Maternal high-salt diet alters redox state and mitochondrial function in newborn rat offspring’s brain

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Abstract
Excessive salt intake is a common feature of Western dietary patterns, and has been associated with important metabolic changes including cerebral redox state imbalance. Considering that little is known about the effect on progeny of excessive salt intake during pregnancy, the present study investigated the effect of a high-salt diet during pregnancy and lactation on mitochondrial parameters and the redox state of the brains of resulting offspring. Adult female Wistar rats were divided into two dietary groups (n 20 rats/group): control standard chow (0.675 % NaCl) or high-salt chow (7.2 % NaCl), received throughout pregnancy and for 7 d after delivery. On postnatal day 7, the pups were euthanised and their cerebellum, hypothalamus, hippocampus, prefrontal and parietal cortices were dissected. Maternal high-salt diet reduced cerebellar mitochondrial mass and membrane potential, promoted an increase in reactive oxygen species allied to superoxide dismutase activation and decreased offspring cerebellar nitric oxide levels. A significant increase in hypothalamic nitric oxide levels and mitochondrial superoxide in the hippocampus and prefrontal cortex was observed in the maternal high-salt group. Antioxidant enzymes were differentially modulated by oxidant increases in each brain area studied. Taken together, our results suggest that a maternal high-salt diet during pregnancy and lactation programmes the brain metabolism of offspring, favouring impaired mitochondrial function and promoting an oxidative environment; this highlights the adverse effect of high-salt intake in the health state of the offspring.

Key words: High-salt diets: Redox state: Metabolic programming: Mitochondrial dysfunction

In general, the worldwide population consumes much more Na as dietary salt (NaCl) than is necessary for physiological functions(3). Currently, average Na consumption is 3.95 g/d(2), whereas the WHO recommends that adults, including pregnant and lactating women, should consume <5 g of salt/d (equivalent to 2 g Na)(13). Such values should be adjusted downwards for children, based on their energy requirements(3). The main public health concern related to excessive salt intake is its association with high blood pressure(4–5), a major risk factor for CVD, which are the leading causes of death worldwide(6–9). Furthermore, raised blood pressure is also associated with renal failure, cerebrovascular diseases, impaired cognitive function, hippocampal atrophy, as well as an increased risk of stroke and dementia(10–15). Cost-effective preventive policies to reduce salt intake result in reduction in blood pressure(11), which can decrease the risk of cerebrovascular problems(15,16–18). On the other hand, the Framingham Heart Study did not consider salt intake to be an important influence on blood pressure, defining the environment modifying factors responsible for hypertension, such as smoking, physical activity, diet/alcohol and air pollution(19). Clearly, more studies are necessary to clarify the impact of salt intake on brain health and disease. Pregnancy is a decisive period for fetal metabolic programming(20), therefore, maternal salt intake should be controlled. Gestational hypertension increases the risk of pre-eclampsia, a clinical condition that increases fetal and maternal morbidity and mortality(21). Elevated blood pressure during pregnancy can lead to adverse outcomes in the offspring, such as fetal growth restriction, high childhood blood pressure(22,23), neurodevelopmental delay(21) and childhood obesity and an increased risk

Abbreviations: CAT, catalase; GPx, glutathione peroxidase; RAS, renin-angiotensin system; SOD, superoxide dismutase.

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of CVD in adulthood (25). However, the underlying cellular and molecular mechanisms of these effects on metabolism are unknown. According to the Barker hypothesis, the prenatal and early postnatal environments, including maternal diet, exert long-term effects on the health status of offspring (26–27) through the modification of gene expression by epigenetic mechanisms (28–29). In this context, metabolic programming in the uterus alters the risk of chronic disease development in adulthood (29–30).

A high-salt diet in rodents is used to model the phenotypic condition of hypertension (31–34), and it can give additional data concerning underlying cellular and molecular mechanisms, such as the involvement of oxidative stress in several tissues (35–37), as well as impaired synaptic plasticity (38), although this remains elusive clinically. Although evidence from rodents fed a high-salt diet during pregnancy reinforces the long-term impact on the cardiovascular health of offspring (39, 40), there is a lack of information about the effects of high maternal salt consumption on offspring brain development.

