Fructose Feeding Increases Insulin Resistance but Not Blood Pressure in Sprague-Dawley Rats

Gerard D’Angelo, Ahmed A. Elmarakby, David M. Pollock, David W. Stepp

Abstract—Fructose feeding has been widely reported to cause hypertension in rats, as assessed indirectly by tail cuff plethysmography. Because there are potentially significant drawbacks associated with plethysmography, we determined whether blood pressure changes could be detected by long-term monitoring with telemetry in age-matched male Sprague-Dawley rats fed either a normal or high-fructose diet for 8 weeks. Fasting plasma glucose (171±10 versus 120±10 mg/dL), plasma insulin (1.8±0.5 versus 0.7±0.1 μg/L), and plasma triglycerides (39±2 versus 30±2 mg/dL) were modestly but significantly elevated in fructose-fed animals. Using the hyperinsulinemic euglycemic clamp technique, the rate of glucose infusion necessary to maintain equivalent plasma glucose was significantly reduced in fructose-fed compared with control animals (22.9±3.6 versus 41.5±2.9 mg per minute; P<0.05). However, mean arterial pressure (24-hour) did not change in the fructose-fed animals over the 8-week period (111±1 versus 114±2 mm Hg; week 0 versus 8), nor was it different from that in control animals (109±2 mm Hg). Conversely, systolic blood pressure measured by tail cuff plethysmography at the end of the 8-week period was significantly greater in fructose-fed versus control animals (162±5 versus 139±1 mm Hg; P<0.001). Together, these data demonstrate that long-term fructose feeding induces mild insulin resistance but does not elevate blood pressure. We propose that previous reports of fructose-induced hypertension reflect a heightened stress response by fructose-fed rats associated with restraint and tail cuff inflation. (Hypertension. 2005;46:806-811.)

Key Words: plethysmography

Obesity afflicts >30% of all Americans and is the major emerging risk factor for cardiovascular disease, including hypertension.1–2 Despite this prevalence, the mechanisms linking obesity and cardiovascular disease remain poorly understood. Because the prediabetic state of insulin resistance and elevated blood pressure commonly present together in obese patients,3–5 many have hypothesized that insulin resistance is a causal factor in the development of obesity-induced hypertension. In support of this hypothesis is a significant body of literature in which insulin resistance induced by high-fructose diet has been reported to increase arterial pressure in the absence of obesity.6–21 A caveat of most of these observations is that arterial pressure was measured by tail cuff plethysmography, a noninvasive measure that reports only systolic pressure and requires restraint and comparable vasodilation of the tail between groups.6–13,16–20 Measurement of blood pressure directly with an indwelling catheter has either failed to report elevated blood pressure over a period of <2 weeks22 or required ≥4 weeks of fructose feeding.21 Thus, the hypothesis that insulin resistance independent of obesity causes hypertension remains controversial and has yet to be critically tested.

The advent of high-resolution radiotelemetry alleviates the limitations of tail cuff and tethered catheters by allowing 24-hour monitoring of unrestrained animals for significant periods of time. The objective of the current study was to use this method to critically test the hypothesis that fructose-induced insulin resistance causes chronic elevation of mean arterial pressure (MAP). Sprague-Dawley rats were fed a 66% fructose diet for 8 weeks to induce insulin resistance, and arterial pressure was monitored by telemetry implants continuously for 9 weeks (1 week previous and 8 weeks of diet). The presence of insulin resistance was verified by hyperinsulinemic euglycemic clamp (HEC) and measurements of fasting plasma glucose, insulin, cholesterol, and triglyceride levels. For reference and comparison, systolic pressure was assessed by tail cuff plethysmography at the 8-week time point.

Methods

Animal Model

Nine-week-old male Sprague-Dawley rats were purchased from Harlan Laboratories (Indianapolis, Ind). Rats were housed in the animal care facility at the Medical College of Georgia, which is approved by the American Association for the Accreditation of Laboratory Animal Care. On arrival, all animals received standard rat chow containing 4% fat, 4.5% fiber, and 24% protein (No. 8604; Harlan Teklad Laboratories). Those animals receiving telemetry...
transmitters had undergone surgery 1 week after their arrival. At the age of 12 weeks, animals were divided into 2 groups: those that continued to receive the standard rat chow (control) and those switched to a high-fructose diet (fructose-fed). The fructose-rich diet contained, as a percentage of total calories, 66% fructose, 22% casein, 12% lard, plus essential vitamins and minerals (No. 89247; fructose diet formula TD pellets). As noted previously,\textsuperscript{23} the magnesium content is reduced in the fructose diet (0.049% versus 0.28%). All protocols have been approved by the institutional animal care and use committee.

