Protective effect of prenatal water restriction on offspring cardiovascular homeostasis in response to hemorrhage

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Desai, Mina, Catalina Guerra, Shengbiao Wang, and Michael G. Ross. Protective effect of prenatal water restriction on offspring cardiovascular homeostasis in response to hemorrhage. Am J Physiol Heart Circ Physiol 288: H2659–H2665, 2005. First published January 21, 2005; doi:10.1152/ajpheart.00875.2004.—We determined the cardiovascular and AVP responses of prenatally dehydrated (PreDehy) neonates to intravascular hemorrhage. Ewes with singleton fetuses were subjected to water restriction from 110 days of gestation to full term to achieve hypernatremia of 8–10 meq/l. Water and food were provided ad libitum to control ewes. After delivery, water and food were provided ad libitum to ewes from both groups, and newborns were allowed to nurse ad libitum. At 15 ± 2 days of age, PreDehy and control lambs were prepared with bladder and femoral catheters and studied at 25 ± 2 days of age. After a 2-h basal period, lambs were hemorrhaged to 30% of blood volume over 1 h (0.5% of blood volume/min) and monitored 1 h after hemorrhage. Neonatal arterial blood pressure was measured, and blood samples were collected. Basal plasma sodium levels, plasma osmolality, hematocrit, and mean arterial pressure were increased in PreDehy lambs compared with controls. Both groups had similar basal AVP levels and heart rate. In response to hemorrhage, all parameters remained significantly elevated in PreDehy lambs. Blood pressure decreased less in PreDehy lambs than in controls. The hemorrhage-AVP threshold (percent blood volume withdrawal at which plasma AVP values significantly increased) was markedly elevated (20 vs. 15%) and peak hemorrhage-induced AVP plasma levels were lower (5.6 ± 1.5 vs. 10.1 ± 1.5 pg/ml, P < 0.01) in PreDehy lambs than in controls. Thus offspring of dehydrated ewes demonstrate enhanced AVP secretory responses to hypotension. Despite potential long-term adverse effects of systemic hypertension, these results suggest a protective effect of prenatal water restriction on offspring cardiovascular homeostasis during blood volume reduction.

programming; hypernatremia; hypertension; arginine vasopressin

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 impact fetal developmental processes and may alter homeostatic regulatory mechanisms among the offspring (2, 9, 10). Whereas genetic mutations that may provide a survival advantage generally require prolonged, evolutionary time periods to influence the species population, gestational programming may be rapidly adaptable to changing environmental conditions. Furthermore, effects may be expressed during basal conditions or restricted to environmental stress or disease states in the offspring.

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 growth retardation, have been associated with the development of a “thrifty-phenotype” offspring (3, 12). Because these offspring are better able to acquire and utilize nutrients, this phenotype has a survival advantage in a continued environment of relative famine. We previously explored the effects of simulated drought during ovine gestation. Among water-restricted pregnant ewes in which maternal plasma hypertonicity was maintained during the terminal 25% of pregnancy, 3-wk-old offspring demonstrated a syndrome of hypernatremic hypertension, indicating a programming of osmoregulatory function and fluid homeostasis (8). Furthermore, prenatally dehydrated (PreDehy) newborn arginine vasopressin (AVP) secretory responses to hypertonicity were altered, with an elevated plasma osmolality threshold and an increased sensitivity (i.e., slope) of AVP secretion after threshold osmolality levels (25). Prenatal dehydration may also alter the development of additional homeostatic systems. For instance, besides hypertension, PreDehy offspring demonstrated an elevated hematocrit, suggesting vasoconstriction and/or relative plasma volume contraction (26). In view of evidence of potential vasoconstriction, we hypothesized that the PreDehy offspring may be more sensitive to hemorrhage, either in an enhanced hypotensive response or enhanced AVP secretion.

MATERIALS AND METHODS

Animals and surgery. Twelve time-dated pregnant Western mixed-breed sheep with singleton pregnancies were obtained from a local source (Nebeker Ranch, Palmdale, CA). Study (PreDehy) animals were housed indoors in individual steel study cages and acclimated to a 12:12-h light-dark cycle. Food (alfalfa pellets) was provided ad libitum, and water was provided as described below. The care and use of the animals were approved by the Animal Research Committee of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center and in accordance with the American Association for Accreditation of Laboratory Animal Care and National Institutes of Health guidelines.