On the basis of worldwide dietary habits involving the consumption of a high-salt diet even during pregnancy and the wide range of its related complications for mother and offspring (28, 30), we sought to investigate the effect of such a diet during pregnancy and lactation on the brains of offspring in terms of redox state and mitochondrial viability.

Methods

Reagents

The reagents were obtained from SIGMA® Chemical Co. and Life Technologies.

Animals

Wistar rats, 60-d-old female (forty animals) and 90-d-old male (twenty animals), were housed at Central Animal House of Departamento de Bioquimica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil, under air-conditioned constant temperature (22 ± 1°C) and humidity, on a 12 h light–12 h dark cycle, with free access to food (control diet or high-salt diet) and water. The diet was in accordance with expected macronutrients and micronutrients required by the population (National Research Council (US) Subcommittee on Laboratory Animal Nutrition).

The study was approved by the local Ethics Commission of the Universidade Federal do Rio Grande do Sul (CEUA/UFRGS) under the reference no. 28100. All experiments were conducted according to the National Animal Rights Regulation (Law 11.794/2008), the National Institute of Health Guidance for the Care and Use of Laboratory Animals (NIH publication no. 80–23, revised in 1996), and as well as the Animal Research: Reporting of In Vivo Experiments (ARRIVE) Guidelines for Reporting Animal Research. We further attest that all efforts were made to minimise the number of animals used and their suffering.

Experimental design

In all, forty adult female rats were randomly divided into two groups: control standard diet (0.675% NaCl-containing diet) and high-salt diet (7.2% NaCl-containing diet) (34). The nutritional experiment lasted 5 weeks, starting 1 week before mating, continuing throughout the gestational period and for 1 week of lactation. One male rat was allocated per two female rats over 48 h for mating, and pregnancy was diagnosed by the presence of a vaginal plug. On the 20th day of gestation, dams (pregnant rats) were caged individually for delivery and were observed twice a day (08.00 and 18.00 hours) in order to define the postnatal day (PND) 0 of each litter. Within 24 h after delivery, randomly selected pups were culled in each litter (20 litters/group of study) in order to maintain eight pups per dam to ensure equal nutrition. The offspring remained with the mother up to PND 7. Male offspring were euthanised by decapitation without anaesthesia, and the cerebellum, hypothalamus, hippocampus and prefrontal and parietal cortex of each pup were dissected and stored at −80°C until biochemical analysis, except those samples used for flow cytometry, which were processed immediately. One pup from each litter was used for each technique (6 rats/group for biochemical assays; 8–12 rats/group for flow cytometry), in order to eliminate the litter effect.

High-salt-diet preparation

A high-salt diet containing 7.2% NaCl was made by mixing commercial chow bran, water and commercial salt (34). To obtain the same texture, the control diet containing 0.675% NaCl was prepared by mixing commercial chow bran and water. The chow was dried at low temperature and stored at 4–8°C until use. The body weight and chow intake of dams were recorded daily.

Sample preparation

For flow cytometry, 100 mg of fresh tissue was dissociated with a Pasteur pipette in PBS solution, pH 7.4, containing 1 mg% collagenase IV and 0.5 mg% DNase. Dissociated tissue was filtered and then incubated with fluorescent probes.

For biochemical analysis, each brain structure was individually homogenised in ten volumes (1:10, w/v) of 20 mM sodium phosphate buffer, pH 7.4, containing 140 mM KCl. Homogenates were centrifuged at 1000 g for 10 min at 4°C to discard nuclei and cell debris. The pellet was discarded and the supernatant was used in biochemical assays.

