Dietary Sodium Chloride Increases Blood Pressure in Obese Zucker Rats

Sreenivas R. Reddy and Theodore A. Kotchen

In the rat, elevated arterial pressure is not consistently associated with obesity. The purpose of this study was to compare measurements of blood pressure, cardiac output, and total peripheral resistance in obese and lean Zucker rats on different NaCl intakes. Obese and lean rats drank either water or isotonic NaCl for 18 days. Tail systolic blood pressures of saline-drinking obese rats were higher than all other groups (p<0.05). NaCl intake did not affect blood pressure in lean rats, and blood pressures of water-drinking obese rats did not differ from those of lean controls. In a subsequent experiment, direct arterial pressures and cardiac outputs (thermodilution) were measured in separate groups of conscious rats that had been maintained on a 1% or 4% NaCl intake for 12 weeks. Arterial pressure was higher (p<0.01) in obese rats fed 4% NaCl (130±4 mm Hg) than in obese rats fed 1% NaCl (118±2 mm Hg) or than in lean rats fed either NaCl intake (118±3 mm Hg and 116±3 mm Hg, respectively). Cardiac output of obese rats was higher than that of lean rats (p<0.01); however, the NaCl-induced increase of blood pressure was accounted for by an increase of peripheral resistance (p<0.01). Thus, in contrast to the lean Zucker rat, arterial pressure of the obese Zucker rat is increased by a high dietary intake of NaCl. (Hypertension 1992;20:389–393)

Key Words • sodium, dietary • obesity • cardiac output • vascular resistance • blood pressure • rats, Zucker

In humans, hypertension is associated with obesity. Obesity-related hypertension has been ascribed to hypervolemia and an increased cardiac output without an appropriate reduction of peripheral resistance and to increased sympathetic nervous system activity. Further, it has been suggested that insulin resistance associated with obesity contributes to hypertension. The Zucker fatty rat inherits obesity as an autosomal recessive trait. Rats homozygous for the fatty gene are also insulin resistant and hyperinsulinemic. Based on indirect, tail-cuff measurements and direct measurement of intra-arterial pressure, several reports have indicated that blood pressure of the obese Zucker rat does not differ from that of lean controls. In contrast, other reports have indicated that arterial pressure is increased in this animal model. One purpose of the present study was to compare measurements of arterial pressure, cardiac output, and peripheral resistance in obese Zucker rats and lean controls.

In the human, there is some evidence that obesity-related hypertension is salt sensitive. Consequently, we hypothesized that blood pressure in this rat model of obesity would be increased by a high NaCl intake. In the present study, arterial pressures were compared in obese and lean Zucker rats on normal and high NaCl intakes.

Methods

In protocol 1, we evaluated the effect of a high NaCl intake in obese and lean rats by measuring indirect blood pressures in the tail. In protocol 2, direct arterial pressures and cardiac outputs were measured in separate groups of chronically instrumented, conscious obese and lean rats fed either a normal or a high NaCl diet.

For both protocols, lean and obese female Zucker rats were purchased from Harlan Sprague Dawley, Inc., Indianapolis, Ind., shortly after weaning at age 4 weeks. The rats were housed in individual metabolic cages in a temperature- and light-controlled (12-hour light/dark cycle) small animal facility. All rats ate and drank ad libitum, and body weights were measured twice weekly.

In protocol 1, lean and obese rats were fed chow containing 0.45% NaCl (TD 88311, Teklad, Madison, Wis.) and were given either distilled water or 0.9% NaCl (n=5–6 per group) to drink for 18 days. For the measurement of indirect arterial pressure, twice weekly, rats were placed in a heated rodent restrainer (Harvard Apparatus, South Natick, Mass.) and were maintained at a constant temperature of 39°C, beginning 15–20 minutes before the measurement. For each data point, nine tail-cuff measurements were obtained with a pneumatic pulse transducer (Narco BioSystems, Austin, Tex.), a pressure transducer (P23-ID, Gould Electronics, Cleveland, Ohio), and a polygraph (model 7D, Grass Instrument Co., Quincy, Mass.). The first two readings and the highest and lowest remaining readings
were discarded. The remaining five readings were averaged to obtain each data point. The observer reading the blood pressure recordings was unaware of the group assignment of the rats.

In protocol 2, separate groups of 4-week-old lean and obese Zucker rats were placed on either a 1% NaCl diet (Purina chow) or a 4% NaCl intake, prepared by adding NaCl to Purina chow (n = 13–15 rats in each diet–strain group). After remaining on these diets for 12 weeks, direct intra-arterial pressures were measured in all rats in the conscious, unrestrained state. Cardiac outputs were measured in 7–9 rats in each diet–strain group, and after the measurement of arterial pressure, hearts were dissected and weighed in the remaining six rats in each group.