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**Prenatal dehydration.** The animal model for the preparation of chronic prenatal dehydration has been previously described (8, 26). Briefly, at 105 ± 1 days of gestation, ewes (n = 5) were surgically prepared with femoral vein catheters. Maternal blood samples were drawn daily to monitor plasma tonicity and electrolytes. After the baseline plasma osmolality was established, water was removed from the ewes for 2 days, and then water was restricted to ~1 liter daily throughout the remainder of pregnancy. The water intake was titrated to achieve an 8–10 meq/L increase in plasma sodium concentration from 110 days of gestation until spontaneous delivery at full term. Matched groups of prenatally euvhhydrated lambs (controls, n = 5) were born to ewes provided ad libitum water and food throughout gestation. Control ewes were not prepared with vascular catheters and were allowed food and water ad libitum throughout the pregnancy. In study and control groups, ewes were allowed to deliver naturally. Full term was 147 ± 3 days in dehydrated and control ewes, indicating that the length of gestation was not affected by maternal dehydration. Immediately after delivery, water and food were provided ad libitum to ewes, and newborns were allowed to nurse ad libitum.

**Experimental protocol.** At 15 ± 2 days of age, lambs were surgically prepared with bladder and femoral arterial and venous catheters. All experiments were performed on conscious lambs maintained in a specially designed support sling. At 25 ± 2 days, PreDehy and control lambs were studied. At 60 min before the beginning of the basal period, the lamb bladder catheter was drained to gravity, and [1H]Insulin (2 μCi·kg⁻¹·min⁻¹) was infused (0.01 ml·kg⁻¹·h⁻¹·iv) for measurement of glomerular filtration rate (GFR); the infusion continued through the basal and experimental periods. During a subsequent 2-h basal period, arterial blood pressure and urine volume were continuously monitored. Neonatal arterial blood samples were obtained at 30-min periods for determination of arterial pH, blood gases, plasma osmolality, electrolyte and inulin concentration, and hematocrit, and urine samples were assayed for volume, osmolality, and inulin and electrolyte concentrations. After the 2-h basal period, lambs were continuously hemorrhaged to 30% of estimated blood volume over a 60-min period at a rate of 0.5% of estimated blood volume per minute. Blood volume was estimated to be 75 ml/kg body wt on the basis of published information (18, 32) and measured body weights for each lamb. During this period, 1.0-ml lamb blood samples (30 and 60 min) were replaced with an equal volume of heparinized maternal blood withdrawn before each experiment and filtered through a 20-μm antimicrobial filter. Throughout the hemorrhage period, lamb arterial blood samples were collected from the blood withdrawn by the hemorrhage protocol. Blood withdrawn during or after hemorrhage was not replaced. Previous studies were performed at 21 days of age to determine the response to hypotonic saline infusion (26) and at 23 days of age to determine the response to hypertonic saline infusion (8). All animals were in a basal state, with values comparable to those at 21 days of age.

**Analytic methods.** Throughout the measurement periods, neonatal arterial blood pressure was monitored continuously by means of a recorder (model R-612, Beckman Instruments, Fullerton, CA) and pressure transducers (Statham P23, Garret, Oxnard, CA). All signals were digitized at 50 Hz and acquired on an IBM-compatible computer. Heart rate, systolic and diastolic pressures, and mean arterial pressure (MAP) were calculated from the pressure traces.

Plasma and urinary electrolyte levels were determined with an electrolyte analyzer (model 5, Nova Biomedical, Waltham, MA). Osmolality was measured by freezing-point depression on a Digi-matic Osmometer (model MO, Advanced Instruments, Needham Heights, MA). Blood pH, arterial PCO₂, and arterial PO₂ (PaO₂) were measured at 39°C with an acid-base analyzer system (model BM 33 MK2-PHM 72 MKS, Radiometer, Copenhagen, Denmark). Inulin concentrations were assessed by counting 100-μl aliquots diluted to 10 ml with Hydrofluor (National Diagnostics, Somerville, NJ) in a liquid scintillation counter (model LS-355, Beckman, Irvine, CA). Plasma AVP levels were measured by radioimmunoassay (33).

**Statistics.** Values are means ± SE. Basal values represent the mean of measurements obtained during the basal period from −2 to 0 h. All urinary values of excretion or clearance were adjusted for actual body weight and expressed per kilogram. Differences over time were assessed with repeated-measures analysis of variance with Dunnett’s post hoc test. The hemorrhage-AVP threshold was defined as the percent blood volume withdrawal at which plasma AVP values significantly increased vs. mean basal values. Analysis of covariance was used to assess the differences in slopes of the relation between AVP and decrease in blood pressure. Once it was established that the slopes were comparable, analysis of covariance was used to determine the differences in the intercept of these relations. The AVP values were first logarithmically transformed to ensure linearity. Statistical significance was accepted at P ≤ 0.05.

