Heart

High Fructose Diet Increases Mortality in Hypertensive Rats Compared to a Complex Carbohydrate or High Fat Diet

Naveen Sharma, Isidore C. Okere, Monika K. Duda, Janean Johnson, Celvie L. Yuan, Margaret P. Chandler, Paul Ernsberger, Brian D. Hoit, and William C. Stanley

Background: Chronic hypertension leads to cardiac hypertrophy, heart failure, and premature death. Little is known about the impact of dietary macronutrient composition on hypertension-induced cardiac hypertrophy and mortality. We investigated the effects of consuming either a high complex carbohydrate diet, a high simple sugar diet, or a high fat diet on cardiac hypertrophy and mortality in hypertensive Dahl salt-sensitive (DSS) rats.

Methods: Rats were assigned to four diets: complex carbohydrate (CC; 70% starch, 10% fat, 20% protein by energy), high fat (FAT; 20% carbohydrates, 60% fat, 20% protein), high fructose (FRU; 70% fructose, 10% fat, 20% protein), and “western” (WES; 35% fructose, 45% fat, 20% protein). Hypertension was initiated by adding 6% NaCl (+S) to the chow of half the animals within each diet (n = 10 to 13/group). Tail cuff blood pressure measurements were assessed after 5 and 11 weeks of treatment, and echocardiography were assessed after 12 weeks of treatment.

Results: All rats fed a high salt diet had similar levels of hypertension (CC+S 220 ± 2 mm Hg, FAT+S 221 ± 3 mm Hg, FRU+S 221 ± 1 mm Hg, WES+S 226 ± 3 mm Hg). Echocardiography results show that the addition of salt to FRU resulted in increased regional wall thickness that was not observed in other dietary groups. All rats fed a low salt diet (CC, FAT, FRU, WES) and the FAT+S group survived 90 days. On the other hand, there was 90-day mortality in the WES+S group (18% mortality) and the CC+S group (30% mortality). In addition, FRU+S rats started dying after 45 days of salt feeding, and only 15% survived the full 90 days.

Conclusions: These results demonstrate that a high fructose diet consumed during hypertension increases mortality and left ventricular (LV) wall thickness compared to either a high fat, high starch, or a “western” diet. Am J Hypertens 2007;20:403–409 © 2007 American Journal of Hypertension, Ltd.

Key Words: Diet, heart failure, hypertension, hyper trophy, metabolism.

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findings are unclear; however, the influence of high levels of simple sugar in a hypertensive setting may enhance hypertrophy attributed to hypertension. Ingestion of simple sugars has also been observed to be a causative factor of hypertension. In recent years there has been a substantial increase in the amount of dietary mono- and disaccharide consumption due to increased intake of sucrose and high fructose corn syrup, common sweeteners used in the food industry. The increased prevalence of dietary sugars in developed countries has been cited as a potential factor for the increased occurrences of cardiovascular diseases.

The goal of the present study was to investigate whether the composition of dietary carbohydrates contribute to cardiac hypertrophy and mortality in hypertension. We hypothesized that a diet high in simple sugar will lead to increased cardiac hypertrophy and mortality in hypertensive rats compared to a high starch, a high fat, or a mixed “western” diet. Studies were performed in the well-established Dahl salt-sensitive (DSS) rat, which develops progressive LVH and mortality in response to dietary sodium.

**Methods**

**Experimental Design**

All procedures for this study were conducted according to the guidelines for the care and use of laboratory animals (NIH publication no. 85-23) and were approved by the Institutional Animal Care and Use Committee (IACUC) of Case Western Reserve University. This study was conducted on the DSS hypertensive rat model. The DSS rat is an animal model that develops systemic hypertension with increased intake of dietary sodium. This animal model offers the advantage of not requiring a surgical procedure to induce pressure overload and thus is devoid of any inflammatory responses from surgical trauma.

All personnel performing the echocardiographic, tail cuff blood pressure (BP), and left ventricular pressure measurements were blinded to treatment. In addition, offline analysis of the echocardiograms were also performed blinded to treatment. Male DSS rats (initial weight 300 to 320 g) were obtained at 9 to 11 weeks of age from Harlan (Indianapolis, IN), and were housed in controlled conditions (23°C ± 1°C) with a 12-h reverse light/dark cycle (6 AM to 6 PM) with free access to food and water. Initial pretreatment measurements were made for systolic arterial blood pressure BP and body mass before the rats being assigned to their respective dietary groups (n = 10 to 13 rats/group), and with the rats all fed standard lab chow (14% fat, 60% carbohydrates, 26% protein, 0.26% sodium; LabDiet, St. Louis, MO). After a week of receiving the low salt diets (complex carbohydrate [CC], high fat [FAT], high fructose [FRU], and “western” [WES]), chronic hypertension was initiated in half of the rats through the administration of salt in their diets (hypertension was initiated by adding 6% NaCl (+S) to the diet), as previously described. All rats were maintained on their assigned diets for 90 days until the terminal procedure. Rats were observed for activity and responsiveness each day, and those observed to be moribund were immediately anesthetized and euthanized for ethical reasons.

