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ORIGINAL ARTICLE

Fetal development and renal function in adult rats prenatally subjected to sodium overload

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Abstract The aims of this study were (1) to evaluate two factors that affect fetal development—placental oxidative stress (Ox) and plasma volume (PV)—in dams with sodium overload and (2) to correlate possible alterations in these factors with subsequent modifications in the renal function of adult offspring. Wistar dams were maintained on 0.17 *M* NaCl instead of water from 20 days before mating until either the twentieth pregnancy day/parturition or weaning. Colorimetric methods were used to measure Ox in maternal and offspring tissues, PV, 24-h urinary protein ($U_{Prot24\ h}$) and serum triacylglycerols (TG) and cholesterol (Chol). Renal hemodynamics was evaluated in the offspring at 90 days of age using a blood pressure transducer, a flow probe and inulin clearance to measure mean arterial pressure (MAP), renal blood flow and glomerular filtration rate (GFR), respectively. The number of nephrons (NN) was counted in kidney suspensions. Dams showed unchanged PV, placental Ox and fetal weight but increased $U_{Prot24\ h}$ (150%, $P<0.05$). Prenatally sodium-overloaded pups showed increased $U_{Prot24\ h}$ (45%, $P<0.05$) but unchanged MAP, renal hemodynamics, NN and kidney Ox. Prenatally and postnatally sodium-overloaded rats showed increased $U_{Prot24\ h}$ (27%, $P<0.05$) and kidney Ox (44%, $P<0.05$), reduced GFR (12%, $P<0.05$), increased PV (26%, $P<0.05$) and unchanged MAP and NN. The TG increased in both groups of treated offspring (21%, $P<0.05$), whereas Chol increased only in the postnatally sodium-overloaded group. We conclude that salt overload from the prenatal stage until weaning leads to alterations in lipid metabolism and in the renal function of the pups, which are additional to those alterations seen in rats only overloaded prenatally.

Keywords Fetal development · Maternal sodium overload · Placental oxidative stress · Proteinuria · Renal dysfunction in the offspring

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Introduction

There is evidence for a relationship between altered prenatal growth and adult renal disease. NaCl overload during the perinatal period has been associated with renal dysfunction [1, 2] and changes in lipid metabolism [3] during adult life. Sodium overload may influence fetal development through its effects on plasma volume and on the level of placental oxidative stress [4, 5], which in turn influence placental blood flow [5]. In addition, sodium overload can severely affect maternal nutrition: high NaCl intake [6]—as well as dehydration [7] with hypernatremia—reduces dietary intake. In these ways, sodium overload may compromise fetal nutrition. Furthermore, sodium overload decreases maternal

plasma renin levels [6] and has been correlated with lower angiotensin II formation in the offspring kidney during nephrogenesis [1]. The renin–angiotensin system (RAS) appears to be fundamental to nephrogenesis [8], and variations that occur in it during the fetal and early postnatal days of development may have long-term repercussions for renal function [8, 9].

Nephrogenesis in rats is completed around postnatal day 10 [10, 11]. Consequently, it may be hypothesized that maternal sodium overload during lactation may perturb nephrogenesis since the sodium may be transferred to the pups through the milk [12].The access of pups to drinking water during the last days of lactation may also influence renal function in later life as the window of programming for adult RAS may include this period [9].

The maternal intake of 0.3 *M* NaCl increases placental oxidative stress [4], and the maternal intake of 0.15 *M* NaCl during pregnancy and lactation affects renal function in weanling [1] and adult [2] rats. The study reported here investigated: (1) whether a maternal intake of 0.17 *M* NaCl in place of drinking water from 20 days before mating until the twentieth day of pregnancy changes plasma volume and placental oxidative stress, factors known to be correlated with fetal development that could predict later consequences for the offspring and (2) whether this maternal intake of NaCl programs renal function and lipid metabolism in the offspring during adult life.

Material and methods

Animal care

All of the animal experimental procedures described in this study were approved by the Committee for Ethics in Animal Experimentation of the Federal University of Pernambuco and carried out in accordance with the Committee guidelines.

