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Gestational programming: population survival effects of drought and famine during pregnancy

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Ross, Michael G., and Mina Desai. Gestational programming: population survival effects of drought and famine during pregnancy. Am J Physiol Regul Integr Comp Physiol 288: R25–R33, 2005; doi:10.1152/ajpregu.00418.2004.—The process whereby a stimulus or stress at a critical or sensitive period of development has long-term effects is termed “programming.” 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. These programmed changes may be the origins of adult diseases, including cardiovascular disease, obesity, and diabetes. Throughout evolution and development, humans and animals have been exposed to two common environmental stresses, drought and famine. Notably, drought-induced water deprivation is associated with dehydration anorexia and thus a concomitant potential nutrient stress. Our laboratory has performed studies among pregnant rat and sheep in which we simulate drought conditions via maternal dehydration and famine conditions via nutrient restriction. Maternal dehydration results in low-birth-weight offspring, which demonstrate gender-specific plasma hypernatremia and hypertonicity and arterial hypertension. Gestational nutrient restriction also resulted in low-birth-weight offspring. If permitted rapid catch-up growth by nutrient availability, these offspring demonstrate evidence of increased body weight and body fat, and leptin resistance as adults. Conversely, if the catch-up growth is delayed by nutrition restriction, the offspring exhibit normal body weight, body fat, and plasma leptin levels as adults. These studies indicate that osmoregulatory and cardiovascular homeostasis and phenotypic predisposition to obesity may be programmed in utero. Importantly, these results suggest that programming effects may be either potentiated or prevented by interventions during the neonatal period.

osmoregulation; hypertension; obesity; appetite hormones

GESTATIONAL PROGRAMMING

Programming is a process whereby a stimulus or stress at a critical or sensitive period of development has lasting or lifelong significance. Recent studies in humans and animals have provided convincing evidence that the in utero environment may have an impact on fetal developmental processes and may alter homeostatic regulatory mechanisms among the offspring. One principle of gestational programming is the observation that physiological effects of an in utero permutation may vary depending on the developmental period of the fetus or neonate and on the species. Programming may result in altered cell number, organ structure, hormonal set points, and gene expression, among others. Effects may be permanent or expressed only at select offspring ages (e.g., newborn, adult) and may be dependent on the in utero environment (e.g., nutrition, glucocorticoids). Furthermore, expression of physiological abnormalities may be present during basal conditions or restricted to environmental stress or disease states in the offspring.

It is well recognized that genetic mutations within species populations may provide a survival advantage, either to promote population growth under static environmental conditions or to ensure survival under a long-term environmental alteration. Genetic mutations generally require prolonged, evolutionary time periods to influence the species population. Furthermore, mutations are not likely to be reversible or rapidly adaptable to altering environmental conditions. Conversely, perinatal programming may provide a species survival benefit, facilitating varying offspring phenotypes that are adaptable to environmental condition changes that may resolve or reverse frequently.

Throughout evolution and development, humans and animals have been exposed to environmental stresses, with drought and famine representing two of the most frequent conditions. Should drought or famine occur during the gestational period, developmental programming of specific offspring phenotypes may be of value in adapting the offspring to survival in this environment. For example, nutritional constraints during fetal life, which may result in intrauterine
Gestational Programming of Drought and Famine

Invited Review

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Gestational Programming of Drought and Famine

Gestational programming may have evolved for species survival benefit, the etiology of select offspring phenotypes has shifted dramatically in recent eras. For example, in modern society IUGR offspring commonly result from factors other than nutritional restriction, including disease states that may not have permitted maternal fecundity before 20th-century medical treatment (e.g., autoimmune disease) or are unique to the current era [e.g., placental insufficiency associated with prior cesarean section (68); or higher-order multiple gestations associated with in vitro fertilization]. As the etiologies have changed, and the ancestral environmental conditions no longer exist, programming mechanisms may produce offspring with maladaptive phenotypes in modern society. For example, growth-restricted ("thifty phenotype") offspring exposed to Western high-fat diets demonstrate an increased risk of obesity, hypertension, and diabetes as adults (3).

