Prenatal Malnutrition-Induced Changes in Blood Pressure
Dissociation of Stress and Nonstress Responses Using Radiotelemetry

John Tonkiss, Monika Trzcinska, Janina R. Galler, Nelson Ruiz-Opazo, Victoria L.M. Herrera

Abstract—A link between prenatal malnutrition and hypertension in human populations has recently been proposed. Rat models of prenatal malnutrition have provided major support for this theory on the basis of tail-cuff measurements. However, this technique requires restraint and elevated temperature, both potential sources of stress. To determine the effect of prenatal protein malnutrition on blood pressure under nonstress conditions, 24-hour radiotelemetric measurements were taken in the home cage. Male rats born to dams fed a 6% casein diet for 5 weeks before mating and throughout pregnancy were studied in early adulthood (from 96 days of age). During the waking phase of their cycle but not the sleep phase, prenatal malnutrition gave rise to small but significant elevations of diastolic blood pressure and heart rate compared with well-nourished controls. Direct effects of stress on blood pressure responses were determined in a second experiment using an olfactory stressor. Prenatally malnourished rats showed a greater increase in both systolic and diastolic pressures compared with well-nourished controls during the first exposure to ammonia. A different pattern of change of cardiovascular responses was also observed during subsequent presentations of the stressor. These findings of a small baseline increase in diastolic pressure consequent to prenatal malnutrition, but an augmented elevation of both systolic and diastolic pressures after first exposure to stress, suggest the need to reevaluate interpretation of the large elevations in blood pressure previously observed in malnourished animals using the stressful tail-cuff procedure. (Hypertension. 1998;32:108-114.)

Key Words: malnutrition ■ prenatal insult ■ growth retardation, intrauterine ■ ammonia ■ stress ■ rats

On the basis of epidemiological data, Barker et al1 and others2 have suggested that normal-term babies that are born small have an increased rate of cardiovascular disease later in life. Fetal undernutrition is one of the primary causes of growth retardation, and it has been postulated that such undernutrition may lead to programming of persisting changes in a range of metabolic, physiological, and structural parameters, thereby leading to high blood pressure and other cardiovascular problems.3,4 However, there has been criticism of the epidemiological evidence supporting this link between fetal undernutrition and hypertension in human populations.5 In their critical review, Paneth et al6 concluded that “the inverse relationship of birthweight to blood pressure is found inconsistently and, when present, is not strong.” Moreover, the findings are potentially confounded by variables such as social class, which generally have not been taken into account.

Major support for the theory that prenatal undernutrition is critically linked with later hypertension comes from animal studies in which rat dams are fed a low protein diet (9% casein) for 3 weeks before mating and throughout pregnancy and give birth to offspring that manifest SBP elevated by as much as 28 mm Hg later in life.7–11 However, these data are all based on indirect blood pressure measurements obtained via a tail cuff while the rat is under restraint in a Plexiglas tube. Woodall et al12 also used this indirect measurement technique to examine blood pressure in rats born to dams with a severe protein-calorie restriction throughout pregnancy (ie, they were fed only 30% of the amount of food consumed by control dams). A modest elevation of SBP was observed (5 to 8 mm Hg) despite a severe level of growth restriction (33% weight deficit compared with well-nourished controls at day 22 of gestation). There have been few studies that have obtained direct measurements of blood pressure after prenatal malnutrition. The only study of this type to date has been that of Persson and Jansson,13 who induced IUGR in guinea pigs via unilateral ligation of the uterine artery. They found that moderate IUGR was not associated with an increase in blood pressure but that severe IUGR (48% to 57% reduction in birth weight) was associated with a small but significant elevation of SBP (7 mm Hg).