Animal groups

Female Wistar rats, weighing 200–250 g, 70 days old, were randomly assigned to groups. From then to parturition, the Control group (n=12) was maintained on tap water and the Saline group (n=15) was maintained on 0.17 *M* NaCl. The rats were mated at 90 days; the presence of a vaginal plug determined the first day of pregnancy. Water balance in the dams was evaluated on the first and 18th days of pregnancy. Gestation was interrupted on the 20th day in some dams in each group (Control, n=4; Saline, n=8) for the evaluation of plasma volume, hepatic and placental oxidative stress and a number of fetal parameters. Only the embryonic part of the placenta associated with male pups was weighed and selected for the evaluation of oxidative stress, and only male fetuses were selected using an illuminated magnifier (2×). Some dams (n=4) were maintained on saline until weaning. The placentas, fetuses and livers were dissected out in sequence.

A balanced commercial rodent chow (Purina Agribrands) was given to the rats (dams; offspring after weaning). The offspring of mothers maintained with tap water throughout the study were the Control group (C, n=16). Those maintained with saline (S) until parturition (P) were labeled SP (n=16), and those maintained with saline throughout the prenatal and lactation (L) periods were labeled SPL (n=16). At birth, the litters were culled to eight pups, including females, and these were maintained until weaning. Female pups were not included in the protocol carried out after weaning because of the known variations in plasma estrogen levels during the estrus cycle, which directly influence renal vascular resistance. At 90 days of age, eight animals from each group were assigned for the evaluation of plasma volume, renal oxidative stress and lipid metabolism. Early in the morning they were anesthetized with sodium pentobarbital [Cristália Produtos Químicos Farmacêuticos, Itapira, SP, Brazil; 60 mg/kg, intraperitoneal (i.p.)] for femoral artery catheterization. One blood sample was collected for measurement of postprandial serum triacylglycerols and cholesterol. Plasma volume and renal oxidative stress were subsequently evaluated. At the same age, eight animals from each group were assigned for the evaluation of water balance, proteinuria, renal hemodynamics and glomerulus counts.

Plasma volume measurement

Plasma volume was measured using Evans Blue dye (Sigma-Aldrich, St. Louis, MO) as previously described [13–15], after the animal had been anesthetized with sodium pentobarbital (60 mg/kg, i.p.). Briefly, a femoral artery was catheterized and a basal blood sample (1 ml) collected. The dye (0.1% in physiological saline) was then administered (100 μg/100 g body weight) through the catheter. The catheter had previously been filled with physiological saline and following dye administration it was flushed with 200 μl physiological saline. After 7.5 min, the physiological saline in the catheter was discarded, and a 1-ml blood sample was collected in a heparinized syringe. The blood was then centrifuged to obtain the plasma. The dye concentration in the plasma was determined spectrophotometrically at 610 nm and compared to a standard curve constructed using known concentrations of Evans Blue dye and samples of basal plasma.

Oxidative stress

Tissue oxidative stress was evaluated by measuring the levels of thiobarbituric acid reactive substances (TBARS) by the method of Buege and Aust [16]. Each placenta, liver or kidney was macerated for 15 min in an ice bath with 5 ml 1.15% KCl per gram tissue and then transferred to test tubes. The reagents, 0.375% thiobarbituric acid (Sigma-Aldrich) and 75% trichloroacetic acid (Vetec Química Fina, Rio de Janeiro, RJ, Brazil), were added (1 ml of each) to each milliliter of tissue homogenate. Duplicate tubes for each reaction were sealed and heated in a water bath at 100ºC for 15 min. After cooling, the protein precipitate was centrifuged for 10 min, the supernatant was then separated and the absorbance measured at 535 nm.

Water balance and 24-h proteinuria

Animals were placed in individual metabolic cages (Tecniplast Gazzada Sarl, Buguggiate, Italy). Diet and water intake were evaluated over a 24-h period, and urine was collected during the same period. Twenty-four-hour urinary protein ($U_{Prot24\ h}$) was measured by precipitation with 3% sulfosalicylic acid [17].