**Arterial Pressure Measurement**

Telemetry transmitters (Data Sciences, Inc.) were implanted according to manufacturer specifications as described previously.\textsuperscript{24} Rats were anesthetized with ketamine–xylazine (50 mg/kg and 10 mg/kg IP). The abdominal aorta was then exposed by a midline incision and briefly occluded. The transmitter catheter was inserted into a hole made by a 21-gauge needle just proximal to the iliac bifurcation and secured in place with tissue glue (Vetbond). The transmitter body was attached to the abdominal wall along the incision line with 4–0 prolene suture as the incision was closed. The skin was closed with staples that were removed 7 days after the incision had healed. Rats were allowed to recover from surgery and were returned to individual housing for data collection before being placed on dietary protocols. The individual rat cages were placed on top of the telemeter receivers, and MAP and heart rate (HR) were recorded continuously throughout the study using the Daqdata Advanced Research Technologies Acquisition program (Transoma Medical, Inc.). All animals were kept on the normal diet for 1 additional week after the allotted surgery recovery period. After this time (i.e., at the age of 12 weeks), half of the animals were maintained on the normal diet (n=8), whereas the other half was switched to the high-fructose diet for 8 weeks (n=8). After this period, systolic arterial pressure was measured by tail cuff plethysmography, as described previously,\textsuperscript{25} in both animal groups. Training was accomplished by subjecting the animals to plethysmography 4 times, performed every other day; data reported are from the last tail cuff session.

**Hyperinsulinemic Euglycemic Clamp**

Insulin resistance was quantified using HEC in control rats and rats fed a high-fructose diet for 8 weeks (n=8 for each group). All animals were fasted overnight for 16 hours before all experiments were conducted. Animals were anesthetized with isoflurane (2%) and maintained at 37°C with a thermistor-controlled heating pad. The carotid artery was catheterized to sample arterial blood, whereas the jugular and femoral veins were catheterized for infusion of insulin and glucose, respectively. Two baseline samples were obtained at 5-minute intervals, after which insulin (Novolin; 30 mU/kg per minute; Novo Nordisk Pharmaceuticals) infusion was started. Glucose infusion (100 μg/μL glucose in saline) was begun 5 minutes later, and samples were subsequently obtained at 5-minute intervals. Glucose infusion was adjusted so as to maintain a plasma level of 125 mg/dL. Clamp was achieved by 60 minutes and maintained for 30 minutes. The final 7 samples obtained over this 30-minute period were averaged and reported as the glucose infusion rate (mg/kg per minute) required to maintain euglycemic conditions in the face of hyperinsulinemia.

**Plasma Analysis**

Trunk blood samples were taken from overnight fasted animals. Samples were centrifuged at 2000g for 10 minutes at 4°C, and plasma was removed and aliquoted for the respective analytical determinations. Plasma glucose was measured with a standard glucometer (Precision Xtra) and expressed as milligrams per deciliter. Plasma total cholesterol and triglycerides were measured by individual kits (WakoUSA). Rat plasma insulin was assayed by rat-specific enzyme immunoassay (Alpco).

**Table 1. Baseline Metabolic Parameters in Sprague-Dawley Rats Maintained on Normal or High-Fructose Diet for 8 Weeks**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Fructose-Fed</th>
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</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>417±12</td>
<td>411±8</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>120±10</td>
<td>171±10*</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dL)</td>
<td>81±6</td>
<td>84±7</td>
</tr>
<tr>
<td>Serum triglyceride (mg/dL)</td>
<td>28±2</td>
<td>37±3*</td>
</tr>
<tr>
<td>Plasma insulin (μg/L)</td>
<td>0.7±0.1</td>
<td>1.8±0.5*</td>
</tr>
</tbody>
</table>

*P<0.05 vs control.