**Diets**

All diets were custom made and obtained from Research Diets Inc. (New Brunswick, NJ). The complex carbohydrate (CC) diet was composed of 70% carbohydrate (82% cornstarch, 18% maltodextrin), 10% fat (lard base: 37% saturated, 45% monounsaturated, 11% polyunsaturated), and 20% protein by energy. The high fat (FAT) diet consisted of 60% of total energy from fat comprised mainly of long chain saturated fatty acid from cocoa butter as previously described, 20% carbohydrates (65% maltodextrin, 35% sucrose), and 20% protein. The high fructose (FRU) diet contained 60% carbohydrates (87% fructose, 13% cornstarch), 20% protein, and 10% (lard base) fat. The “western” (WES) diet contained 45% fat (cocoa butter base), 35% carbohydrates (71% fructose, 29% maltodextrin), and 20% protein by energy. The salt content was 0.29% and 6.0% by mass in the low and high salt chows, respectively.

**Cardiovascular Measurements**

Systolic arterial BP was measured using the tail cuff method at baseline before treatment and after 5 and 11 weeks of treatment as previously described. The LV contractile function and dimensions were evaluated by echocardiography under isoflurane anesthesia after 12 weeks of treatment, as previously described in detail. The myocardial performance index was calculated as the sum of the isovolumic contraction and relaxation times divided by the ejection time.

**Metabolic Measurements**

After 63 days of treatment, 0.5 mL of blood was drawn from the tail vein using heparinized capillary tubes. Plasma glucose was measured using a commercial enzymatic spectrophotometer assay kit (StanBio, Boerne, TX) and plasma insulin was measured with a spectrophotometric immunoassay method (ALPCO Diagnostics, Salem, NH). After 90 days of treatment rats were anesthetized with isoflurane (1.5% to 2%) between 3 and 6 h after the initiation of the dark phase of the light/dark cycle, and left ventricular pressure was measured with a high fidelity catheter as previously described. Then a midline sternotomy was performed, and a 3-mL sample of blood was drawn from the inferior vena cava for plasma samples. Plasma fatty acids and triglyceride, and cardiac triglyceride were measured spectrophotometrically previously described. The heart was rapidly removed and the right ventricle was sliced away from the left ventricle and both sections were quickly weighed. Rats that died before 90 days of treatment underwent an autopsy within 24 h of
death. The LV and right ventricular (RV) weights of these rats were recorded before discarding the tissue.

**Statistical Analysis**

A two-way analysis of variance (ANOVA) followed by Bonferroni t tests was used to make comparison between all of the dietary groups both with and without the addition of salt. A two-way repeated measures ANOVA was used to make comparisons for serial tail cuff systolic BP measurements. Differences in mortality were assessed by a Kaplan-Meier survival curve with \( \chi^2 \) analysis (Graph Pad Prizm 4.0, Hearne Scientific Software, Chicago, IL). A \( P < .05 \) was accepted as statistically significant. All data are presented as means ± SEM.

**Results**

**Blood Pressure**

Systolic arterial BP was similar among groups before treatment (Fig. 1). After 5 and 11 weeks of treatments, rats fed a high salt diet had significant hypertension compared to rats fed the same diet without high salt and pretreatment values. In addition, treatment with FAT, FRU, and WES diets with high salt increased systolic arterial BP above pretreatment values (Fig. 1). There were no differences between 5 and 11 weeks within any treatment group. Heart rate was not different among treatment groups and was not different at all time points (data not shown).

**Survival Data**

All rats fed a low salt diet (CC, FAT, FRU, WES) and the FAT+S group survived 90 days on their respective diets (Fig. 2). However 82% (9 of 11) of WES+S and 70% (7 of 10) of CC+S survived, and only 15% (2 of 13) of FRU+S survived, indicating a significant and dramatic increase in mortality in the FRU+S group. Of the 17 rats that died prematurely, 7 were found moribund in there cage and immediately anesthetized and euthanized.

**Echocardiography**

Echocardiography measurements at 12 weeks of treatment indicate that all high salt groups had increased LV mass to body mass (LV/BM) ratios compared to the same diets with low salt (Table 1). In addition the FRU+S and WES+S groups had significantly higher myocardial performance indexes (MPI), a measure of combined systolic and diastolic dysfunction, compared to the same diets with low salt. The FAT+S and the WES+S groups had higher LV end-diastolic (EDV) and end-systolic (ESV) volumes compared to the same diets with low salt. The CC+S, FRU+S, and WES+S groups had lower velocity of circumferential shortening (Vcf) values, an echocardiographic index of LV systolic contractility, compared to diets with low salt. Rats in the FRU+S group had significantly decreased LV systolic contractile function as evidenced by a decrease in fractional shortening compared to the same diet with low salt. The FRU+S group had increased relative wall thickness compared to FRU alone, as well as to all other high salt groups.