Mitochondrial parameters and oxidant level measurement

According to the manufacturer’s instructions, the samples (100 μl) were incubated at 37°C with the following fluorescent probes: 4-amino-5-methylamino-2’,7’-difluorofluorescein diacetate to measure nitric oxide levels, MitoSOX™ Red® (Invitrogen, Molecular Probes) to measure mitochondrial superoxide levels and MitoTracker® Green FM and MitoTracker® Red CM-H2Ros (Invitrogen, Molecular Probes) to measure mitochondrial mass and membrane potential, respectively. In addition, reactive species levels were measured using dichloro-dihydrofluorescein diacetate (DCFH2) according to Crnkovic et al. (41). Cells were gated on the basis of the forward scatter (FSC) and side scatter (SSC) pattern of the sample cells and 10,000 events
were acquired per sample in a FACSCalibur flow cytometer (BD Biosciences). Data were analysed using the software FlowJo®.

**Antioxidant enzyme activities**

Antioxidant enzyme activities were measured spectro photometrically and the results are expressed as units/mg of protein.

Superoxide dismutase (SOD, EC 1.15.1.1) activity was measured by quantifying the inhibition of superoxide-dependent autoxidation of epinephrine, verifying the absorbance of the samples at 480 nm (42). SOD activity was expressed as the amount of enzyme that inhibits the oxidation of epinephrine by 50%, which is equal to 1 unit.

Catalase (CAT, EC 1.11.1.6) activity was evaluated by measuring the change in absorbance at 240 nm, corresponding to hydrogen peroxide concentration (43). One CAT unit is defined as 1 μmol of hydrogen peroxide consumed per minute.

Glutathione peroxidase (GPx, EC 1.11.1.9) activity was determined by a coupled GSH reaction, according to Wendel (44). The assay used tert-butyl hydroperoxide as substrate. NADPH disappearance was monitored spectrophotometrically at 340 nm. One GPx unit is defined as 1 μmol of NADPH consumed per minute.

**GSH level assay**

GSH levels were measured by fluorimetry (45). The samples were diluted in PBS 100 mM, pH 8.0, containing EDTA 5 mM, and incubated with o-phthaldialdehyde (1 mg/ml of methanol) for 15 min at room temperature. Fluorescence was measured using excitation and emission wavelengths of 350 and 420 nm, respectively. A standard curve of GSH (0–0.01–1 mM) was performed in parallel. Results are expressed as nmol/mg of protein.

**Protein concentration assay**

Protein concentration was determined using the Folin phenol reagent, and bovine serum albumin was used as a standard, in accordance with Lowry et al. (46). Data were expressed as mg protein/ml.

**Statistical analysis**

Data are expressed as means with their standard errors, and statistical analyses were performed using the GraphPad Prism 6.0 software. All data were tested for normality. Differences between nutritional groups were determined using a Student’s t test, and results were considered statistically significant when P < 0.05. Daily body weight and food consumption were analysed using repeated-measures ANOVA.

**Results**

**A hypersaline diet during pregnancy influences the weight gain of dams but does not affect consumption of chow or offspring birth weight**

During pregnancy, adult female rats receiving control standard diet or high-salt diet were weighed daily. From the 8th up to 21st gestational day, high-salt-diet-receiving dams presented with a reduced body weight (F(1, 16) = 16.20, P = 0.001) (Fig. 1), as well as weight gain, during pregnancy (K(15) = 2.305, P = 0.036) (online Supplementary Fig. S1), compared with the control diet group. Food consumption was also measured daily; chow intake was calculated as consumed chow in g/100 g body weight. Food intake throughout pregnancy was similar in both groups (F(1, 11) = 1.588, P = 0.234) (online Supplementary Fig. S2).

We further assessed pregnancy rate and pup body weight at birth, and these parameters were not affected by maternal diet (online Supplementary Fig. S3 and S4, respectively).

