Prenatal programming of renal salt wasting resets postnatal salt appetite, which drives food intake in the rat

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ABSTRACT

Sodium retention has been proposed as the cause of hypertension in the LP rat (offspring exposed to a maternal low-protein diet in utero) model of developmental programming because of increased renal NKCC2 (Na+/K+/2Cl− co-transporter 2) expression. However, we have shown that LP rats excrete more rather than less sodium than controls, leading us to hypothesize that LP rats ingest more salt in order to maintain sodium balance. Rats were fed on either a 9% (low) or 18% (control) protein diet during pregnancy; male and female offspring were studied at 4 weeks of age. LP rats of both sexes held in metabolism cages excreted more sodium and urine than controls. When given water to drink, LP rats drank more and ate more food than controls, hence sodium intake matched excretion. However, when given a choice between saline and water to drink, the total volume of fluid ingested by LP rats fell to control levels, but the volume of saline taken was significantly larger [3.8 ± 0.1 compared with 8.8 ± 1.3 ml/24 h per 100 g of body weight in control and LP rats respectively; P < 0.001]. Interestingly food intake also fell to control levels. Total body sodium content and ECF (extracellular fluid) volumes were greater in LP rats. These results show that prenatal programming of renal sodium wasting leads to a compensatory increase in salt appetite in LP rats. We speculate that the need to maintain salt homeostasis following malnutrition in utero stimulates greater food intake, leading to accelerated growth and raised BP (blood pressure).

INTRODUCTION

Prenatal exposure to an adverse environment has a marked impact upon the developing kidney. People whose birthweights were towards the lower end of the normal range have fewer nephrons [1] and are at greater risk of developing hypertension and coronary heart disease in later life [2]. This risk is further increased by rapid childhood weight gain [2]. LP rats (offspring exposed to a maternal low-protein diet in utero) have a reduced nephron number, small body size at birth and later hypertension [3]. Nephron deficit is thought to lead to hypertension through sodium retention [4], in part because LP rats show increased expression of the bumetanide-sensitive NKCC2 (Na+/K+/2Cl− co-transporter 2 or BSC1) in the ascending limb of the

Key words: developmental programming, extracellular fluid, hyperphagia, kidney, salt appetite.
Abbreviations: AngII, angiotensin II; BP, blood pressure; ECF, extracellular fluid; FENa distal, fractional excretion of sodium by the distal nephron; IMCD, inner medullary collecting duct; LP rat, offspring exposed to a maternal low-protein diet in utero; NKCC2, Na+/K+/2Cl− co-transporter 2; RAS, rennin–angiotensin system; TAL, thick ascending limb.
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loop of Henle [5]. However, we have shown that renal sodium excretion is increased in LP rats [6]. The loss of sodium appears to be due to a change in tubular function, rather than altered glomerular filtration, as fractional excretion of sodium, which represents the proportion of filtered sodium that is excreted, was also increased in LP animals. The underlying mechanism responsible for this renal sodium loss seems to be a marked decrease in activity of the Na\(^+/\)K\(^+\)-ATPase pump, which is the driving force for sodium reabsorption by the renal tubule. In particular, the Na\(^+/\)K\(^+\)-ATPase pump appeared to be virtually absent from the IMCDs (inner medullary collecting ducts) of LP rats [6] in which fine tuning of the final urinary sodium content occurs.

To resolve this seeming paradox between renal sodium transporter expression and kidney function, we postulated that LP rats must ingest more sodium in order to achieve sodium homoeostasis. Accordingly, we measured fluid and electrolyte turnover in young, post-weaning LP and control animals held in metabolism cages. We also assessed salt appetite by means of a saline preference test to determine whether the greater renal sodium excretion seen in our previous study [6] is offset by increased salt intake. Finally, we measured total body water, ECF (extracellular fluid) volume and total body electrolyte content to determine whether the high BP (blood pressure) of LP rats is attributable to an expanded fluid volume.