Clearly, tail-cuff plethysmography has been the procedure used in the majority of animal research supporting the theory that prenatal malnutrition gives rise to later hypertension. There are potential inaccuracies inherent in this technique. These include restraint as a likely source of stress in and of itself,14 accuracy to only within 10 mm Hg,15 and reliance on a temperature-induced increase in blood flow in the tail

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artery, which can introduce a measurement artifact across subjects. Hence, the present study was devised to assess the adult blood pressure of prenatally protein malnourished rats using a direct, minimally stressful, continuous telemetric procedure. This procedure involved implanting a radiotelemetric pressure transducer into the descending aorta where it continuously (and simultaneously) transmitted data on the SBP, DBP, MAP, HR, and activity of the rat to remote computers for later analysis. Hypothesis 1 was that prenatally malnourished rats would not exhibit elevated blood pressure with respect to well-nourished controls under such nonstressful test conditions. In a second experiment, we examined the blood pressure response of prenatally malnourished rats to an acute stressor (ammonia odor) to determine whether prenatally malnourished rats might show a differential response to acute stress, such as might be expected with restraint. Noxious or offensive odors are well validated as stressors in this species. Hypothesis 2 was that prenatally malnourished rats would exhibit a greater elevation of blood pressure than the well-nourished controls on exposure to stress. Contrary to hypothesis 1, prenatal malnutrition brought about a small but significant elevation of DBP during the dark phase of the cycle. However, a heightened BP response in prenatally malnourished rats, on first exposure to stress, confirmed hypothesis 2.

Methods

All procedures described below were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (publication No. 8023) and institutional guidelines (IACUC approval numbers 94-045, 96-002, and 96-068).

Nutritional Treatment

The model of malnutrition chosen was our standard model of prenatal protein restriction (6% casein diet). This model was developed more than 15 years ago as a model of IUGR, with the pups having significantly smaller body and brain weights at birth while remaining otherwise healthy. Transferring the pups to a healthy mother for fostering serves to restrict malnutrition to the prenatal period, thereby ensuring prompt nutritional and environmental rehability with minimal disruption of the early environment.

Briefly, nulliparous Sprague-Dawley VAF plus female rats (Charles River Laboratories, Kingston, Mass) were allowed ad libitum access to one of two isocaloric diets (Teklad): a diet of adequate protein (25% casein) content or one of low protein (6% casein) content (detailed description given in Reference 20) for 5 weeks before mating and throughout pregnancy. After parturition, litters were culled to 8 pups (6 males and 2 females) and placed with well-nourished mothers for fostering. Pups born to dams fed the 6% casein diet and fostered by other lactating dams fed the 25% casein diet are designated 25/25W (prenatally well-nourished controls). Housing conditions and nutritional, mating, and fostering procedures are described in more detail in a previous article. All offspring were given ad libitum access to regular rat chow (Purina formula 5001) after weaning at 21 days.

Subjects

One male offspring was randomly selected from each of 10 6/25M and 11 25/25W litters for testing, which began at 96 days of age. Males were selected to allow comparison with recent literature in this field and because they have generally been reported to be more sensitive to prenatal and perinatal insults than females.

Radiotelemetric Measurement of Blood Pressure and Activity

The Datascience telemetric system was used to monitor blood pressure. This system of measurement has been validated in earlier published studies. Briefly, test conditions were as follows: Newly calibrated implants were surgically placed into the descending aorta of each rat under sodium pentobarbital (50 mg/kg IP) anesthesia. Insertion of a catheter and hemostasis were usually achieved in seconds. Only animals without surgical complications were included in the study. After surgery, animals were transported to a dedicated blood pressure room (entry of personnel was strictly controlled) and housed individually in regular shoebox cages on telemetric receiver pads (1 per rat). All rats were allowed to recover for 2 weeks, during which time blood pressure was closely monitored. Data were collected once blood pressure measurements had stabilized. Cages were arranged on the cage racks in an alternating order between the two nutritional groups. The amount of activity was also determined via the telemetric system, with 1 U pulse being generated per 2.5 cm (1 inch) of movement over a fixed reference point, with greater signal strength corresponding to greater lateral movement.

Part 1: Nonstress 24-Hour Study

After full postoperative recovery, baseline monitoring was begun during a 12-hour light (6 AM to 6 PM)/12-hour dark (6 PM to 6 AM) cycle. Rats normally sleep during the light phase and are awake during the dark phase. SBP, DBP, HR, MAP, and activity of the rats were monitored every 5 minutes (mean of 10-second samples per 5 minutes) from 6 AM Saturday to 5:55 AM Sunday. This observation time was chosen to ensure minimal disruption to the animals. Pulse pressure (ie, SBP−DBP) was subsequently calculated for each time point.