Currently, in the United States and Western societies, there are major health epidemics of obesity, hypertension, and diabetes. In the United States, approximately 65% of adults are overweight, and 31% are obese. Childhood obesity represents a major public health crisis with 20% of children classified as obese. In conjunction with the rates of obesity, the incidence of hypertension is increasing. Among adults in the United States, nearly 30% of the population is hypertensive. Similarly, type II diabetes has dramatically increased in Western society. The World Health Organization predicts a rise in the prevalence of type II diabetes from 1995 to 2025 of 170% (84–228 million) in the industrializing world.

There has been increasing interest in the association of the development of the “metabolic syndrome” with effects of gestational programming. The paradoxically increased risk of adult obesity, hypertension, and diabetes among small-for-gestational-age newborns has been convincingly demonstrated in human epidemiological studies and animal studies in species including rat, sheep, and others. As discussed above, environmental stresses that have threatened population survival include famine, which creates a nutrient stress, and drought, which creates an osmotic stress. Notably, drought-induced water deprivation and the accompanying plasma hypernatremia is associated with dehydration-anorexia and thus a concomitant potential nutrient stress. In the studies performed in our laboratory, we hypothesized that both nutrient and osmotic stress independently contribute to small-for-gestational-age newborns and offspring programming of phenotypes that may demonstrate adaptability to subsequent environments of famine or drought. However, when exposed to Western diets, these phenotypes may contribute to offspring programming of obesity and/or hypertension.

IN UTERO DEVELOPMENT OF OSMOREGULATORY AND OREXIGENIC SYSTEMS

In order for gestational stresses to program offspring responses, the affected physiological systems must be exposed during the period of functional development. Our laboratory and others have confirmed that both osmoregulatory and orexigenic systems become functional, although not fully mature, during the last half of pregnancy and/or the newborn period.

Although fetal plasma osmolality is maintained parallel to maternal levels (via placental equilibration), functional osmoregulatory mechanisms develop in utero in sheep and humans and perhaps during both the fetal and newborn period in altricial species (e.g., rat) (76). Wirth and Epstein (76) postulated that thirst responses develop during the neonatal period in the comparatively altricial rat species. However, we have recently demonstrated central osmotic responsiveness in the near-term fetal rat (80). In the more precocial ovine fetus, systemic and central osmotic-dipsogenic mechanisms are functional near term, as swallowing activity and arginine vasopressin (AVP) secretion are evoked in response to putative dipsogens (61, 64). Osmoregulatory development is also indicated by metabolic activity in select newborn brain regions, including the supraoptic and paraventricular (PVN) portions of the anteroventral third ventricle (33). Although fetal osmotic-dipsogenic responses are intact near term, the level of osmotic sensitivity suggests a functional immaturity, as the fetus requires a significantly greater increase in plasma osmolality compared with the adult to stimulate ingestion (13, 79).

