism also showed circadian variation in

Circadian clocks are synchronized mainly through light var-
(zeitgeber for the central clock) and by neurohumoral
factors for peripheral clocks (81). Disruption of mechanisms
controlling the synchronization of such clocks could also be
explained by genetic and environmental factors. It has been
shown that high-fat feeding in mice induced overweight ac-
companied by attenuation of the diurnal variation in clock gene
expression (88). We therefore suggest that nutrition disruption
gestation could also alter the circadian pattern and
therefore contribute to programming of the offspring via dys-
function in diurnal variations. There are several ways in which
disruption of the circadian timing can manifest, including
changes in the number of neurons in the SCN or by changes in
the function of these cells. Interconnections and the de-
velopment of the neural network within the SCN occur in late
gestation in humans and during the early postnatal period in
rodents (89). As a consequence, fetal SCN cells are exposed to
maternal hormone rhythms in response to the environment. Very
few data exist on which maternal factors influence the de-
velopment of circadian variation mechanisms. In animals, only
a few studies have investigated the link between maternal food
restriction and circadian rhythms in adult offspring. Researchers
have shown altered sleep/wake behaviors as adults in rats that
were prenatally malnourished. Prenatal protein malnutrition had
adverse consequences on the quality and quantity of adult sleep
in rats (90). Similarly, rats submitted to hypoxia in utero showed
impaired circadian synchronization and an altered response of
the biological clock to light in adulthood (91). Programming of
deregulation in the day-light behavior was also observed for
food intake rhythm in rats after drastic maternal food restriction
during gestation. A decrease in food intake in the dark phase and
an increase in food intake during the light phase were observed
in rats under this condition compared with a control group (92).
Another recent study evaluated the consequences of early or late
catch-up growth after intrauterine growth retardation due to
maternal protein restriction on feeding behavior during the day
and night. It was found that the duration of the meals influenced
nutritional programming more so than did the quantity of food
ingested (34). In this model, early catch-up growth reduced the
abnormal organization of hypothalamic pathways involved in
energy homeostasis (93).

Our data, together with the data reported above, open new
perspectives for investigating another pathway involved in early
programming because disturbances in circadian rhythmicity may
influence food behavior, obesity, hypertension, and other diseases
which have been found to have an early origin.

Developmental programming of atherosclerosis

Only a few studies have examined, in animal models, the
maternal factors that influence the development of atherosclerosis
in the progeny. Because wild-type rodents do not usually develop
plasma cholesterol concentrations sufficiently high enough to
cause atherosclerosis, transgenic mice with an altered lipoprotein
metabolism based on apolipoprotein E (ApoE) or LDL receptor
genes are important tools. The effect of maternal hypercholes-
terolemia is mainly what has been studied in mice models (56).
For example, breeding ApoE+/− heterozygous mice produced offspring in which the lack of the ApoE gene, provided by the

dam, demonstrated a strong effect of maternal hypercholester-
omia on the development of atherosclerotic lesions (94). In
other experiments with the same model, no significant athero-
sclerosis appeared, because of an insufficient degree of hyper-
cholesterolemia. However, pathogenic programming manifested
itself in the form of dramatically increased carotid neointimal
formation, once an additional atherogenic stimulus was added—
in this case a nonconstricting carotid cuff (95).

Studies of the link between fetal undernutrition and the de-
velopment of atherosclerosis in adulthood in rodent models are
even scarcer. Another recent study investigated the programming
of atherosclerosis by a fetal low-protein diet in ApoE+3 Leiden
mice (96). No changes in cholesterol concentrations or in ath-
ersclerosis were observed when the offspring were fed a nor-
al diet, but a postweaning atherogenic diet induced a higher
concentration of cholesterol and more severe atherosclerotic
lesions within the aortic arch in animals exposed to a low-protein
diet in utero than in those exposed to the control diet, but this
was noted only in females (96). We used another model of trans-
genic mice, LDLr−/− mice, to study the effect of mismatched
early nutrition on the development of atherosclerosis (67). Feed-
ing an atherogenic diet to animals after weaning increased the
concentration of cholesterol and the number of atherosclerotic
lesions, but we were unable to show an effect on atherogenesis
due to intrauterine growth retardation followed by catch-up growth.
However, plasma total cholesterol concentrations increased in
this group because of increased amounts of LDL and VLDL
cholesterol (67). Thus, it appears that maternal malnutrition cre-
ates a metabolic background favorable to atherogenesis, which
manifests under precise conditions. Additional studies are re-
quired to confirm this trend.

CONCLUSIONS

Obesity and cardiovascular disease are among the most im-
portant public health issues worldwide, currently and in the near
future. The mechanisms responsible for the developmental pro-
gramming of these conditions can be analyzed by using particular
rodent models. The importance of the growth trajectory imposed
on the progeny, namely by maternal nutrition, on enhancing the
propensity to develop obesity and cardiovascular deregulation in
adulthood has been highlighted. Even if the link between these 2
pathologies is well established, changes in blood pressure reg-
ulation may appear independently of obesity. Of the physiologic
mechanisms responsible for such programming, the role that
hypothalamic circuitry plays in the regulation of energy intake
and expenditure and circadian rhythms should be clarified.

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research and obtained the funding; and VB and FB: conducted most of the
animal experiments reported in articles cited in the references, which included
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