**Statistical Analysis**

Data are expressed as mean±SE. All baseline pressure and HR values are reported as the 24-hour average. Peak and nadir MAP of circadian rhythm were calculated as the average pressure from 11:00 PM to 1:00 AM and 11:00 AM to 1:00 PM, respectively. Statistical analysis was made by 2-way ANOVA, followed by Newman–Keuls test for multiple comparisons. Differences in systolic blood pressure, glucose infusion rate, plasma glucose, insulin, and lipids were analyzed by unpaired t test. Differences are considered significant at P<0.05.

**Results**

Animals were either maintained on a control diet or placed on a high-fructose diet for 8 weeks. Table 1 lists the pertinent metabolic features of the fructose-fed model. At the end of the 8-week period, body weights were similar between control and fructose-fed rats. Animals maintained on the high-fructose diet exhibited modest but significant hyperglycemia, hyperinsulinemia, and hypertriglyceridemia compared with the control group. Conversely, plasma cholesterol was not different between control and fructose-fed animals. Before the start of the high-fructose diet (week 0), 24-hour MAP, as determined by telemetry, was similar in animals from the 2 groups (Figure 1A). MAP did not change in rats maintained on the control diet (112±2 versus 109±2 mm Hg; week 0 versus week 8; NS) or in fructose-fed rats over the 8-week period (111±1 versus 114±2 mm Hg; week 0 versus week 8; NS). There was no significant difference in MAP between animals on the control versus high-fructose diets. Moreover, no differences in HR (Figure 1B), diastolic, systolic, and pulse pressures (Table 2), and blood pressure variability (diurnal variation; Table 3) between the 2 groups were found throughout the study. At the end of the 8-week period, systolic blood pressure was measured using tail cuff plethysmography. Systolic blood pressure was significantly elevated in the fructose-fed rats (162±5 versus 139±1 mm Hg; fructose-fed versus control; P<0.001; Figure 2).

The extent of insulin resistance caused by the high-fructose diet was determined using the HEC technique. After a bolus insulin infusion, plasma glucose was clamped at 125 mg/dL over a 30-minute period (60 to 90 minutes after insulin infusion; Figure 3A). The rate of glucose infusion necessary to maintain the plasma level of 125 mg/dL was ~45% less in the fructose-fed rats (22.9±3.6 versus 41.5±2.9 mg/kg per minute; fructose-fed versus control; P<0.01; Figure 3B).

**Discussion**

We tested the hypothesis that fructose-induced insulin resistance causes hypertension. Contrary to our original hypothe-
sis, we report that a high-fructose diet produced no change in baseline MAP in Sprague-Dawley rats monitored continu-
ously by telemetry. Conversely, systolic blood pressure measured by tail cuff plethysmography was significantly greater in fructose-fed rats compared with those animals fed a control diet. Despite the absence of any change in baseline MAP using telemetry, as expected, fructose-fed rats exhibited mild insulin resistance, hyperglycemia, hyperinsulinemia, and hypertriglyceridemia. Thus, whereas our results are in agree-
ment with previous reports documenting the metabolic ab-
normalities produced by fructose feeding, we show that a high-fructose diet does not elevate blood pressure in a common strain of normotensive rats.

An important distinction of the present study was the use of telemetry to monitor arterial pressure for a prolonged period and thereby assess the chronic effect of the high-fructose diet. As noted, we found that the average daily pressure did not change over the 8-week period with fructose feeding. Unlike studies using indwelling catheters, our measurements were continuous over the entire 8 weeks, starting ≥1 week after the surgery to implant the transmitter. Thus, blood pressure was not influenced by postsurgical trauma and encompassed measurements obtained throughout each day.

As a point of reference to the existing literature, we also measured systolic blood pressure by tail cuff plethysmography at the end of the feeding period. Systolic pressure was 23 mm Hg higher in fructose-fed animals compared with control, an increase comparable to that reported previously.6–13,16–20 Because of the contrasting results with tail cuff and telemetry, this raises the question whether the daily average pressure reported with telemetry conceals momentary differ-
ences in blood pressure that may be caused by the high-
fructose diet. We therefore analyzed indices of blood pressure lability in the telemetry-instrumented animals and observed that diurnal variation of blood pressure and the SD of blood pressure over a 24-hour period were not different between the 2 animal groups over the course of the study. Together, these data argue against the possibility that the reported 24-hour average masks any difference in blood pressure between the 2 groups that has been found previously with plethysmography.