It is likely that appetite-mediated ingestion also develops in utero, in part to aid in the newborn nutrient intake and survival. Bradley and Mistretta (7) using electrophysiological taste responses recording from neurons in the solitary complex in the medulla demonstrated functional acid taste response very early in the ovine gestation (0.6 gestation), whereas salt taste response became functional later (0.8 gestation). In rat pups, behavioral responses to taste stimuli demonstrated functionality to salt, acid, and sweet during the first postnatal days (30). Similarly, human neonatal facial expressions suggest the functional responses to sweet, sour, and bitter stimuli by 2 days of age (6). Earlier studies in the near-term ovine fetus suggested behavioral responses to bitter taste but not sweet stimuli (60). However, we have demonstrated an increase in near-term ovine fetal swallowing with sublingual infusions of oral sucrose (28), suggesting that sweet taste-mediated ingestive behavior is functional near term. Furthermore, fetal ingestion is stimulated in response to central neuropeptide Y (NPY), with activation of putative orexigenic hypothalamic neurons (27). Although leptin inhibits food intake in adults, there is evidence that leptin is ineffective in inhibiting food intake in the neonatal rodent (55), and leptin stimulates rather than suppresses ovine fetal ingestion (58). The inability of leptin to affect food intake in the rodent pups may be due to hypothalamic resistance to leptin-modulating effects on the arcuate nucleus (ARC)-NPY and melanocortin systems (62) or immaturity of ARC-PVN axis, which has been shown to be essential for leptin to modulate an inhibitory feeding behavior (11, 65). Thus, in a parallel to dipsogenic function, orexigenic pathways appear to be functional, although not fully mature near term.

GESTATIONAL PROGRAMMING RESPONSES TO SIMULATED DROUGHT AND FAMINE

Our laboratory has performed studies among pregnant animals in which we simulate drought conditions via maternal dehydration and famine conditions via relative nutrient restriction. We have examined offspring responses both in the rat, an
altricial species, and sheep, a precocial species with developmental patterns more similar to the human.

**Simulated drought: maternal dehydration.** In utero programming of osmoregulatory and sodium homeostatic systems (35) has been demonstrated in rats, sheep, and humans. Extracellular dehydration during pregnancy increases salt appetite (50) and blood pressure (1) of offspring rats. Renal responsiveness to AVP also may be programmed as neonatal rat exposure to AVP results in a long-lasting decrease in renal AVP responsiveness (34) due to a reduction in AVP binding sites in the adult kidney (35). AVP administration during the first month of life increases 24-h water intake and decreases urine osmolality in diabetes insipidus rats 6 wk after cessation of treatment (78). In adult rats (59), prolonged tonicity alterations alter AVP mRNA content (59). More importantly, similar studies of young rats suggest a permanent programming of AVP synthesis in response to tonicity alterations (29). Recent human studies also suggest the programming of neonatal osmoregulatory/salt appetite systems as a result of the maternal pregnancy osmotic environment, as mothers with moderate/severe emesis during pregnancy, likely resulting in maternal dehydration and plasma hypertonicity, have infants with significantly enhanced salt preference at 16 wk of age (12, 47). Thus in utero alterations in fluid and electrolyte endocrine systems may result in permanent effects on offspring.

To investigate the effect of water restriction in pregnant rats, maternal dams were water restricted to increase plasma sodium by ~6 meq/l from 10 days of pregnancy until term (18). Water restriction was maintained throughout the period of lactation until newborn weaning at 21 days of age. Newborns were weaned to ad libitum food and water and studied at both 1 day and 12 wk of age. Maternal food intake was markedly reduced (40%) in both pregnancy and lactation in response to maternal water restriction. Similarly, maternal body weight gain was reduced to a greater extent in pregnancy (64%) than lactation (24%), consistent with the effects of dehydration anorexia. As expected, maternal plasma sodium increased significantly during both periods of pregnancy and lactation compared with control dams, such that the relative decrease in plasma sodium and osmolality observed in rat pregnancy was prevented in the water-restricted dams. As anticipated, the rat offspring of water-restricted dams weighed 17% less at birth. In addition, 1-day-old offspring had increased plasma sodium osmolality and hematocrit, in part a result of the delivery from the in utero hypertenie (18).

As adults at 12 wk of age, these offspring continued to exhibit significantly decreased body weights, with males showing 11% and females 19% reduction from controls. More importantly, despite 9 wk of ad libitum food and water, the male offspring demonstrated persistent and significantly elevated plasma sodium levels, osmolality, and hematocrit. In contrast, the female offspring had similar plasma sodium levels and osmolality, although a persistently elevated hematocrit (15).