Part 2: Stress Study

In part 1 (above), differences between prenatally malnourished and well-nourished rats were observed during the dark phase of the cycle, but the two groups were similar in the light phase. To determine whether stress (ammonia odor) would reveal differences in blood pressure regulation between these two groups, the stress response was studied at a time of day when their baseline values were similar (ie, the light phase). Thus, beginning at about 10 AM on each of 3 consecutive days, SBP, DBP, MAP, pulse pressure, HR, and activity were measured every 30 seconds for 5 minutes to determine baseline (mean of 7-second samples per 30 seconds). A gauge swab soaked with 2 mL of ammonium hydroxide was then introduced, suspended by thread from the cage bars so that it did not come into contact with the bedding, cage sides, or the rat. After 5 minutes, during which time SBP, DBP, MAP, pulse pressure, HR, and activity were measured every 30 seconds, the stressor was removed and recovery of the various measures was assessed over the next 15 minutes. Ammonia odor was chosen because (1) this particular stressor is of ethological significance to rodents, (2) it occurs naturally in the rats’ environment (ammonia is present in soiled bedding), and (3) this agent is believed to be more psychologically than physically stressful.
### Data Analysis

Only one rat per litter was selected for testing. Therefore, a “litter” was taken as the unit for all analyses. Body weight and litter size were compared between groups using 1-way ANOVA. The 24-hour monitoring of baseline activity, SBP, DBP, MAP, pulse pressure, and HR consisted of measurements recorded every 5 minutes. For analysis, 30-minute blocks were averaged (6 measurements per block) and analyzed according to 12-hour phases (dark and light). Hence, there were 24 30-minute blocks during the light phase and 24 30-minute blocks during the dark phase. Initial analyses using 3-way ANOVA (Nutrition×Light/Dark Phase×Block, with activity as a covariate) revealed the presence of significant Nutrition×Phase or Nutrition×Phase×Block interactions for DBP, pulse pressure, HR, and activity. To simplify interpretation of these effects, the dark-phase data were analyzed separately from the light-phase data using 2-way ANOVAs (Nutrition×Block), with block as a repeated measure. Activity was used as a covariate because the rats’ physical activity could potentially influence these measures. Analysis of activity did not use a covariate.

The ammonia stress data were analyzed in 3 separate phases: baseline, stress, and recovery. Baseline was defined as the average of the 10 prestress measurements (5 minutes) for each day, and these values were compared between groups using 2-way ANOVAs (Nutrition×Day, with activity as a covariate). Day was a repeated measure. For both the stress and recovery components, differences from baseline were calculated for each 30-second measurement (within each test day). The 10 measurements taken during stress were averaged within a day and compared between groups using 2-way ANOVAs (Nutrition×Day), with day as a repeated measure. Sporadic bursts of elevated activity were observed during application of the stressor and during recovery. To control for the effect of this increased activity on blood pressure and HR measures, activity (difference from baseline) was used as a covariate. The recovery data were converted to 10 consecutive 30-second averages (ie, 3 blocks of 5 minutes) on each test day and analyzed by 3-way ANOVAs (Nutrition×Day×Block), with activity (difference from baseline) as a covariate. Day and block were repeated measures. Orthogonal components were extracted for all repeated measures. Unless stated otherwise, only main effects of nutrition and significant interactions involving nutrition are reported ($P<0.05$).

### Results

#### Litter Size and Body Weights

As observed previously, litter size was slightly smaller in the 6/25M group compared with the 25/25W group, but this difference did not achieve statistical significance (mean±SD: 6/25M, 13.50±1.77; 25/25W, 14.91±2.55). Although, prenatally malnourished rats weighed significantly less than well-nourished controls [$F(1,19)=12.15$, $P<0.01$] on the day of birth (6/25M, 5.61±0.44 g; 25/25W, 6.38±0.56 g), the body weight of the two groups was no longer statistically different at the time of the surgical implants in adulthood (6/25M, 492±85 g; 25/25W, 536±83 g). Thus, differential effects of body size on implant accommodation and subsequent effects on blood pressure measurements can therefore be ruled out.