Maternal high-salt diet alters mitochondrial mass and membrane potential in offspring’s cerebellum

Mitochondrial mass and membrane potential were measured by flow cytometry as indicators of functional mitochondria (47) in the cerebellum, hypothalamus, hippocampus, prefrontal and parietal cortices from 7-d-old pups born to dams receiving control or high-salt diets (Fig. 2). As shown in Fig. 2, maternal high-salt diet promoted a statistically significant reduction in mitochondrial mass (t(18) = 2.250, P = 0.037) (Fig. 2(a)) and membrane potential (t(18) = 2.477, P = 0.023) (Fig. 2(b)) in the cerebellum of offspring, resulting in a 21% reduction of both mitochondrial parameters. Mitochondrial mass and membrane potential in the hypothalamus (t(17) = 0.776, P = 0.448; t(17) = 1.570, P = 0.188, respectively), hippocampus (t(8) = 1.962, P = 0.085; t(8) = 2.128, P = 0.066, respectively), prefrontal cortex (t(10) = 0.761, P = 0.464; t(10) = 0.006, P = 0.995, respectively) and parietal cortex (t(19) = 0.122, P = 0.904; t(18) = 0.499, P = 0.623, respectively) were not altered by maternal high-salt diet.

Maternal high-salt diet alters oxidative parameters differentially in encephalic regions

Overall reactive species, nitric oxide and mitochondrial superoxide levels were measured by flow cytometry in order to assess the oxidative status of the cerebellum, hypothalamus, hippocampus, prefrontal and parietal cortices from 7-d-old pups born to dams receiving control or high-salt diets (Fig. 3). DCFH2 is a target molecule of oxidant species, especially
hydrogen peroxide, hydroxyl radical and peroxynitrite, giving rise to a fluorescent product if oxidised (48). DCFH₂ oxidation increased significantly in the cerebellum of pups born to dams fed a high-salt diet, by 15% in comparison with control pups (t(8) = 2.666, P = 0.028) (Fig. 3(a)). Conversely, a statistically significant reduction (13.6%) in hippocampal DCFH₂ oxidation (t(19) = 3.788, P = 0.001) was observed in pups born to dams fed a high-salt diet compared with pups born to control-diet-fed dams. In the cases of the hypothalamus and prefrontal and parietal cortices, maternal high-salt diet did not alter DCFH₂ oxidation (t(19) = 0.324, P = 0.749; t(19) = 0.326, P = 0.748; t(19) = 1.503, P = 0.149, respectively).

To investigate the contribution of other oxidant species, we further measured nitric oxide (Fig. 3(b)) and mitochondrial superoxide (Fig. 3(c)) levels in encephalic regions. Offspring cerebellar (t(18) = 2.549, P = 0.020) and hypothalamic (t(18) = 3.884, P = 0.001) nitric oxide levels were significantly altered by maternal diet. Nitric oxide was reduced by 17.6% in the cerebellum and increased by 55% in the hypothalamus of offspring born to high-salt-diet-fed dams in comparison with control-diet-fed dams. Although parietal cortex nitric oxide levels tended to be increased (14%) (t(19) = 1.748, P = 0.096) in the offspring of dams fed a high-salt diet, this was not statistically different from the control diet group. Similarly, nitric oxide levels in the hippocampus (t(19) = 0.105, P = 0.917) and prefrontal cortex (t(19) = 0.326, P = 0.748) were not altered by a maternal high-salt diet. By analysing offspring cerebellum (t(18) = 1.092, P = 0.289), hypothalamus (t(19) = 0.689, P = 0.499) and parietal cortex (t(19) = 0.1777, P = 0.861), mitochondrial superoxide levels were found to be similar to those in the control group. Conversely, maternal high-salt diet caused mitochondrial-specific superoxide levels to increase in the hippocampus (t(19) = 2.325, P = 0.031) and prefrontal cortex (t(19) = 2.720, P = 0.014) of offspring. Such results were statistically significant and account for an increase of 8.5% in hippocampus and 19% in the prefrontal cortex.

**Maternal high-salt diet modulates antioxidant enzymatic activity in the brains of offspring**

The activities of the antioxidant enzymes SOD, CAT and GPx were measured as part of the assessment of the effects of a maternal high-salt diet on the antioxidant system of offspring in the encephalic regions. SOD activity (Fig. 4(a)) increased significantly in the cerebellum of pups born to the maternal high-salt diet group compared with the maternal control diet
Maternal high-salt diet alters redox state and mitochondrial function

Discussion

Salt intake at concentrations above physiological requirements is a common food habit worldwide, and, if combined with an unhealthy lifestyle, can represent a public health problem (69). The main effect of excessive salt intake is the elevation of blood pressure, which in addition to other factors, such as hyperlipidaemia, hyperglycaemia and high BMI, contributes to an increased risk of hypertension and vascular diseases (70).