To examine the effects of water restriction during pregnancy in a precocial species, pregnant ewes were prepared with maternal catheters and water restricted to increase maternal plasma sodium 8–10 meq/l. Lambs exposed to plasma hypernatremia from 110 days gestation until term demonstrated increased pituitary AVP content and decreased hypothalamic AVP mRNA at 1 day of age (56). At 28 days, lambs demonstrated persistently elevated pituitary AVP content and plasma sodium levels (74). To further investigate the physiological responses of offspring exposed to maternal hypernatremia, prenatally dehydrated and control singleton lambs were normally delivered and nursed by ewes provided ad libitum food and water after delivery (16, 62). At the time of birth, prenatally dehydrated lambs weighed 18% less than controls, although the offspring demonstrated catch-up growth to equivalent weight as controls by 3 wk of age. Furthermore, at 3 wk of age, prenatally dehydrated lambs had significantly increased plasma osmolality, sodium concentration, and hematocrit, although normal plasma AVP levels. Moreover, the prenatally dehydrated offspring demonstrated markedly elevated systolic, diastolic, and mean arterial pressures, with values 10 mmHg above control levels (62). The increase in basal plasma osmolality and sodium levels suggested an altered plasma osmolality threshold for AVP secretion. Accordingly, we performed an intravenous infusion of hypertonic saline to the offspring to assess the relation between AVP and plasma osmolality (16). Throughout the hypertonic saline infusion, prenatally dehydrated offspring maintained persistently elevated plasma osmolality, sodium, and hematocrit, as well as elevated systolic, diastolic, and mean arterial pressures (Fig. 1). The prenatally dehydrated offspring demonstrated an increased plasma osmolality threshold for AVP secretion compared with the controls (Fig. 2). We have recently reevaluated the AVP secretory responses and demonstrated that the prenatally dehydrated offspring have an increased slope of the plasma AVP vs. plasma osmolality regression lines (0.28 ± 0.07 vs. 0.13 ± 0.04, P < 0.05).

Thus it appears that gestational hypertonicity in both rat and sheep results in offspring with increased plasma sodium and osmolality and hematocrit. Studies from rat offspring further indicate persistence of these gender-specific changes into adulthood, whereas studies from sheep demonstrate that the prenatally dehydrated singleton lambs evidence increased arterial blood pressure as well. In addition, these lambs exhibit an altered osmolality threshold for AVP secretion. Collectively, studies from both species illustrate that osmoregulatory homeostatic mechanisms can be programmed in utero.

**Simulated famine: maternal nutrient restriction.** The in utero environment has long been recognized as contributing to offspring behavior, although it was not until the late 1980s that Barker et al. (4) expanded the concept of in utero programming to an association of low birth weight with risks of adult cardiovascular disease, diabetes mellitus, and dyslipidemia (57). Human adult blood pressure is elevated among growth-retarded fetuses (46). Studies in rat, sheep, piglets, and baboons, at varying gestational periods, degrees, and types of nutrient deficiency (17, 40, 67, 73, 77), have confirmed a link, albeit sometimes inconsistent, between IUGR and adult hypertension or metabolic disease. Similarly, increased blood pressure has been demonstrated in adult rat offspring after gestational protein restriction (42, 51, 53, 67). Although rarely has plasma osmolality or sodium been measured, there was no change in maternal plasma sodium of nutritionally deprived dams (45).

Ovine studies of malnutrition demonstrate varying offspring phenotypes depending on the period of gestation. In early gestation to midgestation, undernutrition generally increases placental growth, whereas late-gestation undernutrition re-
duces fetal growth. In response to a 15% reduction in maternal nutrition between gestation days 0 and 70, blood pressure is reduced in near-term fetuses but increased in newborn offspring (36, 39). Thus mechanisms of programming that produce postnatal hypertension may result in lower blood pressure in fetal life by heretofore unexplained mechanisms. In contrast, 15% food restriction during the last 30 days of pregnancy increased fetal mean blood pressure (25). Contrary to the studies of early pregnancy malnutrition, 50% maternal nutrient reduction from 115 days until term increased fetal blood pressure. Furthermore, fetuses at 115 to 125 days demonstrated a heightened pressor response to ANG II, although this was not demonstrated at term. Compared with the studies in the rat, there have been markedly fewer follow-up studies of offspring of undernourished ewes.

