Sucrose Does Not Raise Blood Pressure in Rats Maintained on a Low Salt Intake

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Diets high in sucrose or fructose have been shown by others to induce a modest elevation of blood pressure in rats. The present experiments were conducted to determine whether the sucrose-induced increase of blood pressure is dependent on the intake of sodium chloride. Four groups of Sprague-Dawley rats were studied: 1) a group maintained on a low salt diet and distilled water (0.45% sodium chloride, no added sucrose), 2) a low salt-high sucrose group (0.45% sodium chloride diet and 7% sucrose in distilled water), 3) a high salt group (4% sodium chloride diet and distilled water), and 4) a high salt-high sucrose group on a diet adjusted daily to maintain the same high intakes of sodium chloride and sucrose as those of groups 2 and 3. Systolic blood pressures were measured by tail-cuff plethysmography during weeks 1–3 of treatment, and direct mean arterial blood pressures were recorded in conscious animals during week 4. Animals on the high salt diet gained weight more slowly than those on the low salt intake. On the low sodium chloride intake, blood pressures were not affected by high dietary sucrose (group 1 versus 2). In contrast, on the high sodium chloride intake, blood pressures were 10–14 mm Hg higher in sucrose-drinking animals than in water-drinking animals (group 3 versus 4). The increments in blood pressures of the high sodium chloride–high sucrose group were not accompanied by greater increments in body weight compared with the animals on the high sodium chloride intake alone. Sucrose-fed animals exhibited an increase in basal plasma norepinephrine concentrations and increased responsiveness of both norepinephrine and epinephrine to stress (mild electrical foot shock), regardless of the sodium chloride intake. Thus, in the Sprague-Dawley rat, sucrose elevates blood pressure only when adequate salt is present in the diet. We hypothesize that a high sucrose intake may activate the sympathetic nervous system but that this activation is effective in elevating blood pressure only when there is a concomitant high intake of sodium chloride. (Hypertension 1993;21:779–785)

KEY WORDS • insulin • catecholamines • sympathetic nervous system • hypertension, sodium-dependent

Simple carbohydrate feeding (sucrose, glucose, or fructose) increases blood pressure in several normotensive strains of rats, including the Sprague-Dawley rat, the Wistar-Kyoto rat, and the Dahl salt-resistant rat.1–8 Sucrose feeding also potentiates the development of hypertension in the spontaneously hypertensive rat and in a rat model of adrenal regeneration hypertension.9–11 Sucrose-induced increases of blood pressure have been attributed to increased sympathetic nervous system activity.5,7,10,11

In earlier studies, Hall and Hall9,12 reported that addition of sucrose to a 1% NaCl drinking solution augmented the development of both adrenal regeneration hypertension and hypertension after unilateral nephrectomy, and this augmentation was attributed to increased salt consumption in sucrose-drinking rats. More recent evidence, based on indirect blood pressure measurements, also suggests that sucrose might potentiate the effect of dietary NaCl on blood pressure in both normotensive and spontaneously hypertensive rats.3,4,11,13

The purpose of the present study was to evaluate the effect of high dietary sucrose on arterial pressure in the normotensive Sprague-Dawley rat on either a low (0.45% NaCl) or a high (4% NaCl) salt intake. Systolic blood pressures were measured at regular intervals throughout the study, and direct arterial blood pressures were determined after 4 weeks of dietary treatment in conscious, chronically instrumented animals, both at rest and in response to a standardized foot shock stress. As an index of sympathetic nervous system activity, plasma catecholamine concentrations were determined both before and immediately after the foot shock stress. Additionally, because it has been suggested that sucrose ingestion may lead to an alteration in basal insulin concentrations, altered sensitivity to insulin, or both,14 plasma glucose and insulin concentrations were measured in response to an oral glucose load.

Methods

General Animal Protocol

All procedures involving animals were in accordance with the guidelines of the Animal Care and Use Committee of West Virginia University. Male Sprague-
Dawley rats were purchased (Harlan Sprague Dawley, Inc., Indianapolis, Ind.) at 4 weeks of age. All animals were housed individually in metabolic cages designed for measurement of food and water intakes (Nalgene model 650) under controlled conditions of lighting, temperature, and humidity. Animals were maintained initially on a low salt diet containing 0.45% NaCl (TD 88311; Teklad Premier Laboratory Diets, Madison, Wis.) with distilled water to drink. The diet is essentially a natural diet of ground corn (38%), ground wheat (21%), and soybean meal (27%) supplemented with vitamins and minerals, containing approximately 54% utilisable carbohydrates but no added sugars. The period of study was begun when the animals reached a body weight of approximately 100 g, at which time all animals were continued on the low salt diet with distilled water to drink for 1 additional week.