As we have previously described for measurement of cardiac output, the left carotid artery was catheterized with a thermistor-catheter combination. The right jugular vein was catheterized with Tygon microbore tubing (0.015 inch i.d. x 0.030 inch o.d.), and the catheter was advanced into the right atrium. In those rats not undergoing measurement of cardiac output, a carotid artery was catheterized with a Tygon microbore catheter (0.24 inch i.d. x 0.040 inch o.d.). In all instances, rats were chronically instrumented with catheters that were inserted under Brevital anesthesia (40 mg/kg i.p.). After catheter placement, rats were treated with a single intramuscular dose of penicillin G (20,000 units) and streptomycin (25 mg). Catheters were tunneled subcutaneously to exit at the base of the skull. All measurements of direct arterial pressure and cardiac output were carried out at least 3 days after preparatory surgery.

For measurement of cardiac output, a 100-μl bolus of room temperature (18–19°C) 5% dextrose was injected into the jugular venous catheter with a Hamilton dispensing pipette fitted into an automatic dispensing device. The temperature of the injectate was measured with a platinum-tipped thermometer that was accurate to 0.2°C, and temperature change of the blood was measured with the precalibrated indwelling thermistor. The outputs of both the thermistor in the injectate and the aortic thermistor were recorded with a Cardiomax thermistor microprobe coupled to a thermodilution cardiac output computer (Cardiomax II, model 58, Columbus Instruments, Columbus, Ohio). Three 100-μl injections were performed, and the average cardiac output was computed. Total peripheral resistance (TPR) was calculated by dividing the simultaneously obtained arterial pressure by cardiac output.

Statistical significance of differences between obese and lean rats on each of the two diets was determined with a two-factor (strain and diet) analysis of variance. Where statistically significant, overall differences were observed; specific group differences were identified with the least significant differences test. Results are presented as mean ± SEM.

Results

Protocol 1: Indirect Blood Pressure Measurements

At the completion of the study, the mean weight of obese rats (255±4 g) was greater (p < 0.001) than that of lean rats (140±3 g). Dietary NaCl intake did not affect weight gain in either group. Salt intake also did not affect blood pressure in the lean rats; however, NaCl-drinking obese Zucker rats had significantly higher blood pressures (p < 0.05) than water-drinking obese rats (Figure 1). Blood pressures in the water-drinking obese rats did not differ from those in the lean rats.

Protocol 2: Direct Arterial Pressure, Cardiac Output, and Peripheral Resistance

Within each strain, weight gains in the rats on the two NaCl intakes were similar, and at the completion of the study, mean body weight of obese rats was approximately two times that of lean rats (Table 1). Among obese and lean rats, body weights did not differ significantly on the two NaCl intakes. Further, among the obese rats, the heart weight-to-body weight ratio was higher (p < 0.01) in rats on the 4% NaCl intake than in those on the 1% NaCl intake. The heart weight-to-body weight ratio was not affected by NaCl intake in the lean animals. On the 1% NaCl intake, direct mean intra-arterial pressures of obese and lean animals did not differ (Figure 2). However, arterial pressure was significantly higher in obese rats on the 4% NaCl intake than in obese rats on the 1% NaCl intake (p < 0.01) or in lean animals on either NaCl intake (p < 0.01). Arterial pressure was not affected by NaCl intake in lean animals.

Cardiac output was higher (p < 0.001) in obese than in lean rats. Among obese rats, cardiac output was lower (p < 0.01) and TPR was higher (p < 0.01) in those fed the 4% NaCl than in those fed the 1% NaCl diet.
Among lean rats, cardiac output and TPR did not differ significantly between those on the two NaCl intakes. Because of their greater body weight, cardiac index of obese rats was less than that of lean rats (p<0.001). In both strains, cardiac index was not significantly affected by NaCl intake. Consequently, the computed TPR based on cardiac index (rather than cardiac output) was higher in obese than in lean rats (p<0.01). However, among obese rats, similar to results based on cardiac output, TPR computed on the basis of cardiac index was also higher (p<0.03) in those on the 4% NaCl intake (3.03±0.11 mm Hg·ml⁻¹·min⁻¹·100 g⁻¹) than in those on the 1% NaCl intake (2.72±0.12 mm Hg·ml⁻¹·min⁻¹·100 g⁻¹); TPR was not significantly affected by NaCl intake in lean rats.

Discussion

In the conscious animal, both indirect and direct intra-arterial pressures did not differ in Zucker obese and lean rats on a “normal” NaCl intake, although cardiac output was higher and TPR was lower in obese animals. Blood pressures were increased by a high NaCl intake in obese but not in lean animals, and the NaCl-induced elevation of blood pressure was due to an increased TPR.