To examine the effects of nutrient restriction, we have studied models of nutrient restriction in both sheep and rats. In sheep, natural twin gestation was utilized as a model of nutrient restriction during pregnancy, while twin nursing by the maternal ewe was utilized to continue nutrient restriction throughout the 3 wk of lactation. Ovine twin lambs were 30% smaller at birth than control singletons and demonstrated a further relative weight reduction to 50% of singletons after twin nursing at 3 wk of age. When studied at 3 wk, twins demonstrated a significantly increased plasma sodium (144 vs. 140 meq/l) compared with singletons, despite having similar plasma osmolality, plasma AVP levels, and arterial hematocrit. At 3 wk, twins demonstrated elevated arterial systolic, diastolic, and mean arterial blood pressure with the mean arterial pressures ~5 mmHg greater than singletons (63). As described above, we also performed a determination of the plasma osmolality threshold for AVP secretion in twin offspring (16). During the hypertonic saline infusion, twins maintained persistently elevated plasma sodium levels and blood pressure (Fig. 1). The plasma osmolality threshold for AVP secretion was greater in twins than singletons although intermediate between prenatally dehydrated singletons and singleton controls (Fig. 2). Notably, the control twins exhibited markedly decreased glomerular filtration rate and urinary osmolar excretion and clearance compared with control singletons and prenatally dehydrated singletons (Table 1).

We have explored the effects of maternal nutrient restriction in pregnant rats and specifically sought to determine the effects of rapid newborn catch-up growth (14). Rat dams were 50% food restricted during the second half of pregnancy (i.e., 10 days to term) and/or lactation. The offspring were nursed by either ad libitum-fed dams, to facilitate immediate catch-up growth from their expected low birth weight, or nursed by food-restricted dams to continue a model of delayed catch-up growth. Male and female rats were studied at 1 day, 3 wk, and 9 mo. Among the male offspring, those born to food-restricted dams showed 15% reduction in body weight compared with controls at 1 day of age but increased to significantly greater weights at 3 wk and a further increase to 15% greater than controls at 9 mo of age. The body weights of female offspring born to food-restricted dams followed a similar pattern (14). The percent body fat of the low-birth-weight, prenatally food-restricted offspring was similar at 3 wk of age although markedly exceeded the controls at 9 mo (Fig. 3). Despite the similar percent body fat at 3 wk of age, prenatally food-restricted offspring had significantly elevated plasma leptin levels at 3 wk of age, which persisted to 9 mo of age (Fig. 4). Notably, in agreement with the studies performed in the twin sheep, the prenatally food-restricted rats demonstrated a significantly elevated plasma sodium level at 9 mo of age (146 vs. 141 meq/l).

To prevent the rapid catch-up growth among low-birth-weight rat pups, newborns were nursed by dams who were provided 50% food-restricted diet during the 21 days of lactation. These offspring showed further growth retardation during lactation, weighing significantly less (55%) than controls, with reduced percent body fat, at 3 wk of age (14). However, by 9 mo of age, these offspring had attained body weight and body fat equivalent to the controls (Fig. 3). Additionally, plasma leptin levels were equivalent to controls at 3 wk and 9 mo (Fig. 4).