Animals were then assigned randomly to one of four dietary treatment groups for the remaining 4.5-week study period. 1) Low NaCl, no sucrose group: Animals in this group were continued on the low NaCl diet, with distilled water to drink. 2) Low NaCl, high sucrose group: Animals in this group were maintained on the low NaCl diet but received sucrose in their drinking water (7% by weight). 3) High NaCl, no sucrose group: These animals received a high salt diet (4% NaCl by weight), prepared by adding NaCl to the low NaCl diet. These animals also received distilled water to drink. 4) High NaCl, high sucrose group: This group received both added NaCl in their food and sucrose in their drinking water. The sucrose content of the water and the NaCl content of the chow were adjusted daily so that the daily NaCl and water intakes of this group matched the sucrose intakes of group 2 and the NaCl intakes of group 3.

Body weights were determined weekly throughout the study. Systolic blood pressures were measured twice a week by tail-cuff plethysmography.

On day 26 or 27 of the dietary treatment period, each animal was anesthetized with Brevital (50 mg/kg i.p.), and a catheter was implanted in a femoral artery by a method we have described previously. The catheter was tunneled to the back of the neck, where it exited the skin, and then was passed through a stainless-steel wire spring. The spring was attached to the animal by means of a vest worn by the animal. Animals were housed thereafter in the laboratory in cages that were designed for complete freedom of movement but that did not permit measurement of food and water intakes. Resting mean arterial blood pressures were recorded on the morning of the 28th day of the dietary regimen with a model 7 polygraph (Grass Instruments, Quincy, Mass.) and a pressure transducer (Statham Division, Gould Inc., Oxnard, Calif.).

**Basal and Stress-Induced Changes in Plasma Catecholamines and Blood Pressure**

On day 29 or 30, an acute foot shock protocol was used to determine stress-induced changes in blood pressure, heart rate, and plasma epinephrine and norepinephrine concentrations in all animals. Resting mean arterial blood pressure on the salt diet were recorded from the unrestrained rat in its home cage, and an arterial blood sample (0.8 mL) was drawn for later determination of plasma catecholamine concentrations. Each rat was then exposed to a short period of mild electrical foot shock (0.3 mA, 0.5-second duration, every 6 seconds for 5 minutes) via a series of metal bars that constituted the floor of the cage. A second blood sample was drawn in the final minute of the shock period. The shock was then turned off, and mean arterial blood pressure and heart rate were again recorded.

Blood samples were transferred to chilled tubes containing EGTA and glutathione, and the plasma from centrifuged samples was stored at −70°C for later determination of catecholamine concentrations.

**Oral Glucose Tolerance Test**

One to 2 days after the foot shock protocol, plasma insulin and glucose concentrations were measured in response to an oral glucose load in most animals. Animals were fasted overnight and given only distilled water to drink. On the morning of the test, a control blood sample (0.8 mL) was drawn, and each animal received an oral glucose load of 1 mL per 100 g of body weight of a 17% (wt/vol) solution of dextrose by oral gavage. Additional blood samples were drawn at 15, 30, and 60 minutes after the glucose load. All samples were collected without anticoagulant, centrifuged, and stored at −20°C until assay for plasma concentrations of glucose and insulin.

**Analytical and Statistical Methods**

Plasma epinephrine and norepinephrine concentrations were assayed by a commercially available radioenzymatic method (Amersham Corp., Arlington Heights, Ill.). Minimum detectable doses were determined for each catecholamine in each assay as the dose equivalent to a counting rate that was more than two standard deviations from that of a blank performed in quadruplicate. The average minimum detectable doses of 11 separate assays were 0.36 pg for epinephrine and 0.58 pg for norepinephrine, corresponding to sensitivities of 7 and 12 pg/mL, respectively. The interassay coefficients of variation of a pooled quality control sample were 8% and 15% for epinephrine and norepinephrine, respectively. Because the variances for the plasma catecholamine data were unequal, plasma catecholamine values underwent a logarithmic transformation before statistical analysis. Differences in log-transformed basal and stimulated catecholamines between treatment groups were then determined by two-way analysis of variance. Serum glucose was measured with a Beckman autoanalyzer. The interassay and intra-assay coefficients of variation of the method are 2.0% and 1.5%, respectively. Serum insulin was measured by a radioimmunoassay method (Incstar, Stillwater, Minn.) that uses a guinea pig antibody to porcine insulin and a rat standard. Interassay and intra-assay coefficients of variation of the method are 8% and 5%, respectively, and the sensitivity is 0.4 ng/mL.