In the present study, we hypothesised that maternal high-salt diet during pregnancy and lactation might programme the brain metabolism of offspring differentially from a standard diet, with regard specifically to cellular mitochondrial function and redox status. We demonstrate a redox status modulation elicited by maternal high-salt diet in the cerebellum, hypothalamus, hippocampus and prefrontal and parietal cortices of 7-d-old pups. Furthermore, maternal high-salt diet impairs cerebellar mitochondrial function. Few studies have investigated the effect of high-salt intake on neurocellular metabolism (34, 38, 51).

Maternal high-salt diet did not affect GSH content in offspring’s brain

GSH content was measured in the cerebellum, hypothalamus, hippocampus, prefrontal and parietal cortices of 7-d-old pups born to dams receiving a control or high-salt diet (Fig. 5). Hippocampal GSH content was reduced by 33.6% in maternal high-salt diet pups; although a tendency was observed, the difference was not statistically significant (10). Similarly, maternal high-salt diet did not affect GSH content in the cerebellum or parietal cortex of 7-d-old pups born to dams receiving a control diet (3) or high-salt diet (4) during pregnancy and lactation. Values are means (56 pups/group) with their standard errors. Student’s t test showed no statistically significant difference between maternal control and high-salt diets.

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observed no effect of high salt on food intake. Notwithstanding, dams fed a high-salt chow displayed a reduction in weight gain of 14% during pregnancy, and also had a body weight lower than that of dams fed control chow. Data from literature about the effects of a high-salt diet body weight and food intake are controversial. Gray et al. (58) and Reynolds et al. (57) have demonstrated that a 4% NaCl diet did not evoke increased food consumption or an alteration of dam body weight. Similarly, Ding et al. (56) and Piecha et al. (59) demonstrated that an 8% NaCl diet did not affect dam body weight. However, contrary to the former, which did not observe any effect of a high-salt diet in food intake, the latter showed that an 8% NaCl diet increased food intake. Discrepancies are observed not only in dams but also in males (54, 58, 54, 60) and young rodents (61). In concordance with our data, Pitnyski-Miller et al. (62) demonstrated that an 8% NaCl diet reduced body weight but did not alter food intake in female weaning Sprague–Dawley rats. On the other hand, Ge et al. (58) observed a reduction in body weight despite increased food intake in male mice fed 8% NaCl for 7 weeks. On the basis of these data, such differences do not seem to be due to salt load or rodent strain. In agreement with the literature (62, 63), the birth weight of pups born to high-salt-fed dams was similar to that of the control group, despite lower gestational weight gain. Previous research has demonstrated that mitochondrial dysfunction and redox status imbalance play an important role in the pathogenesis of hypertension (64–68), which is thought to be associated with the development of cerebrovascular diseases in clinics (69–72). The brain is highly susceptible to oxidative species and a high-salt diet is able to induce inflammation (73) and oxidative stress (54). High maternal salt intake seems to affect the structure and function of different tissues, including the heart and kidney (64, 65, 76, 72), and to a much lesser extent the hypothalamus (62), during fetal development, as well as in adult offspring. We showed that a maternal high-salt diet differentially affected biochemical parameters in all brain areas studied. Mitochondrial mass and membrane potential indicators were decreased in the cerebellum, indicating a reduction in the number of functional mitochondria. Data published by our research group demonstrated that maternal exercise causes mitochondrial biogenesis in offspring (73), and others showed an association between mitochondrial biogenesis and neurogenesis (74–76). In contrast, this study suggests that a maternal high-salt diet can promote mitochondrial dysfunction, at least in the cerebellum. Despite superoxide levels remaining unchanged, we verified an increase in SOD activity, which, allied with non-altered CAT and GPx, might be connected to increased hydrogen peroxide levels, one of the oxidants measured by DCFH oxidation. This oxidant molecule can be reduced to a hydroxyl radical by iron in the Fenton reaction (77, 78). It is important to note that our cells do not have enzymatic defences to eliminate hydroxyl radicals (79). Enhanced levels of hydrogen peroxide and/or hydroxyl radicals favour oxidative stress and can result in oxidative damage to carbohydrates, proteins, lipids and nucleic acids (78). In addition, hydrogen peroxide is able to overcome the membrane and affect multiple cellular compartments (90). Further, the offspring of high-salt-diet-fed dams presented reduced levels of nitric oxide in the cerebellum. Nitric oxide plays several important roles in our body, including vasodilation, maintenance of the endothelial barrier of blood vessels and apoptosis regulation, besides being a neurotransmitter (80). The cerebellum is responsible for learning and motor control, as well as being involved with cognitive functions (82). Concerning the role of nitric oxide on vasodilatation, the reduced levels seen in this study could be crucial for an increased risk of hypertension and cerebrovascular disease development in adulthood (83). Data from the literature have demonstrated that oxidative damage can impair the physiological function of the cerebellum and, owing to its connection with other brain structures such as the cerebral cortex, can spread the damage to adjacent areas (84).