These results confirm that pregnancy nutrient restriction may result in reduced birth weight. Rapid catch-up growth provided

**Fig. 1.** Plasma osmolality (left), sodium levels (middle), and mean arterial blood pressure (right) in control singletons, control twins, and dehydrated singleton neonates during hypernatremia; 0 h represents basal period before infusion, followed by intravenous infusion of hypertonic NaCl (0.83 M NaCl, 0.075 ml/kg/h) over a 2-h period and subsequent recovery period over the next 2 h. Values are means ± SE. *Significantly different compared with control singletons. [Adapted from Ref. 16 with permission. Copyright 2003, The Endocrine Society.]
by normal nutrition and lactation results in catch-up growth beyond controls by 9 mo in rats, with offspring demonstrating increased body fat and increased plasma leptin. Elevated plasma leptin is evident before an increase in percent body fat and thus suggests a developmental programming of leptin resistance. Delayed catch-up growth induced by food restriction during lactation results in catch-up growth to values similar to controls but with normal body fat and plasma leptin. These results suggest that programming of offspring obesity may be dependent on the timing of nutrient reduction and/or nutrient availability. One may speculate that the prevention of immediate rapid newborn catch-up growth may reduce the risk of adult-onset obesity in humans.

**MECHANISMS OF GESTATIONAL PROGRAMMING**

The physiological mechanisms that account for gestational programming remain largely unknown. Notably, it is unlikely that low birth weight per se results in the increased risk of adult disease. More likely, there are common factor(s) that influence both growth and adult physiological system set points (75). A potential role for the hypothalamic-pituitary-adrenal (HPA) axis has been suggested, as a mediator of the fetal response to nutrient stress. In sheep and primates, HPA function fluctuates during the course of pregnancy. In midgestation there is a suppression of ACTH-induced cortisol response, while in later gestation the negative feedback from cortisol to the pituitary is suppressed (10). Upregulation of circulating corticotropin binding globulin, downregulation of hypothalamic glucocorticoid receptors, and increased 11β-hydroxysteroid dehydrogenase (11β-HSD) contribute to the suppression of negative feedback. These and other mechanisms protect the fetus from effects of maternal cortisol. Accordingly, prenatal glucocorticoid treatment has demonstrated the potential to increase offspring mean blood pressure. In rat dams treated with dexmethasone (a synthetic glucocorticoid that crosses the placenta) or carbenoxolone (11β-HSD inhibitor), offspring consistently demonstrate increased blood pressure (5, 9, 43, 44, 48). A critical role of glucocorticoids in programming was demonstrated by studies in which increased endogenous or exogenous glucocorticoids resulted in reduced birth weight and hypertension in adult progeny (5). In ovine pregnancy, prenatal glucocorticoid treatment of the pregnant ewe at the end of the first but not the second month of gestation resulted in offspring that had significantly higher mean blood pressure at 4 to 19 mo of age (23). When followed through 7 years of age, offspring demonstrated hypertension, cardiac hypertrophy, and reduced cardiac functional capacity (20). Later in gestation, betamethasone treatment to the ovine fetus and ewe has demonstrated varying effects, including increased (69), no change (41), and decreased blood pressure (31). Specifically, in regard to gestational nutrient stress, fetuses of mildly undernourished ewes

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**Table 1. Basal urinary values in control singletons, control twins, and prenatally dehydrated singletons**

<table>
<thead>
<tr>
<th></th>
<th>Control Singletons</th>
<th>Control Twins</th>
<th>Prenatally Dehydrated Singletons</th>
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<tbody>
<tr>
<td>GFR, ml/min kg⁻¹</td>
<td>4.1 ± 0.9</td>
<td>2.5 ± 0.3†</td>
<td>3.9 ± 0.4</td>
</tr>
<tr>
<td>Volume, ml/min kg⁻¹</td>
<td>0.086 ± 0.009</td>
<td>0.084 ± 0.007</td>
<td>0.085 ± 0.008</td>
</tr>
<tr>
<td>Osmolality, mosmol/kg H₂O</td>
<td>359 ± 34</td>
<td>279 ± 28*</td>
<td>402 ± 40</td>
</tr>
<tr>
<td>Osmolar clearance, μmol·min⁻¹·kg⁻¹</td>
<td>29.3 ± 3.9</td>
<td>20.3 ± 1.7†</td>
<td>33.8 ± 2.9</td>
</tr>
<tr>
<td>Osmolar excretion, μmol·min⁻¹·kg⁻¹</td>
<td>0.089 ± 0.009</td>
<td>0.054 ± 0.006*</td>
<td>0.099 ± 0.006</td>
</tr>
</tbody>
</table>