#### Light Phase

Prenatally malnourished and well-nourished control rats did not differ in SBP (overall mean values: 25/25W, 125.82 mm Hg; 6/25M, 124.31 mm Hg), DBP (25/25W, 89.25 mm Hg; 6/25M, 90.10 mm Hg), HR (25/25W, 309.94 bpm; 6/25M, 318.47 bpm), or activity (25/25W, 3.92 U; 6/25M, 3.73 U) during the light phase (Figure 1). MAP (25/25W, 105.23 mm Hg; 6/25M, 105.05 mm Hg) and pulse pressure (25/25W, 36.56 mm Hg; 6/25M, 34.22 mm Hg) also proved to be similar in the two groups of rats (data not shown).

#### Dark Phase

Quite distinct from the light phase, significant changes were noted between the two nutritional groups, with each parameter affected differently. The activity of the prenatally malnourished rats followed a rising quadratic trend during the dark phase, whereas that of the controls showed increasing levels, up to the midpoint of the cycle, and then a decline (Figure 1D). Thus, the prenatally malnourished rats showed higher levels of activity than the controls (21.53 versus 11.26 U, respectively) in the period immediately before light onset (values derived from regression lines). A significant Nutrition×Block (quadratic) interaction [$F(1,19)=4.44$, $P<0.05$] confirmed the difference in activity pattern between the two nutritional groups. These data suggest that under baseline nonstressed conditions, 6/25M and 25/25W differed in spontaneous activity during the latter portion of the wake cycle. Because of the baseline difference in activity patterns, blood pressure and HR were corrected for activity level using activity as covariate to determine the long-term consequences of prenatal protein malnutrition independent of this variable. DBP (Figure 1A) did not differ between the prenatally malnourished and control rats. Figure 1B illustrates the mean DBP of prenatally malnourished and well-nourished control rats. The two nutritional groups differed in the manner in which DBP changed over blocks, as indicated by a significant Nutrition×Block (quadratic) interaction [$F(1,18)=6.43$, $P<0.03$]. Specifically, the prenatally malnourished rats showed an increasing DBP until the midpoint of the dark phase, after which it declined. In contrast, the well-nourished control animals exhibited a slowly rising DBP throughout that phase. Consequently, in the early part of the dark phase, the DBP of the two groups diverged, with the malnourished rats exhibiting higher levels than the controls (25/25W, 91.11 mm Hg; 6/25M, 95.49 mm Hg; values derived from the regression lines); then before light onset, the groups began to converge once more. Figure 1C demonstrates that the mean HR of the prenatally malnourished rats was higher than that of controls in the early part of the dark phase (25/25W, 338.03 bpm; 6/25M, 362.67 bpm; values derived from the regression lines) but that this difference declined toward “daybreak.” This observation was confirmed by the presence of a significant Nutrition×Block (linear) interaction [$F(1,18)=5.64$, $P<0.03$]. MAP and pulse pressure (data not shown) proved to be similar in 6/25M and 25/25W rats.

#### Part 2: Stress Study

To investigate whether mild, acute stress might elicit differential cardiovascular and behavioral responses during the

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light phase, both nutritional groups were exposed to ammonia odor. With repeated exposure on 3 consecutive days, we examined whether the animals’ responses to the noxious smell became habituated or sensitized. Day 1 values for SBP, DBP, and HR (all without correction for activity) are plotted in Figure 2 to show the basic relationship between these measures during 5 minutes of baseline determination, 5 minutes of exposure to ammonia odor, and 15 minutes of recovery. In this phase of the experiment, baseline was taken to confirm the similarity of the two groups for the time of day selected. Within a test day, baseline for all measures was stable. During exposure to the stressor, SBP and DBP increased while HR dropped dramatically. During recovery, SBP and DBP returned toward baseline but remained elevated. HR not only recovered but it became elevated in comparison to prestress baseline. This basic relationship was observed in both nutritional groups of rats. To determine whether there were quantitative differences between the nutritional treatment groups, the three experimental phases (baseline, stress, and recovery) were analyzed separately.