The high-salt-diet pro-oxidative effect was previously demonstrated by Koga et al. (85), reporting an association between high salt intake and the production of oxidant species in the rostral ventrolateral medulla in an animal model of hypertension. Furthermore, the authors observed increased expression levels of angiotensin II receptor and NADPH oxidase activity. Results indicated that the increased production of oxidants may be associated with the activation of NADPH oxidase by angiotensin II (85). Another study has shown that the administration of a hypertensive diet (8% NaCl) during 3 weeks was able to increase angiotensin II levels in heart and kidney of Dahl salt-sensitive rats (86). Angiotensin II participates in the renin–angiotensin system (RAS) and is produced in response to decreased blood pressure, stimulating the vasoconstrictor response. Angiotensin II does not pass the blood–brain barrier under physiological conditions and the brain has a local RAS that works independently of the peripheral RAS. However, the CNS receives the peripheral signal from angiotensin II by receptors located in circumventricular areas (87, 88). Furthermore, the permeability of the blood–brain barrier seems to be altered in hypertensive rats, suggesting that angiotensin II could overpass it (89–91). It is already known that hypertensive individuals present with RAS hyperactivity (31). In contrast to the cerebellum results, we detected increased levels of nitric oxide in the hypothalamus from offspring delivered to high-salt-treated dams. Insofar as angiotensin-converting enzyme levels are supposedly increased in the hypothalamus suggesting a dysfunction in the RAS (72), nitric oxide levels may represent an adaptation to imbalance in the RAS, in order to normalise the function of the vascular endothelium. However, more studies are required to confirm this hypothesis.

Finally, we reported increased levels of mitochondrial superoxide in the hippocampus and prefrontal cortex, allied with reduced CAT activity in the latter as a result of maternal high-salt diet during pregnancy and lactation. In this context, Liu et al. (34) demonstrated that a high-salt diet induced high levels of superoxide production, reduced GSH concentration and decreased CAT and SOD activities in the hippocampus of adult mice, allied to cognitive decline. On an overview, these data suggest that superoxide anions probably produced by the mitochondria favour hippocampal oxidative stress in response to a maternal high-salt diet during fetal and newborn development. Further studies are needed to reveal whether a high-salt diet during pregnancy and lactation has long-lasting effects on the offspring's brain cellular function, as well as on cognitive function.
Conclusions

The intra-uterine environment and the lactation period are known to be influenced by the external environment, including maternal lifestyle, resulting in the adaptation of fetal and newborn metabolism. Herein, we have demonstrated for the first time that a high-salt diet during pregnancy and lactation promotes a pro-oxidant state, modulating oxidant species levels and the enzymatic antioxidant system, in addition to impairing mitochondrial function in the brains of offspring, suggesting that maternal diet is able to programme offspring neurometabolism.

Clinical extrapolation of our experimental results raises the need for population awareness concerning salt intake, particularly during pregnancy and lactation, owing to possible adverse effects on the metabolism and development of offspring.

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The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114518000235

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