Previous studies have indicated that hypertension is not consistently associated with obesity in the rat. Results in the obese Zucker rat are conflicting. Obesity-inducing lesions of the ventromedial hypothalamus either have no effect on blood pressure or result in hypotension, and these lesions prevent the development of hypertension in several experimental models. However, these lesions also decrease sympathetic output. Blood pressures have been reported to be normal or slightly elevated in rats with obesity induced by programming the animals to eat a high fat diet. Based on indirect tail-cuff measurements, it has been reported that blood pressure in obese spontaneously hypertensive rats (SHR) is lower than in nonobese littermates. The only obese rat model with persistent hypertension was originally developed by Kottetsky, who bred rats that were spontaneously hypertensive with genetic traits for obesity.

There is little information in the literature concerning salt sensitivity of blood pressure in the obese rat. Pawloski et al have recently reported that a continuous intravenous sodium infusion (6 meq sodium per day) for 1 week did not significantly increase blood pressure in a small group (n=5) of obese Zucker rats. However, Kasikse et al reported that tail systolic blood pressures were significantly but modestly increased in obese Zucker rats fed standard chow supplemented with 4% NaCl for 22 weeks, but not for 8 weeks. The high NaCl intake did not affect blood pressure in lean rats.

Although blood pressure of the Dahl salt sensitive (Dahl-S) rat is more salt sensitive than the obese Zucker rat, similar mechanisms may account for salt sensitivity of blood pressure in both models. Similar to the present observations in the obese Zucker rat, NaCl-induced elevations of blood pressure in the Dahl-S rat are also due to an increase of TPR. Fat-fed obese rats and Dahl-S rats have augmented vasoconstrictor responses to pressor agents. An impairment of arterial baroreceptor reflex activity has been implicated in the salt sensitivity of blood pressure in the Dahl-S rat. Baroreceptor reflex control of heart rate is also impaired in the obese Zucker rat and in the obese Wistar rat maintained on a high fat diet. In both the Dahl-S rat and the obese Wistar rat, the decreased baroreceptor reflex control of heart rate appears to be due to an impairment in the parasympathetic limb of the reflex. In contrast, arterial baroreceptor reflex control of heart rate is not reduced in the obese, fat-fed dog.

**FIGURE 2.** Bar graph shows direct arterial pressure in obese and lean Zucker rats on normal or high NaCl intakes.

**TABLE 1.** Mean Body Weight, Heart Weight-to-Body Weight Ratio, and Hemodynamic Measurements in Obese and Lean Rats Fed 1% or 4% NaCl Diet for 12 Weeks

<table>
<thead>
<tr>
<th>Diet</th>
<th>Obese</th>
<th>Lean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>426±12</td>
<td>403±10</td>
</tr>
<tr>
<td>Heart weight g</td>
<td>1.70±0.06</td>
<td>2.09±0.07*</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>118±2</td>
<td>130±4*</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>191±6</td>
<td>171±5*</td>
</tr>
<tr>
<td>TPR (mm Hg·ml⁻¹·min⁻¹)</td>
<td>0.62±0.03</td>
<td>0.74±0.03*</td>
</tr>
</tbody>
</table>

TPR, total peripheral resistance. Values are mean±SEM.

*p<0.01 compared with obese rats fed 1% NaCl.
Sympathetic tone is also increased in the Dahl-S rat and in the SHR fed a high-NaCl intake.\textsuperscript{18,40,41} However, sympathetic tone is actually decreased in the obese Zucker rat, as demonstrated by decreased release of norepinephrine from nerve terminals in response to stress.\textsuperscript{42} Conceivably, reduced sympathetic tone may account for the relatively modest effect of dietary NaCl on blood pressure in this rat model of obesity.

Obesity is associated with resistance to insulin-stimulated glucose uptake and hyperinsulinemia.\textsuperscript{4} We have recently demonstrated that the Dahl-S rat is also insulin resistant, whereas the one-kidney, one clip hypertensive rat and the two-kidney, one clip hypertensive rat are not.\textsuperscript{43,44} Insulin resistance has also been observed in the SHR\textsuperscript{45} and in human hypertension\textsuperscript{46-48}; in hypertensive humans, insulin resistance appears to be associated with salt sensitivity of blood pressure.\textsuperscript{49,50} Consequently, insulin resistance may contribute to the salt sensitivity of blood pressure in the obese Zucker rat.

In conclusion, blood pressure of the obese Zucker rat is increased by a high dietary intake of NaCl. Similar to earlier observations in the Dahl-S rat, the NaCl-induced elevation of blood pressure is accounted for by an increased TPR. We hypothesize that similar mechanisms account for the NaCl-induced elevation of arterial pressure in both the obese Zucker rat and the Dahl-S rat.

References

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Hypertension. 1992;20:389-393
doi: 10.1161/01.HYP.20.3.389

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/20/3/389

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