Telemetry affords significant advantages for long-term blood pressure monitoring; nevertheless, there are several caveats to our study. Some,10,20,21 but not all,18,19 studies have found there is a latency before which the blood pressure

<table>
<thead>
<tr>
<th>Week</th>
<th>Control</th>
<th>High-fructose</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>95±1</td>
<td>94±1</td>
</tr>
<tr>
<td>8</td>
<td>90±2</td>
<td>95±2</td>
</tr>
</tbody>
</table>

TABLE 2. Diastolic, Systolic, and Pulse Pressures in Sprague-Dawley Rats Maintained on Normal or High-Fructose Diets for 8 Weeks

<table>
<thead>
<tr>
<th>Week</th>
<th>Control (mm Hg)</th>
<th>High-fructose (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>131±2</td>
<td>131±1</td>
</tr>
<tr>
<td>8</td>
<td>136±2</td>
<td>131±3</td>
</tr>
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</table>

Figure 1. Baseline MAP (A) and HR (B) in Sprague-Dawley rats maintained on either control or high-fructose diet for 8 weeks. MAP and HR were monitored continuously by telemetry. Points represent average values over a 24-hour period expressed at weekly intervals.

Figure 2. Comparison of systolic blood pressure (SBP) determined by tail cuff plethysmography in Sprague-Dawley rats after 8 weeks of being fed either control or high-fructose diet.

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<table>
<thead>
<tr>
<th>Week</th>
<th>Control (Peak MAP mm Hg)</th>
<th>High-fructose (Peak MAP mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>115±2</td>
<td>115±1</td>
</tr>
<tr>
<td>8</td>
<td>112±2</td>
<td>116±2</td>
</tr>
</tbody>
</table>

TABLE 3. Circadian Rhythm in Sprague-Dawley Rats Maintained on Normal or High-Fructose Diet for 8 Weeks

An important distinction of the present study was the use of telemetry to monitor arterial pressure for a prolonged period and thereby assess the chronic effect of the high-fructose diet. As noted, we found that the average daily pressure did not change over the 8-week period with fructose feeding. Unlike studies using indwelling catheters, our measurements were continuous over the entire 8 weeks, starting ≥1 week after the surgery to implant the transmitter. Thus, blood pressure was not influenced by postsurgical trauma and encompassed measurements obtained throughout each day.

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effects of the high-fructose diet are detected. In the present study, animals were maintained on the high-fructose diet for 8 weeks, thus extending the monitoring period used in previous studies. Despite this extended observation period, we found no change in the 24-hour MAP over this period. It remains possible that at some point beyond our 8-week monitoring period, baseline MAP may be significantly elevated in fructose-fed animals. Moreover, we tested the effect of a high-fructose diet only in male Sprague-Dawley rats, in which animals were placed on the diet starting at 12 weeks of age. Thus, our findings do not preclude the possibility that other factors such as strain, sex, age at the start of the diet, and additions to the fructose diet regimen such as salt, fat, or trace elements may render animals more susceptible to developing fructose-induced hypertension.

Insulin Resistance and Hypertension
Despite the fact that baseline MAP did not change, we found that the high-fructose diet produced metabolic abnormalities similar to those reported previously, albeit with minor differences. The most accurate assessment of the degree of insulin resistance is obtained using HEC technique. Our results using this technique suggesting that fructose feeding causes moderate insulin resistance are in close agreement with those reported previously. Therefore, it cannot be argued that the failure to detect an increase in baseline MAP was attributable to the lack of an overall effect of the diet. On the other hand, we cannot conclude that insulin resistance does not cause or contribute to hypertension under all conditions.

