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Perinatal salt restriction: A new pathway to programming adiposity indices in adult female Wistar rats

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Abstract

Low birth weight has been associated with increased obesity in adulthood. It has been shown that dietary salt restriction during intrauterine life induces low birth weight and insulin resistance in adult Wistar rats. The present study had a two-fold objective: to evaluate the effects that low salt intake during pregnancy and lactation has on the amount and distribution of adipose tissue; and to determine whether the phenotypic changes in fat mass in this model are associated with alterations in the activity of the renin–angiotensin system. Maternal salt restriction was found to reduce birth weight in male and female offspring. In adulthood, the female offspring of dams fed the low-salt diet presented higher adiposity indices than those seen in the offspring of dams fed a normal-salt diet. This was attributed to the fact that adipose tissue mass (retroperitoneal but not gonadal, mesenteric or inguinal) was greater in those rats than in the offspring of dams fed a normal diet. The adult offspring of dams fed the low-salt diet, compared to those dams fed a normal-salt diet, presented the following: plasma leptin levels higher in males and lower in females; plasma renin activity higher in males but not in females; and no differences in body weight, mean arterial blood pressure or serum angiotensin-converting enzyme activity. Therefore, low salt intake during pregnancy might lead to the programming of obesity in adult female offspring.
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Keywords: Salt; Perinatal period; Obesity; Adiposity; Leptin; Renin–angiotensin system

Introduction

The early nutritional environment has been associated with the amount and distribution of adipose tissue in childhood and adult life (Breier et al., 2001). Although the association between birth weight and adult fat mass is usually negative, some studies have shown a J-shaped or U-shaped relationship (Curhan et al., 1996; Parsons et al., 2001). Ravelli et al. (1976) reported that a low nutrient supply in early pregnancy results in increased fat mass in adulthood. However, the authors found no such association when the nutrient restriction occurred in the final trimester. Various authors have reported that the low birth weight/adult obesity combination is associated with the development of insulin resistance and cardiovascular disease (Bavdekar et al., 1999; Eriksson et al., 2002).

The perinatal alterations in fetal nutrition that most often result in low birth weight in rats are general malnutrition (a 30–50% reduction in food intake) and a low-protein diet (9% protein content). It has also been shown that salt restriction during pregnancy is associated with low birth weight in male and female rat offspring (Roy-Clavel et al., 1999; Vidonho et al., 2004). Vidonho et al. (2004) observed that, comparing the adult offspring of salt-restricted rat dams to those of dams fed a normal-salt diet, insulin sensitivity was lower in the males but not in the females. In addition, the authors found no significant differences between genders in terms of blood pressure and body weight. Despite the fact that adult body weight is not affected by salt restriction during the perinatal period, obesity cannot be ruled out in this group. Furthermore, obesity might be a mechanism related to the insulin resistance detected in the

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adult offspring of salt restricted dams (Vidonho et al., 2004). Moreover, there is evidence that angiotensin II has a trophic effect on adipose tissue (Ailhaud et al., 2000). To date, there have been no studies focusing on the long-term impact that intrauterine salt restriction has on susceptibility to obesity. Therefore, the present study had a two-fold objective: to evaluate the effects that low salt intake during pregnancy and lactation has on the amount and distribution of adipose tissue; and to determine whether the phenotypic changes in fat mass in this model are associated with alterations in the activity of the renin–angiotensin system (RAS).

Methods

For the purposes of this study, female Wistar rats were obtained from the Animal Facilities of the University of São Paulo School of Medicine, São Paulo, Brazil. All experiments reported herein are in accordance with the guidelines of the Ethics Committee of the University of São Paulo School of Medicine, São Paulo, Brazil.