Values are means ± SE. GFR, glomerular filtration rate. Significant difference, control singleton vs. control twin: *P < 0.01, †P < 0.001.
demonstrate reduced corticotropin releasing hormone (CRH) mRNA and increased AVP mRNA in the PVN and reduced plasma adrenocorticotropic hormone (ACTH) and cortisol responses to peripheral CRH/AVP and ACTH, respectively (37, 38). Further support for the role of the HPA axis comes from studies of McMillen and colleagues (24, 25, 71). Periconceptual undernutrition resulted in higher fetal plasma ACTH levels at term, while gestational undernutrition continuing from 8 days until term stimulated the relative expression of ACTH receptor mRNA in the fetal adrenal.

The renin-angiotensin system (RAS) is likely central to offspring programming of hypertension. Central ANG II may influence arterial pressure at numerous brain sites, including the lateral third ventricle, PVN, forebrain regions, nucleus of solitary tract, area postrema, and subfornical organ (SFO) (49), with both pressor and depressor pathways, acting via both AT1

![Figure 3](http://ajpregu.physiology.org/)

**Fig. 3.** Body mass and percentage body fat in 3-wk-old offspring (male and female combined; top) and in 9-mo-old male (solid bars) and female (open bars) offspring (bottom) from control [prenatal/postnatal: ad libitum fed (AdLib)/AdLib], immediate catch-up growth [food restricted (FR)/AdLib], and delayed catch-up growth (FR/FR) groups. Values are mean ± SE. *P < 0.001 vs. control offspring. [Adapted from Ref. 14.]

![Figure 4](http://ajpregu.physiology.org/)

**Fig. 4.** Plasma leptin levels in 3-wk-old offspring (male and female combined; A) and at 9 mo (B) in male (solid bars) and female (open bars) offspring from control (AdLib/AdLib), immediate catch-up growth (FR/AdLib), and delayed catch-up growth (FR/FR) groups. Values are mean ± SE. *P < 0.001 vs. control offspring. [Adapted from Ref. 14.]
and AT2 receptors (49). Circulating ANG II also may activate central sites by neurons in the SFO and organum vasculosum laminae terminalis (OVLT), which lack a blood-brain barrier. In the fetus and adult, central ANG sites in the anteromedial third ventricle mediate dipogenic responses and release of AVP via AT1 receptors (26, 49). Studies of increased expression of ANG in the hypothalamus and AT1 receptors in medulla oblongata of early gestation ovine fetuses (19, 21) indicate a possible contributory role of the central RAS system in programmed hypertension. Although intrafetal cortisol infusion increased AT1 receptor mRNA expression in the fetal heart (66), the increased ANG II pressor response after nutrient restriction demonstrated at 115–125 days gestation (versus near term) may be a result of only a transient increase in AT1 peripheral receptor populations. Results of Wintour and colleagues (21) also indicate upregulation of angiotensinogen and AT1 centrally in fetuses at 130 days gestation, although not in offspring at 2 mo of age. In contrast, there does not appear to be an alteration in the peripheral RAS, as basal renin, angiotensinogen, ANG I, ANG II, and angiotensin-converting enzyme, as well as the response to peripheral angiotensin stimulation and AT1 receptor blockade, were identical in prenatal exposed offspring compared with controls (22, 54).