**RESULTS**

**Maternal dehydration.** We previously reported significantly elevated plasma osmolality and sodium levels in water-restricted ewes, with plasma potassium levels and hematocrit comparable to those in euhydrated control ewes (8, 26).

**Neonatal basal values.** As stated in our previous studies, the offspring of PreDehy ewes were growth retarded at birth (8, 26). However, by 25 days of age, similar weights were noted in PreDehy (12.3 ± 0.7 kg) and control (13.2 ± 1.3 kg) lambs.

During the basal period, plasma osmolality, plasma sodium levels, and arterial hematocrit were significantly increased in PreDehy neonates compared with controls, although there were no differences in plasma potassium, chloride, or AVP levels. In addition, peripheral arterial pressures were markedly elevated among the PreDehy offspring, with −10-mmHg increases in systolic/diastolic pressure and MAP. However, no differences were evident in heart rate, pH, PaO₂, or arterial PCO₂ (Table 1).

Basal GFR, urine volume, osmolality, and sodium, including urinary excretion and clearance, values were similar between the two groups (Table 1).

**Neonatal responses to hemorrhage.** In response to arterial hemorrhage, PreDehy neonates continued to exhibit significantly elevated plasma osmolality and plasma sodium levels compared with controls. With the exception of minor changes in the PreDehy lambs, there were no significant alterations in plasma osmolality or sodium levels from the basal values in either group. Although the PreDehy and control lambs demonstrated an overall reduction (5–6%) in hematocrit from the basal value to the end of the hemorrhage period, a statistically significant decrease in hematocrit was observed at a lower percent blood volume withdrawal in the controls (Fig. 1). Plasma AVP levels significantly increased in PreDehy and control lambs during hemorrhage. The peak levels demonstrated in control lambs were significantly above those noted in PreDehy lambs (Fig. 1). Moreover, the threshold for stimulation of AVP secretion was significantly elevated among PreDehy lambs compared with controls (20 vs. 15%).

In the assessment of cardiovascular parameters, PreDehy and control lambs showed significant reductions in systolic/diastolic pressure and MAP. Nonetheless, the absolute and percent changes in blood pressure were significantly different between the groups. During and at the end of hemorrhage, the blood pressures continued to remain significantly elevated in PreDehy compared with control lambs: 71 ± 5 vs. 42 ± 4 mmHg for systolic (P < 0.001), 45 ± 3 vs. 22 ± 3 mmHg for diastolic (P < 0.001), and 55 ± 4 vs. 30 ± 3 mmHg for MAP.
DISCUSSION

The results of the present study confirm the development of a syndrome of hypernatremic hypertension among PreDehy offspring. The elevated hematocrit and arterial blood pressure suggest that these animals may be predisposed to intravascular volume depletion, inasmuch as they were already in an enhanced vasopressor and potentially hemoconcentrated state. In response to the intravascular hemorrhage, PreDehy and control offspring demonstrated a similar overall reduction in hematocrit, but the hypertensive effect was markedly reduced in PreDehy lambs compared with controls. Moreover, the plasma AVP response to hypotension was enhanced and the blood volume threshold for stimulation was elevated in PreDehy lambs.

Our laboratory and others have confirmed the development of osmoregulatory system and AVP secretory responsiveness during the last half of gestation. Systemic and central osmotic and dipsogenic mechanisms are functional in the near-term fetus, as shown by AVP secretion and swallowing activity, and are evoked in response to putative dipsogens (24, 28). Despite the functional responses, the level of osmotic sensitivity suggests a functional immaturity, inasmuch as a significantly greater increase in plasma osmolality is required in the fetus than in the adult to stimulate AVP secretion (7, 37). Whether these relatively suppressed fetal responses are due to primary osmoreceptor insensitivity or are secondary to downstream neural mechanisms is unknown. Similarly, fetuses whose mothers reported moderate/severe emesis during pregnancy exhibited enhanced salt appetite (20) and blood pressure (1) of humans. In utero programming of osmoregulatory and sodium homeostatic systems has been demonstrated in rats, sheep, and humans. For example, extracellular dehydration during rat pregnancy increases salt appetite (20) and blood pressure (1) of the offspring. Similarly, chronic toxicity changes in utero alter AVP synthesis and secretion in neonatal rats (14). Perinatal sodium depletion of rats alters offspring plasma and urinary sodium concentration and hematocrit. As adults, these offspring demonstrated elevated fluid turnover and high sodium concentration and hematocrit. As adults, these offspring demonstrated elevated fluid turnover and high sodium concentration and hematocrit. As adults, these offspring demonstrated elevated fluid turnover and high sodium concentration and hematocrit. As adults, these offspring demonstrated elevated fluid turnover and high sodium concentration and hematocrit. As adults, these offspring demonstrated elevated fluid turnover and high sodium concentration and hematocrit. As adults, these offspring demonstrated elevated fluid turnover and high sodium concentration and hematocrit.