**MATERIALS AND METHODS**

**Animals**

Experiments were performed in accordance with the U.K. Animals (Scientific Procedures) Act 1986 and received local ethical approval. Female Wistar rats (n = 22; Harlan) were fed on a semi-synthetic diet containing 9% low protein from the time of conception until birth, after which the food was switched to standard rodent chow (Rat & Mouse Standard Diet; Bantin & Kingman). Control dams (n = 22) received an isocalorific diet containing 18% protein throughout pregnancy [3]. On the day of birth, the dams diet reverted to standard chow and the litter size was reduced to eight animals (four male and four female). Pups remained with their mothers until studied at 4 weeks of age, at which time their diet comprised a mixture of solid chow and milk. As the experimental manipulation was of the dams rather than the offspring, no more than two rats of either sex were studied per litter. Separate litters were bred for each of the methodologies described below.

**Water and electrolyte turnover**

Age-matched control (eight male and six female) and LP (ten male and nine female) rats were housed individually in metabolism cages from the age of 28 days. A total of 2 days were allowed for acclimatization, after which the body weight, food (standard rat chow ion content per g of dry weight: 0.096 mmol Na\(^+\), 0.179 mmol K\(^+\) and 0.127 mmol Cl\(^-\)) and tap water intake, and urine output were measured every 24 h for 5 consecutive days. Animals were then killed by stunning and decapitation for the collection of trunk blood. Urine and plasma samples were analysed for Na\(^+\) and K\(^+\) [using a Solar Series atomic absorption spectrometer; Thermo Elemental], Cl\(^-\) [using a Chloride Analyser 925; Ciba Corning Diagnostics] and osmolality [using a freezing point depression osmometer; LH Roebling].

**Salt preference test**

A two-bottle choice protocol was used to determine salt preference and total fluid intake. Control (14 male and 14 female) and LP (14 male and 14 female) rats were housed individually in standard cages and were provided with standard rat chow and two water bottles containing either tap water or saline (0.154 mol/l NaCl). A total of 2 days were allowed for acclimatization, after which body weight, food intake and fluid intake were measured every 24 h for 5 consecutive days. Drinking bottles were cleaned, refilled with fluid and repositioned each day to avoid potential positional bias.

**ECF volume**

ECF volume was determined by the dilution of \([\text{H}]\)Inulin [7]. Control (nine male and 12 female) and LP (13 male and 12 female) rats were anaesthetized with Inactin (sodium thiobutabarbital; 100 mg/kg of body weight, intraperitoneal) and cannulae were implanted into an external jugular vein for the injection of \([\text{H}]\)Inulin and a carotid artery to collect blood samples. The abdomen was opened via a midline incision and both pairs of renal arteries and veins were tied off using sterile 3-0 mersilk suture following which the body wall was closed. \([\text{H}]\)Inulin (6 μCi in 0.154 mol/l NaCl) was injected into the rat via the jugular catheter which was flushed with vehicle [total volume injected, 500 μl/100 g of body weight]. After a 1.5 h equilibration period (time taken to achieve a stable plasma \([\text{H}]\)inulin concentration was established in a pilot study; results not shown), blood samples (50 μl) were withdrawn every 10 min for 1 h. The animal was then killed and a sample of urine taken from the bladder to confirm occlusion of the renal vessels and that no \([\text{H}]\)inulin had been filtered by the kidneys. \([\text{H}]\)Inulin activity was determined using a 1900CA Tri-Carb Liquid Scintillation Analyser β-radiation counter (Canberra Industries). ECF volume (ml/100 g body weight) was calculated as:

\[
\text{ECF volume} = \left( \frac{I_{14} \times C}{P_{14} \times C} \right) \times \left( \frac{I_{14} \times V}{1000} \right) \times (100/\text{body weight})
\]
Table 1  Body, kidney and heart weights and plasma composition of 4-week-old rats at the end of the metabolism cage study