Blood pressure and renal function in the adult offspring

Renal hemodynamics was evaluated in animals that had been anesthetized with sodium pentobarbital (60 mg/kg, i.p), as previously described [14, 15]. Briefly, animals were tracheostomized, and the left femoral artery, both jugular veins and the left ureter were catheterized. A flow probe (1.0 V; Transonic Systems, Ithaca, NY) was placed around the left renal artery. Mean arterial pressure (MAP) and hematocrit (Hct) were measured immediately after femoral artery catheterization (initial MAP and initial Hct, respectively). To assess glomerular filtration rate (GFR), 10% inulin in physiological saline was infused (1.2 ml/h) through the left jugular vein; to maintain euvolemia, isoncotic serum (20% v/w) was infused through the right jugular vein during surgery and throughout the evaluation of renal hemodynamics. After the surgical procedure had been completed, anesthesia was supplemented (45 mg/kg, i.p). The evaluation of renal hemodynamics was initiated 1 h after the completion of surgery and comprised two 20-min intervals during which two urinary samples and three blood samples were collected. The MAP and renal blood flow (RBF) were continuously monitored during both periods.

The MAP and RBF were determined using a blood pressure transducer (Transpac, Abbott Laboratory, North Chicago, IL, USA) and a flow probe, respectively. The MAP and RBF recordings were analyzed by a playback program in the Calc Package Windaq. Renal plasma flow (RPF) and renal vascular resistance (RVR) were calculated according to the following equations: $RPF = RBF \times (1 - Hct)$, and $RVR = MAP/RBF$. Each renal hemodynamic parameter was corrected for the corresponding kidney weight (grams).

The right kidney was used to determine the number of glomeruli according to the method of Larsson [18]. Each kidney was sliced and incubated in 50% hydrochloric acid for 2 h at room temperature. After mechanical dissociation, the homogenate was adjusted to 10 ml with distilled water.

Table 1 Maternal data

Parameters	Control (n=4)	Saline (n=8)
Body weight, first day (g)	237.5±3.3	261.7±7.6*
Body weight, 20th day (g)	346.5±7.3	362.4±11.6
Reproductive outcome	11.7±1.2	13.2±0.5
Weight gain (g)	109.0±10.2	95.6±13.2
Fluid intake, first day (ml/100 g)	13.8±4.5	27.3±2.4*
Urinary flow, first day (ml/100 g)	4.5±0.3	12.0±2.5*
Water balance, first day (ml/100 g)	9.7±3.8	13.8±2.7
Fluid intake, 18th day (ml/100 g)	17.8±1.5	29.9±4.9*
Urinary flow, 18th day (ml/100 g)	4.3±0.2	11.2±1.4*
Water balance, 18th day (ml/100 g)	13.5±1.7	18.7±2.5
Diet intake, first day (g/100 g)	7.8±0.8	8.6±0.6
Diet intake, 18th day (g/100 g)	9.3±1.2	8.4±0.4
$U_{Na+}V$, first day (mmol/100 g per 24 hours)	0.4±0.1	2.4±0.4*
$U_{Na+}V$, 18th day (mmol/100 g per 24 hours)	0.2±0.1	2.1±0.6*
$U_{K+}V$, first day (mmol/100 g per 24 hours)	0.9±0.2	1.2±0.2
$U_{K+}V$, 18th day (mmol/100 g per 24 hours)	1.2±0.2	1.2±0.3
Plasma volume, 20th day (ml/100 g)	6.1±2	4.2±1.5

* P <0.05 vs. Control

Results are given as mean ± standard error of the mean (SEM)

Control, Dams maintained with drinking water; saline, dams maintained from 70 days old to parturition, with 0.17 M NaCl; n represents the mean of litters evaluated; 1st, 18th and 20th days are days of pregnancy; $U_{Na+}V$, urinary sodium excretion; $U_{K+}V$, urinary potassium excretion

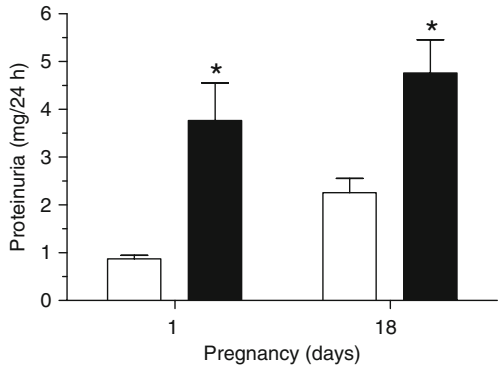

Fig. 1 Twenty-four-hour urinary protein. *Open bars* Control dams (n=4) maintained with drinking water, *filled bars* dams maintained from 70 days of age to parturition with 0.17 *M* NaCl (n=8). Results are given as mean ± standard error of the mean (SEM). *P <0.05 vs. Control

Six aliquots of 30 µl each were spread on glass slides over a surface of 4.5 cm^2. Glomeruli were counted in each aliquot under a light microscope by two researchers blinded to the origins of the specimens.