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withdrawal occurred over 60 min, the lambs likely adapted with intravascular infusion of interstitial fluid to account for the reduction in hematocrit. Although one would expect a continued equilibration, as evidenced by reduced hematocrit after completion of the blood volume withdrawal, PreDehy and control offspring demonstrated a trend toward increased hematocrit immediately after the end of hemorrhage. These results suggest that the lambs are capable of rapid equilibration responses between the vascular and the interstitial compartments. Alternatively, rapid release of fetal red blood cells from hepatic, splenic, and bone marrow stores may have contributed to the hematocrit responses. Notably, comparable studies in adult sheep demonstrate continued decline in hematocrit after acute hemorrhage (34).

The neurohumoral and hemodynamic responses to progressive acute hypovolemia have two distinct phases. In the initial arterial baroreceptor-mediated phase I, the fall in cardiac output is nearly matched by a sympathetically mediated increase in peripheral resistance, such that arterial pressure is maintained near normal levels. In most species, adrenal catecholamines and AVP contribute little to phase I, whereas increased renin release appears to augment the sympathetically mediated vasoconstriction. When blood volume has fallen by a critical amount, phase II develops abruptly. Phase II is characterized by withdrawal of sympathetic vasoconstrictor drive, relative or absolute bradycardia, an increase in release of adrenal catecholamines and AVP, and a profound fall in arterial pressure (31, 35). In the present study, the most unexpected finding was the significantly reduced hypotensive response exhibited by the PreDehy lambs compared with controls. More importantly, PreDehy lambs demonstrated a slight prolongation (10 min) of phase I hemorrhage responses, inasmuch as blood pressure did not significantly decrease until 15% blood volume withdrawal compared with 10% in control newborns. More striking was the difference in the phase II hemorrhage, i.e., marked decrease in blood pressure in the controls (36 mmHg) compared with PreDehy lambs (20 mmHg). Both groups exhibited a similar “vasovagal” decrease in heart rate. The prolonged nonhypotensive phase I in PreDehy lambs suggests an enhanced baroreflex function, whereas the improved blood pressure regulation during the hypotensive phase suggests enhanced vasoconstriction (although angiotensin and catecholamines were not measured in the present study).

Notably, the PreDehy lambs demonstrated an increased secretion of plasma AVP at 20% blood volume withdrawal, whereas control lambs demonstrated an increase at 15% blood volume withdrawal. Both of these threshold levels occurred subsequent to a significant decline in MAP, inasmuch as a hypotensive response was demonstrated initially in the Pre-Dehy lambs at 15% blood volume withdrawal and at 10% blood volume withdrawal in controls. This suggests that the delayed AVP secretory responses occurred in response to arterial hypotension with the expected time delay. Although plasma AVP responses in PreDehy lambs were blunted in regard to the degree of hemorrhage, the plasma AVP response in relation to the degree of blood pressure change was en-

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Fig. 1. Plasma osmolality, sodium concentration, AVP levels, and hematocrit in control (●) and prenatally dehydrated (PreDehy, ○) lambs during hemorrhage. Time 0 represents the basal period, which is followed by 30% of estimated blood volume withdrawal over a 60-min period and another 60 min of monitoring. Values are means ± SE (n = 5). *P < 0.001 vs. control. cSignificantly different from basal value among control lambs. dSignificantly different from basal value among PreDehy lambs.
hanced in the PreDehy lambs. This enhanced AVP secretion in relation to the primary stimulus (hypotension) is consistent with our previous finding of an enhanced slope of AVP secretion (but an altered threshold) in response to hypertonic saline (25). The levels of plasma AVP (6 pg/ml) reached during the study were unlikely to contribute to newborn pressor responses (21, 23). Thus the results of the present study are consistent with an enhanced AVP response to hypotension, although the hypotensive responsiveness to hemorrhage may be protected by other endocrine or cardiovascular pathways.