Results are means ± S.E.M. Statistical analysis was by two-way ANOVA. CM, male control rats; LPM, male LP rats; CF, female control rats; LPF, female LP rats; NS, not significant.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CM (n = 9)</th>
<th>LPM (n = 10)</th>
<th>CF (n = 6)</th>
<th>LPF (n = 7)</th>
<th>Diet</th>
<th>Gender</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>99.4 ± 1.6</td>
<td>103.5 ± 1.6</td>
<td>90.8 ± 1.8</td>
<td>93.3 ± 1.8</td>
<td>NS</td>
<td>P &lt; 0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Kidney weight (g)</td>
<td>1.10 ± 0.02</td>
<td>1.15 ± 0.02</td>
<td>1.03 ± 0.01</td>
<td>1.07 ± 0.03</td>
<td>NS</td>
<td>P &lt; 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>0.50 ± 0.01</td>
<td>0.50 ± 0.01</td>
<td>0.48 ± 0.01</td>
<td>0.45 ± 0.02</td>
<td>NS</td>
<td>P &lt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma Na⁺ (mmol/l)</td>
<td>129.2 ± 1.1</td>
<td>124.5 ± 2.3</td>
<td>123.2 ± 0.7</td>
<td>124.9 ± 1.8</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma K⁺ (mmol/l)</td>
<td>4.0 ± 0.1</td>
<td>4.1 ± 0.1</td>
<td>4.2 ± 0.1</td>
<td>4.1 ± 0.2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma Cl⁻ (mmol/l)</td>
<td>108.0 ± 1.0</td>
<td>111.3 ± 0.9</td>
<td>112.4 ± 1.4</td>
<td>108.2 ± 1.8</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma osmolality (mOsm/kg of water)</td>
<td>311.7 ± 9.8</td>
<td>320.6 ± 11.2</td>
<td>312.0 ± 10.5</td>
<td>308.1 ± 7.2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

where \( I_{In}C \) is the injected inulin count/\( \mu l \), \( P_{In}C \) is the plasma inulin count/\( \mu l \) and \( I_{In}V \) is the injected volume/ml.

Greater urinary sodium loss by LP rats

We determined fluid and electrolyte turnover in LP and control animals held in metabolism cages with free access to food and water. In order to confirm the consistency of sequential 24 h urine collections and food/water intake measurements, results were analysed initially by repeated-measures ANOVA. In all cases, time had no significant effect on the measured variables, so the results are presented as the means ± S.E.M. for the 5-day collection period. Urine flow (\( P = 0.05 \)) and sodium excretion rates (\( P < 0.001 \)) were significantly higher in both male and female LP rats compared with controls (Figure 1). Similar differences between LP and control rats were observed for potassium and chloride excretion rates (Table 2). The greater urinary output of LP rats was associated with increased water and food intake compared with controls (Figures 2A and 2C); consequently electrolyte balance (dietary intake – urinary output) did not differ between LP and control rats (Table 2). Once adjusted for body weight, sex had no effect on any of these variables.

Increased salt appetite in LP rats

We hypothesized that the greater food intake of LP rats was being driven by an increased appetite for salt. To test this 24 h fluid intake was determined for rats that had the choice of drinking water or saline. Total fluid intake (water + saline) did not differ between LP and control rats of either sex (\( P > 0.05 \), Figure 2B), but the volumes of water and saline ingested differed. Both male and female LP rats drank significantly more saline than control rats (\( P < 0.001 \)); conversely, LP rats drank less water than controls (\( P < 0.001 \)). Food intake was also recorded during the saline preference test. In contrast with rats that were offered only water to drink, where LP rats ate more food than controls (\( P < 0.01 \), Figure 2C), LP rats offered both saline and water reduced their food intake to levels similar to those of control rats (\( P > 0.05 \); Figure 2D).
Twenty-four-hour urine flow (A) and sodium excretion rates (B) in 4-week-old control and LP rats

![Figure 1](image-url)

CM, male control rats (n = 9); CF, female control rats (n = 6); LPM, male LP rats (n = 10); LPF, female LP rats (n = 7). Results are means ± S.E.M. for 5 consecutive days. Statistical analysis was by two-way ANOVA. *P < 0.05 and **P < 0.001 compared with control rats. Gender had no effect on either variable, bwt, body weight.