Baseline
Both DBP and activity were found to be stable over the 3 days of testing, with prenatally malnourished and control rats displaying comparable levels (mean DBP, 89.9 versus 88.7 mm Hg; mean activity, 0.26 versus 0.50 U, respectively). HR, SBP, and pulse pressure were somewhat less stable, with each showing a linear decline over the 3 test days [day (linear): HR, F(1,18)=19.05, P<0.001; SBP, F(1,18)=5.55, P<0.05; pulse pressure, F(1,18)=6.14, P<0.05]. Nonetheless, prenatally malnourished and control groups proved to be similar across these measures (mean HR, 304.7 and 305.9 bpm; mean SBP, 124.4 and 123.6 mm Hg; mean pulse pressure, 34.5 and 34.9 mm Hg; respectively), showing comparable changes across days.

Stress
Over the 3 days of testing, prenatally malnourished and control rats demonstrated significantly different alterations of SBP in response to the ammonia stressor [Day (linear)×Nutrition interaction: F(1,18)=8.02, P<0.02]. Figure 3A illustrates the mean difference in SBP from baseline during stress (adjusted for activity) on each of the 3 test days. The prenatally malnourished rats exhibited a greater elevation of SBP than the controls on day 1, but by day 3 the pattern was reversed, with control animals demonstrating a greater rise in SBP than the prenatally malnourished rats. A similar pattern was observed for DBP (Figure 3A), although the Day (linear)×Nutrition interaction [F(1,18)=4.30, P=0.05] only bordered on significance. During the time of stress, the degree to which MAP (Figure 3B) was elevated increased across the 3 test days in 25/25W rats while it remained at the same level in 6/25M rats. These differences were confirmed by a significant Day (linear)×Nutrition interaction [F(1,18)=6.21, P<0.03]. There were no significant differences between nutritional

Figure 1. Part 1, nonstress 24-hour study: mean SBP (A), mean DBP (B), and mean HR (C) (all adjusted for the activity of the animals) and activity (D) of prenatally malnourished (6/25M) and prenatally well-nourished (25/25W) adult male rats during both light and dark periods of the 24-hour cycle. Each point represents the average value for all rats within a group during the preceding 30-minute block of time (eg, 2 AM=1:30 to 2 AM). During the dark (awake) phase, ANOVA indicated significant Nutrition×Time block (quadratic) interactions for DBP [F(1,19)=6.43, P<0.03] and activity [F(1,19)=4.44, P<0.05] and a significant Nutrition×Time block (linear) interaction for HR [F(1,18)=5.64, P<0.03]. Appropriate regression lines (HR, first order; DBP and activity, second order) are drawn to illustrate these significant interactions.
groups with respect to HR or activity (data not shown). In both groups of rats, the observed reduction in HR during ammonia stress was significantly attenuated from the first to the third test day (mean difference from baseline (bpm): day 1, -74.0; day 2, -53.3; day 3, -32.3). This was corroborated by a significant effect of day [linear: F(1,18)=24.20, P<0.001] and indicated some degree of habituation of this response. In contrast, DBP demonstrated a linear increase over days [F(1,18)=4.51, P<0.05], suggesting that this aspect of the animals’ response to stress became sensitized.

Recovery
A significant Day (linear)×Nutrition interaction [F(1,18)=5.41, P<0.05] was revealed for SBP, since the prenatally malnourished rats had a greater elevation from baseline during recovery on day 1 compared with the controls (+13.1 versus +6.7 mm Hg, respectively). The same pattern of results emerged for MAP [F(1,18)=4.98, P<0.05] and for DBP, although the Day (linear)×Nutrition interaction only bordered on significance for the latter [F(1,18)=4.35, P=0.05]. HR, which was depressed during ammonia stress, recovered rapidly over blocks and became elevated with respect to baseline. A significant Block (linear)×Nutrition interaction [F(1,18)=6.10, P<0.03] indicated that the prenatally malnourished rats showed a greater elevation of HR than the controls (+55.6 versus +35.2 bpm, respectively) 10 to 15 minutes after removal of the stressor. Activity and pulse pressure did not differ between nutritional groups.
Discussion