The association of increased basal MAP and increased hematocrit (consistent with relatively reduced intravascular water) may suggest a basal state of vasoconstriction and, thus, greater sensitivity to hemorrhage among PreDehy lambs. The effects of dehydration on baroreflex sensitivity have been studied in animals that were concurrently dehydrated (5, 30). The authors concluded that elevated plasma AVP levels in response to concurrent dehydration improved cardiovascular responses to hemorrhage. In contrast, in the present study, animals were previously (prenatally) dehydrated and, subsequently, allowed to nurse ad libitum after birth. Basal levels of AVP were similar between the PreDehy and control lambs at the time of study. In fact, plasma AVP levels were reduced in PreDehy lambs in response to hemorrhage. Nevertheless, the PreDehy lambs demonstrated a protective cardiovascular response, as evident by the reduced hypotensive response to bleeding.

Fig. 2. Mean arterial blood pressure (MAP), reduction (change) in MAP, relation between change in MAP and plasma AVP levels, and heart rate in control (○) and PreDehy (●) lambs. Time 0 represents the basal period, which is followed by 30% of estimated blood volume withdrawal over a 60-min period and another 60 min of monitoring. Values are means ± SE (n = 5). *P < 0.001 vs. control. †Significantly different from basal value among control lambs. ‡Significantly different from basal value among PreDehy lambs.

Fig. 3. Glomerular filtration rate (GFR) and urine volume in control (○) and PreDehy (●) lambs. Time 0 represents the basal period, which is followed by 30% of estimated blood volume withdrawal over a 60-min period and another 60 min of monitoring. Values are means ± SE (n = 5). *Significantly different from basal value among control lambs. †Significantly different from basal value among PreDehy lambs.
hemorrhage, although heart rate responses to hemorrhage were identical in PreDehy and control lambs. Notably, blood pressure responses to nitroprusside were similar in water-deprived adult dogs, but heart rate responses were different (4).

Changes in plasma osmolality or sodium were minimal, indicating that AVP responses were not due to osmotically mediated stimulation. Furthermore, there was no change in Pao3 values that would indicate a hypoxia-associated AVP secretion. Plasma AVP levels of 15–20 pg/ml are required to induce a hypertensive response (21, 23), and values >20 pg/ml are required to induce a decrease in heart rate (15, 17) in newborn or adult lambs. The plasma AVP values in the present study were ~10 pg/ml and, thus, likely did not contribute to maintenance of blood pressure during the hypotensive phase or the relative decrease in heart rate among control newborns. Plasma AVP levels returned toward basal values in PreDehy and control lambs, although MAP remained significantly reduced in both groups. These findings again suggest that plasma AVP did not contribute to the maintenance of arterial blood pressure after hemorrhage. However, prenatal dehydration may potentially increase V1 receptor expression at cardiac pacemakers or vessels, resulting in potentially enhanced sensitivity to these levels of AVP in the PreDehy lambs.

In the present study, blood volume was not measured in control and PreDehy lambs, and blood volume withdrawal was based on body weight. However, if blood volume were less in the PreDehy lambs, the percentage of blood volume withdrawal would be greater. Under this circumstance, the reduced hypotensive response among PreDehy lambs would be even more remarkable. Thus only an (unlikely) expansion of blood volume in the PreDehy sheep would counteract the differences observed in the present study.

Our previous studies demonstrated increased plasma sodium and total pituitary content but lower hypotalamic AVP mRNA levels in newborn lambs subjected to in utero hypertonicity for the last 20% of gestation than in control newborns (22, 36). As noted above, PreDehy lambs demonstrate an elevated slope of AVP secretion in response to plasma tonicity, suggesting an augmented renal antidiuresis response (25). This may represent a potential survival advantage in facilitating antidiuresis, particularly under conditions of prolonged dehydration. In the present study, PreDehy lambs were better able to maintain blood pressure in response to intravascular hemorrhage than were controls. Thus, despite potential long-term adverse effects of systemic hypertension, these results suggest a potential protective effect of prenatal water restriction on offspring cardiovascular homeostasis. Although programming of enhanced vascular contractility may have long-term adverse health effects, it may protect offspring from acute vascular compromise.

In summary, the present results show that offspring of water-restricted ewes may demonstrate a programmed syndrome of hypertonicity, hypernatremia, and hypertension with clinically significant hematologic and cardiovascular alterations. Nevertheless, the PreDehy lambs demonstrated a protective cardiovascular response, as evident in the reduced hypotensive response to hemorrhage. The prolonged nonhypotensive phase I in PreDehy lambs suggests an enhanced baroreflex function, whereas the improved blood pressure regulation during the hypotensive phase suggests enhanced vasoconstriction.

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