### Extracellular volume expansion

In view of the hypertension displayed by LP rats reported previously [6], we measured total body electrolyte and water content to establish whether an expanded ECF volume contributes to the increase in BP. ECF volume (P < 0.001; Figure 3A) and total body water content (P < 0.01; Figure 3B) were significantly greater in both male and female LP rats compared with controls. Total body Na⁺ (P < 0.05; Figure 3C) and Cl⁻ (male rats, 0.67 ± 0.10 compared with 0.55 ± 0.05 mg/100 g of body weight respectively, P < 0.05; female rats, 0.72 ± 0.09 compared with 0.60 ± 0.05 mg/100 g of body weight respectively, P < 0.05) content were greater in LP rats; however total body potassium did not differ between LP (7.80 ± 0.48 and 7.89 ± 0.37 mg/100 g of body weight in males and females) and control (7.27 ± 0.37 and 8.13 ± 1.10 mg/100 g of body weight in males and females respectively) animals.

### DISCUSSION

We conclude that the hyperphagia observed in rats whose mothers were fed on low-protein diets in pregnancy is driven by an increased need for salt. Development of the fetal kidney is vulnerable to maternal malnutrition. When resources are limited, growth of the fetal brain is given priority over organs such as the kidney and lung that develop late in gestation and whose functions in utero are performed by the mother and placenta [8]. Impaired renal development leads to reduced nephron number, diminished functional capacity [3] and postnatal sodium wasting [6]. Thus, in order to maintain sodium homoeostasis salt appetite increases. When food is the only source of salt, the result is hyperphagia. Hence, prenatal programming of the kidney leads to postnatal adaptation of the brain to correct for salt loss at the expense of weight gain.

An alternative explanation would be that appetite is programmed in utero, leading to greater salt intake and compensatory renal sodium wasting. However, long-term studies have shown that hyperphagia does not persist beyond 8 weeks of age in the LP rat [9] and that male LP rats tend to be lighter than controls while female LP rats have similar body weights to those of controls from the age of 4 weeks until 40 weeks [10]. Furthermore, the renal tubular transport defect observed in LP rats, namely loss of the Na⁺/K⁺-ATPase pump from the IMCD [6], is atypical of sodium wasting mechanisms seen during salt overload. Thus on balance the available evidence suggests that a renal defect that is programmed in utero leads to compensatory changes in postnatal brain function in the LP rat rather than vice versa.

Control of food intake is complex. A number of gut peptides signal satiety during a meal, while adiposity

### Table 2

Twenty-four-hour urinary K⁺ and Cl⁻ excretion rates and electrolyte balances of 4-week-old rats held in metabolism cages

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CM (n = 9)</th>
<th>LPM (n = 10)</th>
<th>CF (n = 6)</th>
<th>LPF (n = 7)</th>
<th>Diet</th>
<th>Gender</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺ excretion rate (mmol/24 h per 100 g of body weight)</td>
<td>0.22 ± 0.02</td>
<td>0.29 ± 0.01</td>
<td>0.20 ± 0.02</td>
<td>0.24 ± 0.02</td>
<td>&lt; 0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cl⁻ excretion rate (mmol/24 h per 100 g of body weight)</td>
<td>0.23 ± 0.02</td>
<td>0.31 ± 0.02</td>
<td>0.20 ± 0.03</td>
<td>0.33 ± 0.03</td>
<td>&lt; 0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Na⁺ balance (mmol/24 h)</td>
<td>1.27 ± 0.04</td>
<td>1.36 ± 0.04</td>
<td>1.14 ± 0.05</td>
<td>1.19 ± 0.04</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>K⁺ balance (mmol/24 h)</td>
<td>2.43 ± 0.09</td>
<td>2.56 ± 0.06</td>
<td>2.32 ± 0.11</td>
<td>2.41 ± 0.08</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cl⁻ balance (mmol/24 h)</td>
<td>1.65 ± 0.05</td>
<td>1.71 ± 0.04</td>
<td>1.49 ± 0.08</td>
<td>1.62 ± 0.04</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

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Salt appetite drives food intake

Figure 2 Twenty-four-hour fluid (A and B) and food (C and D) intake in 4-week-old control and LP rats