Duplicate measurements of systolic blood pressure within a week were averaged before statistical analysis. The blood pressure data for each week from the four dietary groups were analyzed by a two-way analysis of variance, followed by post hoc comparisons between means using Tukey's test. All results are presented as mean±SEM.
Results

Food and Water Intakes, Salt and Sucrose Intakes, and Body Weights

Figure 1 depicts the daily food and water intakes, respectively, of the four dietary treatment groups. Animals placed on the high NaCl intake had a slight, transitory decline in food intake and an increase in water intake. In contrast, fluid intake increased substantially in animals placed on a high sucrose intake, regardless of the NaCl intake. Sucrose-drinking animals consumed less chow than water-drinking animals. In sucrose-drinking animals also fed the high NaCl diet, there was a persistent reduction of food intake and a late increase in water intake compared with animals receiving sucrose alone.

Despite these differences in food and water intakes, the actual NaCl and sucrose intakes of the animals receiving both NaCl and sucrose concomitantly were identical to the corresponding intakes of the animals receiving either NaCl or sucrose alone (Figure 2). This matching of intakes was accomplished by calculating the intakes of NaCl and sucrose of all groups on a daily basis and then adjusting the NaCl concentration of the food and the sucrose concentration of the water in the group receiving both NaCl and sucrose (group 4).

The body weights of the animals at the time of initiation of the different dietary regimens and again at the end of 4 weeks are shown in Table 1. There were no differences in initial body weights. However, two-way analysis of variance revealed a significant main effect of salt on body weight, with those animals on the high salt diet weighing less at the end of 4 weeks than those on the low salt diet ($p<0.01$). The addition of sucrose to the drinking water did not affect body weights, regardless of the dietary salt intakes (no main effect of sucrose).

Systolic and Mean Arterial Blood Pressures and Heart Rates

Figures 3 and 4 depict the systolic blood pressures before and during the first 3 weeks of dietary treatment as well as mean arterial pressure measured from conscious, unstressed animals at week 4 of treatment. Two-way analysis of variance revealed that at each treatment week there was a main effect of sucrose and no main effect of salt, with a salt--sucrose interaction at weeks 3 and 4. Post hoc Tukey's test showed that there were no differences at any time in either systolic or mean arterial blood pressures between the two groups on the low NaCl diet (Figure 3). In contrast, blood pressures (systolic blood pressures at week 3 and mean
blood pressures at week 4) were significantly different between the salt and salt–sucrose groups (Figure 4).

Heart rates were measured only at week 4 from the chronic indwelling catheter. There were no differences between basal heart rates among the four dietary treatment groups.

**Pressor, Heart Rate, and Plasma Catecholamine Responses to Stress**

The mild electrical foot shock paradigm was sufficient to raise mean blood pressures by approximately 20 mm Hg and heart rates by 80 beats per minute, and there were no differences in the stress-induced increments in blood pressure or heart rate among the four dietary treatment groups (data not shown). Nevertheless, during the stress, the mean arterial blood pressure of the group receiving both NaCl and sucrose remained significantly higher than that of the group receiving NaCl alone (\(p<0.05\)). Plasma catecholamines were log-converted before statistical analysis. Plasma catecholamines increased in response to foot shock in all four dietary groups (\(p<0.05\) for both norepinephrine and epinephrine, Table 2). Two-way analysis of variance revealed a main effect of sucrose diet on both the basal and foot shock values for norepinephrine (\(p<0.01\) and \(p<0.05\), respectively). However, there was no main effect of NaCl diet on norepinephrine. Although epinephrine appeared to be similarly affected by the sucrose diet, there was no statistically significant main effect of sucrose on either basal or foot shock values of epinephrine, perhaps because of the wide variability of the epinephrine response.

**Responses to an Oral Glucose Load**

There were no apparent differences among any of the four groups in either the plasma glucose or insulin responses to an oral glucose load (Figure 5).
Arterial pressure was increased by a high sucrose intake in Sprague-Dawley rats on a high but not on a low NaCl diet. Thus, dietary sucrose does not raise blood pressure in the normotensive Sprague-Dawley rat when NaCl is restricted.

Earlier studies attributed the sucrose-induced increase of blood pressure in the rat to considerably greater intakes of NaCl in rats provided with both sucrose and saline in the same drinking solution. However, results of the present carefully controlled study clearly indicate that blood pressure is increased by dietary sucrose, despite an identical NaCl intake in sucrose-drinking and in water-drinking animals fed high NaCl. Consistent with earlier results of other investigators, sucrose-drinking animals did not gain more weight than water-drinking controls, and we observed that sucrose-drinking animals actually consumed less chow than water-drinking animals. Consequently, to assure similar NaCl intakes, we adjusted the NaCl content of the chow of sucrose-drinking animals upward as necessary on a daily basis.