In part 1 (nonstress 24-hour study), small but significant differences were revealed between prenatally malnourished and well-nourished rats in DBP (+4 mm Hg) and HR (+25 bpm) during the dark phase of the light cycle, even after correction for differences in activity. However, SBP did not differ between the two groups at any point, despite the fact that the number of subjects was sufficient to allow differences as low as 11 mm Hg to attain statistical significance (this figure is based on statistical power calculations, setting \( \alpha = 0.05 \), with a power of 80%).6 This differs from previous studies5–11 in which elevations of >20 mm Hg in SBP have been documented using the stressful tail-cuff technique after less marked prenatal protein restriction (9% casein diet versus the 6% casein diet used here). Our data indicate that stress differences may have been a critical factor in revealing such SBP differences. The finding that SBP differed between the prenatally malnourished and control groups in response to acute stress only (part 2) reinforces this notion.

The pattern of essential hypertension in genetic rat models such as the Dahl salt-sensitive strain, which is derived from the same Sprague-Dawley strain as that used here,27 differs from the pattern observed with prenatal malnutrition. Although Dahl salt-sensitive rats exhibit a diurnal variation in SBP and DBP, both pressures remain elevated when compared with those in Dahl salt-resistant controls at every point in the 24-hour cycle. Importantly, the latter pattern resembles that observed in uncomplicated human hypertension.28 Blood pressure changes observed in adult rats with underlying prenatal malnutrition were confined to DBP and to the dark phase of the cycle. These data indicate that prenatal protein malnutrition induces pathogenic changes that are most likely distinct from those associated with genetic models of essential hypertension. However, given the present findings, it is reasonable to propose that prenatal malnutrition, especially in conjunction with stressful conditions, may contribute to hypertension in humans. At the very least, if not addressed, a history of prenatal malnutrition may confound the genetic analysis of essential hypertension.

The cardiovascular responses to repeated acute stress challenges were examined in part 2 during the light phase, where no differences in blood pressure had been detected during the 24-hour measurements. In this second study, the 6/25M rats showed a greater increase in both SBP and DBP compared with 25/25W rats during the first exposure to ammonia, as well as a different pattern of change of these cardiovascular responses during subsequent presentations of the stressor (Figure 3A through 3C). In 25/25W rats, repeated stress caused a parallel increase in both SBP and DBP, hence a corresponding parallel increase in MAP, and a stable pulse pressure. In contrast, the pattern of change in SBP, DBP, MAP, and pulse pressure was markedly different in 6/25M rats. A nonparallel pattern of change of SBP and DBP in these rats generated a stable MAP but a decreasing pulse pressure. These findings highlight a fundamental difference in the blood pressure regulatory systems between the two nutritional groups and may indicate that stress is a useful tool in unmasking this difference. Had we selected the midpoint of the dark phase for this study (a time at which there were the largest group differences under nonstress conditions), we might have observed differences between prenatally malnourished and control animals approaching the levels reported using the stressful tail-cuff procedure.5–11 Thus, the present investigation also highlights the potential importance of the time of day at which blood pressure measurements are taken.

In summary, our results of a small but significant increase in DBP in rats with a history of prenatal malnutrition are at variance with the large (>20 mm Hg) elevations in SBP that have been reported using the tail-cuff procedure.5–11 We conclude that stress may have played a role in eliciting SBP differences in these prior investigations. Nevertheless, the fact that prenatal malnutrition does induce lasting changes in blood pressure regulatory mechanisms suggests that subsequent investigations should attempt to identify putative mechanisms (eg, structural changes in the blood vessels) and/or changes in the central or local control of the vasculature. In addition, future studies should also characterize the cardiovascular responses to different kinds of stressors in malnourished animals and should be extended to include female rats. These studies are especially pertinent given the high prevalence of malnutrition in the world.29

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References


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