Among additional systems, sympathetic nervous system (SNS) activation may be critical to the programmed hypertension associated with chronic hypertonicity, in a manner similar to hypertension associated with increased sodium intake (8). At rest, sympathetic nerves exhibit tonic activity, which contributes to arterial blood pressure maintenance. Both hypertonicity and ANG II act as sympathoexcitatory factors via osmo- or ANG II AT1 receptors in the OVLT and/or SFO. Neural pathways from the median preoptic nucleus and PVN, to the rostral ventrolateral medulla and spinal intermediolateral cell column, and finally the sympathetic preganglionic neurons (2, 52, 72) increase SNS activity. Significant evidence suggests that the absolute level of sympathetic tone is altered under conditions of increased salt intake or plasma hypertonicity (8). In normal individuals, increased salt intake reduces plasma ANG II, although arterial blood pressure is maintained by a balance of reduced ANG II-mediated and increased osmo- or sodium receptor-mediated SNS activity. However, in salt-sensitive individuals or animals, hypertonicity-induced sympathoexcitatory actions dominate, possibly due to decreases in the levels or actions of ANG II.

SUMMARY AND CONCLUSIONS

As indicated in Fig. 5, both simulated drought and famine during pregnancy may result in marked long-term effects on offspring. Maternal water restriction during pregnancy resulted in low-birth-weight lambs, with 3-wk-old offspring demonstrating elevated plasma osmolality and sodium concentration, arterial hematocrit, and arterial blood pressure, and an increased plasma osmolality threshold for AVP secretion. Water restriction of rat dams during pregnancy and lactation caused growth reduction of the adult offspring with evidence of increased plasma osmolality and sodium, and arterial hematocrit, although the osmolality and sodium changes were exhibited only in the male offspring. Nutrient restriction during pregnancy resulted in low-birth-weight offspring as well. The low-birth-weight rats that were permitted rapid catch-up growth demonstrated evidence of increased body weight, body fat, and plasma sodium and leptin resistance. Conversely, low-birth-weight rats with delayed catch-up growth showed normal body weight, body fat, and plasma leptin at 9 mo of age. However, in sheep permitted delayed catch-up growth, offspring demonstrate persistently elevated blood pressure. As discussed above, it is unknown whether the elevated hypertension is dependent on or results from the accompanied plasma hypernatremia.

There are many unanswered questions related to programming responses to drought and famine. Although our laboratory has followed these responses through the neonatal period in lambs, and through 9 mo in rats, it is uncertain whether they represent permanent physiological alterations. Whereas our studies and others suggest that exposure to Western diets may result in obesity, the responses to fluid or plasma tonicity stresses are unknown. The adverse effect of marginal protein deficiency before mating and through gestation on fetal growth suggests that it requires more than one generation to correct the reduction in fetal growth after reinstallation of normal nutrition (70). Conversely, the response of offspring during their own pregnancy, and thus the potential for a transgenerational impact, is unknown. It is accepted that the programming of the “thrifty phenotype” in response to nutrient restriction may be of survival advantage in promoting hoarding of food and gorging behavior (32) among offspring born to famine conditions. Similarly, offspring born to water-restricted dams demonstrate an elevated slope of AVP secretion in response to plasma tonicity, suggesting a more efficient antiuretic benefit during drought. A remaining quandary is whether arterial hypertension represents a survival benefit or detriment or is simply an unrelated adverse effect of gestational programming. Alternatively, one may speculate that hypertension may be a disadvantage for elder survival, after reproductive years.
potentially representing a societal benefit during periods of limited resources associated with famine or drought.

In summary, gestational programming appears to have contributed to species adaptation and population survival. These developmental responses and processes are still functional in humans and have likely contributed to the current epidemic of hypertension, obesity, and diabetes. A concerted scientific effort is required to understand the mechanisms and regulation of gestational programming. The potential exists to modify the pregnancy and/or newborn environment so as to optimize the benefits, and avoid the detrimental effects of gestational programming.

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