Left-hand panels: rats were offered water only as drinking fluid. CM, male control rats (n = 9); CF, female control rats (n = 6); LPM, male LP rats (n = 10); LPF, female LP rats (n = 7). Right-hand panels: rats were offered a choice of water or saline (0.154 mol/l NaCl) as drinking fluid. CM, male control rats (n = 14); CF, female control rats (n = 14); LPM, male LP rats (n = 14); LPF, female LP rats (n = 14). Open bar, water; hatched bar, saline intake. Results are the means ± S.E.M. for 5 consecutive days. Statistical analysis was by two-way ANOVA; **P < 0.01 and ***P < 0.001 compared with control rats. Gender had no effect on either variable. bwt, body weight.

signalling occurs through secretion of insulin and leptin [11]. Changes in the regulation of leptin, the major anorexigenic hormone, have been reported previously in LP rats. In the fasted state, leptin concentrations were elevated in LP rats; however, in the fed state, leptin concentrations were lower than those in control animals, which could lead to an increase in the drive to eat and greater weight gain [12]. Hyperphagia associated with hyperleptinaemia and hyperinsulinism has also been reported in the adult offspring of undernourished mothers (30% of ad libitum intake) [13]. Interestingly, neonatal leptin treatment was able to restore food intake and body weight gain to normal in the adult offspring of undernourished mothers, leading to the suggestion that leptin plays a role in metabolic programming [14]. Here we show that a major determinant of food intake in LP rats is an increased salt appetite.

The present study has also confirmed in conscious rats our previous observations made in anaesthetized rats [6] that sodium excretion and urine flow rates are increased in both male and female LP rats compared with control animals. These results appear to conflict with our previous observations [6] and those of others [5] that renal NKCC2 mRNA and protein expression in the TAL (thick ascending limb) of the loop of Henle are increased in the LP rat. As the ascending limb accounts for approximately 25% of the sodium reabsorbed by the renal tubule, a marked increase in NKCC2 might be expected to result in a reduction in sodium excretion. However, we have shown recently that the increase in NKCC2 expression does not appear to translate into greater sodium reabsorption by the TAL in vivo. Under basal conditions FEna_proximal (fractional excretion of sodium by the proximal tubule) did not differ between LP rats and control rats; however, FEna_distal (fractional excretion of sodium by the distal nephron) was significantly greater in LP rats, implying that there was net sodium loss in the distal tubule of LP rats rather than increased conservation. Using amiloride and bendroflumethiazide to inhibit the principal sodium transporters expressed downstream of the loop of Henle [ENaC (epithelial Na\(^+\) channel) and NCC (Na\(^+\)/Cl\(^-\) co-transporter) respectively], we observed that FEna_distal no longer differed between LP and control rats [15]. These results show that sodium reabsorption in the loop of Henle does not differ between LP and control rats, despite increased expression of NKCC2. The increase in FEna_distal seen in LP rats under basal conditions was abolished by amiloride administration, pointing towards the IMCD as the site at which sodium handling is altered [15]. These functional data are supported by the observation that expression of the Na\(^+\)/K\(^+\)-ATPase pump is virtually absent from the IMCD of the LP rat [6], which would reduce the driving force for sodium reabsorption. Together these results suggest that the observed increase in NKCC2 expression does not result in enhanced sodium retention and that there is salt wasting from the LP rat IMCD.
Figure 3 ECF volume (A), total body water (B) and total body sodium content (C) in 4-week-old control and LP rats.

CM, male control rats (n = 6–9); CF, female control rats (n = 6–12); LPM, male LP rats (n = 6–13); LPF, female LP rats (n = 6–12). Results are shown as the means ± S.E.M. Statistical analysis was by two-way ANOVA. *P < 0.05, **P < 0.01 and ***P < 0.001 compared with control rats. Gender had no effect on any variable. bwt, body weight.

as a result of programmed down-regulation of Na\(^+\)/K\(^+\)-ATPase.

Calculated sodium balance (dietary intake – urinary excretion), while positive, did not differ between LP and control animals, yet the total body sodium increased in LP rats. This implies that there was a period of net sodium retention prior to our observations. LP rats were smaller at birth than their control counterparts, yet by 4 weeks of age they had undergone rapid growth and were of similar weights. Indeed we have shown previously that LP rats that were smaller at birth grew rapidly and were similar in weight to control animals by postnatal day 10 [16], at which time their diet would still consist primarily of milk. Accelerated growth is consistent with the observed accumulation of sodium, so it appears that LP rats underwent a phase of sodium retention during the suckling period. As a result ECF volume and total body water were both increased in LP rats, consistent with the increase in arterial BP that we have reported previously at 4 weeks of age [3,6]. The ECF volume remains expanded because sodium intake matches urinary sodium excretion so there is no net loss of salt and thus water.