Sucrose ingestion has been reported to induce tachycardia, to increase norepinephrine excretion and turnover, to enhance sympathetic nerve responses to hypothalamic stimulation, and to cause an exaggerated depressor response to α-adrenergic blockade in rats. The present experiments show that sucrose ingestion produces an elevation of plasma norepinephrine concentrations both at rest and in response to stress. Together, these data are consistent with the hypothesis that sucrose loading increases sympathetic nervous system activity in rats. Carbohydrate feeding also increases sympathetic outflow in humans.

In the rat, both sucrose and fructose feeding have been shown to cause a defect in insulin-stimulated glucose utilization, as determined by the euglycemic insulin clamp technique. Furthermore, it has been suggested that the increased neural activity in sucrose-fed animals is a consequence of insulin resistance. Insulin also has an antinatriuretic effect, and this is another proposed mechanism by which insulin resistance and hyperinsulinemia may increase blood pressure. However, there is no a priori reason why changes in insulin sensitivity, even if they do occur, need be involved in the cause–effect relation between sucrose or fructose feeding and the elevation in blood pressure. In the present study, those animals receiving high intakes of both sucrose and NaCl showed an elevation of blood pressure compared with those receiving NaCl alone even though their basal plasma insulin and glucose concentrations were similar and even though glucose and insulin responses to an oral glucose load did not differ. Of course, oral glucose loading is not a particularly sensitive technique for evaluating insulin sensitivity, and we are reluctant to exclude entirely the possibility that sucrose may have induced a defect in glucose utilization in our experiments. Nevertheless,
TABLE 2. Basal and Stress-Induced Plasma Catecholamines

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Norepinephrine</th>
<th>Epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low salt groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No sucrose (n=11)</td>
<td>185±25</td>
<td>587±102</td>
</tr>
<tr>
<td>High sucrose (n=11)</td>
<td>294±35</td>
<td>1,075±255</td>
</tr>
<tr>
<td>High salt groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No sucrose (n=11)</td>
<td>145±22</td>
<td>494±113</td>
</tr>
<tr>
<td>High sucrose (n=11)</td>
<td>219±33</td>
<td>809±190</td>
</tr>
</tbody>
</table>

Brands et al report that insulin-induced hypertension in Sprague-Dawley rats is not salt sensitive, suggesting that there is no direct connection between insulin-induced effects on blood pressure and the degree of salt intake. Furthermore, Tomiyama et al recently reported that insulin does not influence blood pressure in the salt-resistant Dahl rat, although it does in the salt-sensitive rat. In contrast, we have reported that a high sucrose intake increases blood pressure in the Dahl salt-resistant but not in the Dahl salt-sensitive rat. Together, these data are consistent with the hypothesis that insulin-induced alterations in blood pressure may operate by an entirely different mechanism than sucrose-induced alterations of blood pressure; that is, sucrose-induced increases in blood pressure may not be dependent on either the presence of hyperinsulinemia or a change in insulin sensitivity.

A considerable body of evidence suggests that a deficient capacity to excrete sodium, increased sympathetic nervous system activity, or both contribute to elevated arterial pressure in both genetic and acquired models of salt-sensitive hypertension in the rat. Furthermore, this "natriuretic handicap" may be related to increased neural activity at the level of the renal tubule. In these models, neural activity is potentiated by a high NaCl intake, even before the onset of hypertension. Failure to appropriately suppress neural activity may also contribute to salt-sensitive hypertension in humans. In the present study, we suggest that stimulation of sympathetic nervous system activity by dietary sucrose renders the normotensive rat salt sensitive. In the spontaneously hypertensive rat, high dietary intakes of both sucrose and NaCl increase both neural activity and blood pressure to a greater extent than provision of either sucrose or NaCl alone.

In the rat, blood pressure is not invariably increased by sucrose feeding. Different blood pressure responses to sucrose may reflect differences in NaCl intake, strain, and model of hypertension. Indeed, we observed that sucrose-induced elevations of blood pressure cannot be...
initiated in the normotensive Sprague-Dawley rat maintained on a low salt diet; that is, the presence of NaCl appears to be an absolute requirement for the expression of sucrose-induced elevations of blood pressure in this strain. With regard to other strains and models, we have reported recently that sucrose feeding does not increase blood pressure in the Dahl salt-sensitive rat or in the one-kidney, one clip hypertensive rat. Furthermore, we suggested that underlying mechanisms of “sucrose sensitivity” were already present in these models, and consequently, sucrose produced no additional effect on blood pressure.

In summary, the present experiments reveal that sucrose does not elevate blood pressure in the normotensive Sprague-Dawley rat unless the NaCl intake is relatively high. The mechanism may involve an activation of the sympathetic nervous system by sucrose, but activation of the sympathetic nervous system alone is insufficient to produce hypertension unless adequate NaCl is present in the diet.

References
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