Analytical methods

The inulin concentrations in urine and plasma were measured by the anthrone method [19]. Urinary Na^+ and K^+ excretion were measured using an electrolyte analyzer (AVL 9180, Roche Diagnostics GmbH, Mannheim, Germany). Serum total cholesterol and triacylglycerols were estimated by enzymatic methods using commercial reagents (Labtest, Lagoa Santa, MG, Brazil).

Statistical analysis

The results are expressed as the mean ± standard error of the mean (SEM). Differences between dam groups were analyzed using an unpaired Student's t test, while differences among offspring were analyzed using the Student–Newman–Keuls multiple comparison test. Statmost 2.5 for Windows was used for statistical analysis (DataMost, Salt Lake City, UT, USA). Differences were considered significant at $P< 0.05$.

Results

Maternal data

Maternal data are shown in Table 1. The mean body weight was higher for Saline than Control dams on the first day of pregnancy (P <0.05). However, the two groups showed a similar weight gain during pregnancy and similar body weights on the 20th day. Reproductive outcome and diet intake were also similar between the two groups. On the first day of pregnancy, fluid intake and urinary flow were higher in the Saline than in the Control group, although both groups showed a similar water balance. On the 18th day of pregnancy, water balance was also similar in the Saline and Control groups, although urinary flow was again higher in the Saline group. The Saline and Control dams showed a marked decrease in urinary sodium excretion from the first to the 18th day of pregnancy (50 and 62%, respectively; P <0.05). Both groups also had similar plasma volumes on the 20th day. $U_{Prot24\ h}$ was very much higher in the Saline than Control dams on the first and 18th days (469 and 252%, respectively; P <0.05; Fig. 1).

Data on placentas and male fetuses are shown in Table 2. Placental weight and placental TBARS were the same for the Saline and Control dams. Hepatic TBARS, which was measured as a positive control, was also the same in the two groups (9.8±2.0 and 8.9±2.5 mmol malondialdehyde (MDA)/g tissue, respectively). For the male fetuses, body weight, kidney weight, and kidney weight/body weight ratio were the same in both groups.

Offspring data

Birth weight was similar in the SP and C groups (5.96± 0.11 and 6.31±0.17 g, respectively). At 25 days of age,

Table 2 Data on placenta and male fetuses on the 20th day of pregnancy

Parameters	Control (n=4)	Saline (n=8)
Placental weight (g)	0.48±0.02	0.44±0.02
Placental TBARS (mmol MDA/g tissue)	8.56±2.24	7.34±1.28
Body weight fetuses (g)	2.89±0.12	2.83±0.32
Kidney weight fetuses (mg)	17±2	16±3
Kidney weight/body weight fetuses (%)	0.62±0.04	0.57±0.05

MDA, Malonyldialdehyde; TBARS, thiobarbituric acid reactive substances

Results are given as mean ± standard error of the mean (SEM)

n represents the mean of litters evaluated; 50 placentas and fetuses were evaluated in the Control (dams maintained with drinking water) and 58 in the Saline (dams maintained from 70 days of age to parturition with 0.17 *M* NaCl) group

Table 3 General data for offspring at 90 days of age

Parameters	C (n=8)	SP (n=8)	SPL (n=8)
Body weight (g)	346.1±11.4	347.6±9.5	382.6±7.9*†
Kidney weight (g)	1.39±0.04	1.32±0.2	1.51±0.04*†
Kidney weight/body weight (%)	0.37±0.01	0.35±0.01*	0.39±0.01†
Number of nephrons	49300±2931	48666±2733	53000±2766
Fluid intake (ml/100 g)	10.9±1.5	11.8±1.2	11.4±1.5
Diet intake (g/100 g)	6.0±0.6	5.6±0.7	6.5±0.3
Urinary flow (ml/100 g)	2.8±0.4	3.3±0.2	3.8±0.3*
$U_{Na+}V$ (mmol/100 g per 24 hours)	0.3±0.1	0.3±0.1	0.3±0.1
$U_{K+}V$ (mmol/100 g per 24 hours)	0.8±0.1	1.4±0.1*	1.3±0.1*
Plasma volume (ml/100 g)	3.0±0.2	3.3±0.3	3.7±0.4*
Triacylglycerols (mmol/dl)	0.8±0.1	1.0±0.1*	1.0±0.1*
Cholesterol (mmol/dl)	1.4±0.1	1.6±0.1	1.8±0.1*†