Salt appetite and thirst are linked closely; however, they do not develop simultaneously in the rat. Salt appetite first becomes apparent in the neonatal rat 72 h after birth, at which time intracerebroventricular injection of renin stimulates NaCl intake [17]. At 12 days of age rat pups first respond to sodium deficit; by 24 days of age rats show the ability to regulate NaCl and water intake in order to balance the tonicity of body fluids [18]. There is good evidence to support the concept of prenatal programming of salt appetite in rats. Extracellular dehydration, induced by subcutaneous poly(ethylene glycol) injection, in pregnant rats results in an enhanced salt appetite in the adult offspring [19]. Other stimuli, such as exposure to a high-salt diet [20] or nicotine [21] in utero also increase the salt appetite of the offspring. Salt appetite is regulated by several hormones, including AngII (angiotensin II) produced both in the brain and the periphery [22]. The systemic RAS (renin–angiotensin system) is suppressed at birth in LP rats [23]; however, by 4 weeks of age renal renin and AngII levels are comparable with control animals, as is plasma aldosterone concentration [24]. Angiotensinogen and ACE (angiotensin-converting enzyme) mRNA, but not protein, are elevated in the brains of fetal LP mice [25] and the central RAS has been reported to be up regulated in adult LP rats [26]. In this context it is interesting to note that treatment of LP rats with the AT\(_1\) (AngII type 1) receptor antagonist losartan from 2–4 weeks of age permanently lowered their adult BP [27]. Furthermore, losartan-treated LP rats were significantly lighter than both untreated LP rats and control animals at 4 weeks, suggesting that AngII blockade had prevented the phase of rapid growth over the suckling period associated with salt-driven hyperphagia.

A limitation of our present study is that we have only focused on one important stage of development, 4 weeks, consistent with our other studies in the LP rat. By this stage the LP rat has undergone accelerated weight gain, BP is beginning to increase, renal salt wasting is established and salt appetite is increased to maintain sodium balance. It remains to be determined whether the down regulation in renal Na\(^+\)/K\(^+\)-ATPase expression is present at birth, as this is the likely cause of renal salt wasting and thus the driver for increased salt appetite in the young LP rat.

Human salt intake exceeds physiological requirements by a considerable degree; consequently, examples of increased salt appetite are rare, being limited to cases of severe salt wasting [28]. However, there is evidence that both the prenatal and postnatal environments affect salt
preference. Maternal dehydration as a result of vomiting during pregnancy (‘morning sickness’) is associated with increased salt preference in infants [29] and greater self-reported salt use in adult life [30]. Adolescents with a history of fluid loss through infantile vomiting and diarrhoea have increased salt preference [31]. Low birthweight also appears to have an adverse effect on salt intake and BP. A negative correlation between birthweight and the salt sensitivity of BP has been reported in adult normotensive subjects [32]. In a much larger study based on the Helsinki Birth Cohort self-reported salt intake was positively associated with systolic BP in both men and women of low birthweight at normal term; interestingly, no such relationship was observed in those whose birthweight was \(\geq 3.050\) kg [33].

In humans rapid weight gain after the age of 2 years adds to the increased risk of hypertension and coronary heart disease associated with low birthweight [2,34]. Numerous animal studies have shown that rapid postnatal growth shortens lifespan [36]. Our study suggests that fetal responses to a sub-optimal nutrient supply \(in utero\) may require postnatal changes in order to maintain salt homeostasis. Salt-driven hyperphagia compensates for renal sodium wasting but contributes to accelerated weight gain and increased BP.

**AUTHOR CONTRIBUTION**

Saleh Alwasel performed the experiments and analysed the data. David Barker co-wrote the paper. Nick Ashton designed the study, analysed the data and co-wrote the paper. All authors contributed to data interpretation.

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