One explanation for the apparent dissociation between insulin resistance and blood pressure reported herein is that the degree of metabolic dysfunction in rats fed a high-fructose diet is not sufficient to yield an effect on blood pressure. Specifically, we found that plasma insulin and triglycerides were 2.5- and 1.3-fold greater, respectively, in fructose-fed rats compared with those on control diet. Moreover, the glucose infusion rate necessary to maintain euglycemia during hyperinsulinemic clamp was 45% less in the animals fed the high-fructose diet. Conversely, previous studies have reported that plasma insulin and triglycerides are 5- to 10-fold and 2.3- to 3.6-fold higher, respectively, and glucose infusion rate 85% lower in the obese Zucker rat, an animal model of the metabolic syndrome that has been shown using telemetry to develop moderate hypertension. Together, these data indicate the metabolic abnormalities found by us and others are mild compared with those seen in the obese Zucker rat. Because the obese Zucker rat exhibits a significant increase in baseline arterial pressure, it therefore remains possible that more severe insulin resistance may cause hypertension.

Nevertheless, numerous studies using the fructose-fed rat have demonstrated that insulin resistance causes pronounced vascular dysfunction, including increased vasoconstrictor sensitivity, suppressed endothelium-dependent relaxation and potassium channel function, and increased vascular superoxide production. Given our finding that baseline MAP does not change with fructose feeding, this would suggest that alterations in vascular function occur independent of hypertension and are most likely related to the metabolic abnormalities. Thus, it is conceivable that these alterations account for the increased stress-mediated pressor response using tail cuff plethysmography yet play no role in the long-term maintenance of arterial pressure.

Telemetry Versus Plethysmography
Our finding that fructose feeding has no effect on arterial pressure directly opposes a sizable body of literature stating that pressure is elevated. Because we found contrasting results using different methods to measure blood pressure, this highlights the potential to draw contrasting conclusions based on telemetry versus tail cuff plethysmography, necessitating a discussion of the respective advantages and disadvantages of each. These differences were detailed recently in a report from the Subcommittee of Professional and Public Education of the American Heart Association Council of High Blood Pressure Research.

A principal advantage of telemetry is that it involves wireless transmission of data and therefore obviates the need for animal handling or tethering. In the present study, aside from normal animal husbandry, activity in the holding rooms was kept to a minimum so as to avoid any disturbance to the animals. Thus, any variance about the reported 24-hour mean
is most likely attributable to the normal diurnal variation and not to observer interference. On the other hand, a major drawback associated with tail cuff measurement is the restraint and thermal stress imposed on the animal, leading to an increase in sympathetic output, and consequently, a rise in MAP. That the tail cuff technique itself can elicit a pressor response was demonstrated by Palaez et al.42 These authors found that the simultaneous measurement of systolic blood pressure by telemetry and plethysmography yielded similar values, but that these were elevated compared with telemetry alone. Because high-carbohydrate diets have been documented to elevate basal sympathetic nerve activity,11,43,44 a more plausible explanation for the reported hypertension using tail cuff measurements is an exaggerated stress response or impaired control of vascular resistance.

Tail cuff plethysmography measures systolic blood pressure over a short time frame. Yet, this value is generally taken to reflect the overall effect resulting from the experimental conditions, despite the significant error that can be introduced by moment-to-moment fluctuations in blood pressure. In several studies, direct cannulation yielded blood pressures comparable to those determined by plethysmography; thus, the authors contended this serves to validate measurements made by the tail cuff approach.8,9 Similarly, measurements made directly with arterial catheters in conscious animals over a brief baseline period indicated that pressure was higher than determined to elevate basal sympathetic nerve activity,11,43,44 a more plausible explanation for the reported hypertension using tail cuff measurements is an exaggerated stress response or impaired control of vascular resistance.

Perspectives

Using tail cuff plethysmography or short-term blood pressure measurements, a large body of literature has emerged suggesting that insulin resistance, as induced by high-sugar diets, can induce hypertension independent of obesity. Using gold standard techniques to assess blood pressure and insulin resistance, our data contradict the standing dogma. Despite moderate insulin resistance, whole body hemodynamics in telemetry-instrumented animals are unaffected by a high-fructose diet. Differences in systolic pressure found in previous studies and our own tail cuff data may reflect a differential response to stress; thus, conclusions based on tail cuff in insulin-resistant animals should be conservative. Whether insulin resistance contributes to the hypertension present in obesity or to the stress sensitivity of blood pressure should be a target for future study.

Acknowledgments

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