*P <0.05 vs. Control, †P <0.05 SPL vs. SP

Results are given as mean ± SEM

C, Offspring from dams maintained with drinking water; SP, offspring from dams maintained with NaCl up to parturition; SPL, offspring from dams maintained with NaCl during pregnancy and lactation

after weaning, animals in the SPL, SP and C groups were similar in body weight (73±2, 69±2 and 69±3 g, respectively). At 90 days of age, the SPL group had higher body weights than the C and SP groups (10 and 11%, respectively; P<0.05; Table 3). Kidney weight was also higher in the SPL group than in the other two groups (14 and 9%, respectively; P<0.05). $U_{Prot24\ h}$ was similar in the SPL and SP groups and higher in both than in the C group (27 and 45%, respectively; P<0.05; Fig. 2). TBARS was higher in the kidneys of the SPL group than in those of the SP and C groups (35 and 44%, respectively; P<0.05; Fig. 3). All three groups had the same number of nephrons (Table 3). Urinary potassium excretion was higher in the SPL and SP groups than in the C group (61 and 65%, respectively, P<0.05), while plasma volume and urinary flow were higher in the SPL group than in the C group (23 and 36%, respectively; P<0.05). Non-fasting serum triacylglycerol levels were higher in the SP and SPL groups than in the C group (20 and 19%, respectively; P<0.05; Table 3). Serum cholesterol levels were similar in the SP and C groups but higher than either in the SPL (17 and 30%, respectively, P<0.05, Table 3). All three groups were similar in mean arterial pressure, renal vascular resistance, renal blood flow and renal plasma flow (Table 4); however, the GFR was lower in SPL than in SP and C (20 and 12%, respectively, P<0.05; Table 4).

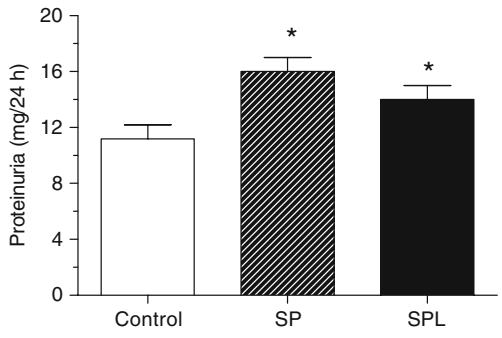

Fig. 2 Twenty-four-hour urinary protein. *C* (n=8) Control offspring from dams maintained with drinking water, *SP* (n=8) offspring from dams maintained with NaCl up to parturition, *SPL* (n=8) offspring from dams maintained with NaCl during pregnancy and lactation. Results are given as mean ± SEM. *P <0.05 vs. C

Discussion

In recent years, evidence has accumulated that hypertension [20–23] and renal disease [24] have developmental origins. In the study reported here, we found that NaCl overload, initiated 20 days before the dams were mated and maintained until parturition, programmed several renal alterations in the adult offspring, including proteinuria, decreased GFR and expanded plasma volume despite an increased urinary output. However, with the exception of maternal proteinuria, NaCl overload did not change either fetal weight or maternal parameters that can influence fetal development, such as plasma volume [25], placental oxidative stress [26, 27] and dietary intake. Collectively, the unchanged placental oxidative stress, maternal plasma volume, dietary intake and normal weight gain suggest that

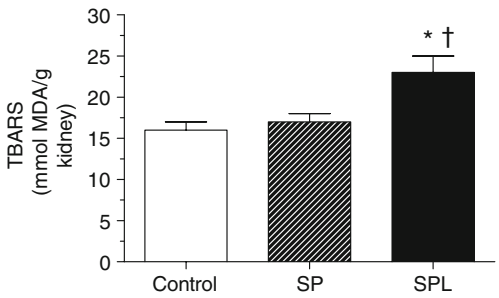

Fig. 3 Renal oxidative stress. Results are given as mean ± SEM. *TBARS* Thiobarbituric acid reactive substances, *MDA* malonyldialdehyde. See Fig. 2 for details. *P<0.05 SPL vs. Control; †P <0.05 SPL vs. SP