Maternal groups

Female Wistar rats were fed regular rat chow from weaning until 8 weeks of age. Thereafter, they received a low-salt (LS) diet (0.15% NaCl) or a normal-salt (NS) diet (1.3% NaCl). Both diets were obtained from Harlan Teklad (Madison, WI, USA), and both had a protein content of 25%. All animals were housed in a temperature-controlled environment (25 °C) and maintained on a 12-h light/dark cycle (lights on at 6 AM) with free access to food and tap water. At 12 weeks of age, they were mated with adult males that were fed regular rat chow. Body weight was measured at weekly intervals from one week prior to pregnancy until the end of pregnancy. Intra-arterial blood pressure was determined at one week after the end of lactation.

Offspring groups

After birth, the litters were culled to 8 pups (4 males and 4 females) per dam. After weaning, all offspring received regular rat chow. Body weight was determined at birth and at 12 weeks of age, at which point intra-arterial blood pressure was also determined.

At 12 weeks of age, all offspring were killed by decapitation. Blood from the trunk was collected into tubes, some containing ethylenediaminetetraacetic acid (for the determination of renin activity) and some containing no anticoagulants (for the determination of angiotensin-converting enzyme activity and serum leptin levels). The blood samples were immediately centrifuged ($3000 \times g$ for 15 min at 4 °C). Plasma and serum were stored at −20 °C. In selected cases, adipose tissue was excised in order to determine its mass.

Mean intra-arterial blood pressure

Rats were anesthetized with pentobarbital (40 mg/kg i.p.), after which a catheter was inserted into the carotid artery and exteriorized at the back of the neck. The catheter was filled with heparinized saline (150 IU/mL) and sealed with stainless steel plugs. At 3 to 5 days after insertion of the carotid artery catheter, mean arterial pressure (MAP) was measured in the conscious, freely moving animals. This was achieved by attaching the catheter to a pressure transducer (model CDX III; Argon Instruments, Athens, TX, USA) connected to an amplifier (GPA-4 model 2; Stemtech, Menomonee Falls, WI, USA), thereby providing the analog blood pressure signal, which was digitized using a computer-based monitoring system (DATAQ Instruments, Akron, OH, USA). The MAP measurements taken over a 10-min period were averaged to obtain the value used in subsequent calculations.

Plasma renin activity

Plasma renin activity was measured using a commercial radioimmunoassay kit (RIA kit; CIS Bio International, Gif-sur-Yvette, France).

Angiotensin-converting enzyme activity

Angiotensin-converting enzyme activity was determined based on the rate of Histidyl-Leucine hydrolysis achieved in a fluorometric assay that uses Hippuryl-Histidyl-Leucine (Hip-His-Leu) as a substrate (Sigma Chemical, St. Louis, MO, USA), as described by Santos et al. (1985). Serum (10 μL) was incubated for 15 min with 490 μL of assay buffer containing 5 mM Hip-His-Leu in 0.4 M sodium borate buffer, pH 8.3, and 0.9 M NaCl at 37 °C. The reaction was halted by the addition of 1.2 mL of 0.34 N NaOH, and 100 μL (20 mg/mL) of *o*-phthaldialdehyde (Sigma Chemical) was then added to the aliquots. The reaction was interrupted with 3 N HCl, and the fluorescence of the His-Leu product was measured at 495 nm, with an excitation wavelength of 365 nm, using a spectrofluorometer (model RF-1501; Shimadzu, Kyoto, Japan). All assays were performed in triplicate. Protein was measured via the method of Bradford, using bovine albumin as a standard.

Serum leptin

Serum leptin levels were measured by radioimmunoassay using a commercial kit (HL-81 K; Linco Research, St. Louis, MO, USA).

Adiposity index

Adipose tissue pads were excised and weighed immediately after the offspring were decapitated. The adiposity index was calculated as the percentage of the sum of all white adipose tissue pads in relation to total body weight.

Statistical analysis

Values are expressed as means ± SEM. Comparisons between means were made using the Student's t test. All data were tested for normal distribution with the Kolmogorov–Smirnov test with

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