Table 4 Blood pressure and renal hemodynamics in the offspring at 90 days of age

Parameters	C (n=8)	SP (n=8)	SPL (n=8)
Mean arterial pressure (mmHg)	111±1	112±4	112±3
Renal vascular resistance (mmHg/ml per minute per gram)	21.70±1.84	23.16±3.42	23.62±1.39
Renal blood flow (ml/min per gram)	5.40±0.70	5.40±0.50	4.92±0.30
Renal plasma flow (ml/min per gram)	2.72±0.38	2.63±0.28	2.52±0.20
Glomerular filtration rate (ml/min per gram)	0.91±0.05	1.03±0.10	0.80±0.04*†

*P <0.05 SPL vs. Control, †P < 0.05 SPL vs. SP

Results are given as the mean ± SEM

fetal nutrition was not compromised. We chose these parameters for study because undernutrition during pregnancy has been related to a low birth weight and to compromised cardiovascular [28] and renal [29] function during adult life.

An important parameter programmed by sodium overload was increased oxidative stress in the kidney, which has recently been shown to be associated with important alterations in active sodium transporters and in the response of these transporters to angiotensin II [30]. Proteinuria also increased significantly in the prenatally sodium-overloaded rats independently of the number of nephrons and the renal hemodynamic profile, which were unchanged. The increased proteinuria may include albuminuria. Microalbuminuria has been considered not only a marker for renal disease but also an early marker for late cardiovascular disease [31, 32]. In line with the results of our study, Porter and coworkers [33] showed that blood pressure was not increased in adult females, although when the animals were exposed to stress, they presented augmented blood pressure.

Nephrogenesis was not affected by either prenatal or prenatal-plus-postnatal sodium overload. Similarly, at 30 days after birth, rats subjected to 0.15 M NaCl from the prenatal period to weaning showed no alteration in the number of nephrons [1]. However, this group showed a reduced GFR. Therefore, the reduction in GFR in rats maintained on sodium overload during the prenatal and lactation periods was independent of the number of nephrons and of changes in other renal hemodynamic parameters. This profile suggests structural changes accompanied by a reduced filtration area that are probably provoked by an incipient glomerulosclerosis. This view is supported by the observation that, at the age of 120 days, rats that had been maintained on 0.15 M sodium overload during pregnancy and lactation also showed reduced GFR and an increased glomerulosclerosis index [2]. Therefore, the increase in plasma volume may possibly be attributed to the increased sodium retention, but may also have been due to a reduced GFR.

Distal disturbances also appeared to be present in sodium-overloaded offspring, since urinary output and urinary potassium excretion were higher than in the animals of the Control group. The increased kaliuresis in combination with normal natriuresis suggests that aldosterone is increased in these animals, since there is evidence that angiotensin II is increased in the kidneys of adult rats subjected to high dietary sodium during prenatal life [34]. As mentioned above, the intrarenal angiotensin II response is altered when a rise in oxidative stress is found [30]. Although the association in these rats between increased plasma volume, increased urinary flow and unaltered fluid intake may appear controversial, water transport in the collecting ducts is dependent on arginine vasopressin, which is known to have a higher plasma osmolality threshold in prenatally dehydrated, hypernatremic animals [35, 36]. Since the group maintained on sodium overload until weaning showed alterations additional to those in the group maintained until birth, it follows that renal functional programming continues during the early postnatal weeks [9].

Other disturbances seen in the prenatally treated offspring were increased levels of serum triacylglycerols and increased levels of both cholesterol and triacylglycerols when the sodium overload was continued from pregnancy to weaning. In contrast to our findings, Vidonho and coworkers [3] found a reduction in fasting triacyglycerols in the offspring of dams maintained on an 8% dietary salt overload during pregnancy. Two factors may explain the difference between their results and the ones obtained in our study: the content of sodium consumed and the fact that in the study of Vidonho et al. [3], in contrast to our study, blood was collected after fasting. Despite this conflict, taken as a whole, the evidence supports the hypothesis that prenatal sodium overload imprints changes in lipid metabolism.

In summary, our results show that prenatal salt overload-induced changes in lipid metabolism and renal function were not associated with fetal growth retardation. Rather, they were associated only with a silent early symptom, maternal proteinuria. These results also show that maintenance of sodium overload during lactation exacerbates the renal dysfunction programmed during the intrauterine period, supporting the view that renal function in pups continues to be programmed during the lactation period.

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