**Body and Heart Masses**

Before treatment, rats in all groups had similar body masses (data not shown). Rats in the FRU and WES groups had less weight gain compared to the FAT group (Table 2). The CC+S and FAT+S groups had significantly less weight gain compared to the same diet groups with low salt. Conversely, the WES+S group had a larger weight gain compared to the same diet with low salt. The FRU and the WES groups had lower absolute LV masses and lower LV masses when normalized to body mass and tibial length compared to the CC and WES groups (Table 2). The addition of salt led to increased LVH in all dietary groups as assessed by LV mass normalized to body mass or tibial length (Table 2). There was no difference in RV mass with the addition of salt when normalized for body mass or
Table 1. Echocardiographic results measured at 12wks of treatment

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>LV/BM (mg/g)</th>
<th>EDV (mL)</th>
<th>ESV (mL)</th>
<th>MPI</th>
<th>Vcf (L/sec)</th>
<th>aFS (%)</th>
<th>EF (%)</th>
<th>RWT(a+p) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>9</td>
<td>3.02 ± 0.18</td>
<td>0.69 ± 0.05</td>
<td>0.13 ± 0.02</td>
<td>0.47 ± 0.02</td>
<td>6.64 ± 0.43</td>
<td>63 ± 3</td>
<td>81 ± 2</td>
<td>0.46 ± 0.01</td>
</tr>
<tr>
<td>CC+S</td>
<td>7</td>
<td>3.48 ± 0.19*</td>
<td>0.67 ± 0.03</td>
<td>0.16 ± 0.01</td>
<td>0.52 ± 0.05</td>
<td>5.40 ± 0.36*</td>
<td>53 ± 3</td>
<td>76 ± 2</td>
<td>0.51 ± 0.02</td>
</tr>
<tr>
<td>FAT</td>
<td>10</td>
<td>2.96 ± 0.10</td>
<td>0.62 ± 0.05</td>
<td>0.12 ± 0.01</td>
<td>0.47 ± 0.06</td>
<td>6.38 ± 0.30</td>
<td>58 ± 4</td>
<td>81 ± 1</td>
<td>0.52 ± 0.03</td>
</tr>
<tr>
<td>FAT+S</td>
<td>9</td>
<td>3.66 ± 0.16*</td>
<td>0.76 ± 0.05*</td>
<td>0.18 ± 0.02*</td>
<td>0.52 ± 0.04</td>
<td>5.67 ± 0.36</td>
<td>55 ± 4</td>
<td>76 ± 2*</td>
<td>0.50 ± 0.02</td>
</tr>
<tr>
<td>FRU</td>
<td>9</td>
<td>2.58 ± 0.23</td>
<td>0.60 ± 0.02</td>
<td>0.10 ± 0.01</td>
<td>0.54 ± 0.03</td>
<td>7.02 ± 0.16</td>
<td>60 ± 1</td>
<td>83 ± 1</td>
<td>0.42 ± 0.02</td>
</tr>
<tr>
<td>FRU+S</td>
<td>2</td>
<td>3.53 ± 0.09*</td>
<td>0.69 ± 0.03</td>
<td>0.17 ± 0.10</td>
<td>0.81 ± 0.47*</td>
<td>4.26 ± 0.34*</td>
<td>34 ± 12*</td>
<td>65 ± 3*</td>
<td>0.72 ± 0.31*</td>
</tr>
<tr>
<td>WES</td>
<td>9</td>
<td>2.75 ± 0.12</td>
<td>0.54 ± 0.04</td>
<td>0.09 ± 0.01</td>
<td>0.44 ± 0.04</td>
<td>7.08 ± 0.05</td>
<td>62 ± 4</td>
<td>84 ± 2</td>
<td>0.48 ± 0.02</td>
</tr>
<tr>
<td>WES+S</td>
<td>9</td>
<td>3.68 ± 0.19*</td>
<td>0.67 ± 0.06*</td>
<td>0.16 ± 0.01*</td>
<td>0.57 ± 0.03*</td>
<td>5.99 ± 0.28*</td>
<td>54 ± 03</td>
<td>77 ± 2*</td>
<td>0.54 ± 0.03</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. aFS = area of fractional shortening; EDV = LV end-diastolic volume; EF = ejection fraction; ESV = LV end-systolic volume; MPI = myocardial performance index ((isovolumic contraction time + isovolumic relaxation time)/ejection time); RWT(a+p) = relative wall thickness (anterior + posterior); Vcf = velocity of circumferential flow.

* P < .05 versus the same diet group with low salt; † P < .05 versus all other high salt groups; ‡ P < .05 versus FAT+S and WES+S.

Table 2. Heart weights normalized to body mass and tibial length measured during the terminal surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>n (at 90d)</th>
<th>Final Body Mass (mg)</th>
<th>Gain in Body Mass From Baseline (g)</th>
<th>Total LV Mass (mg)</th>
<th>Total LV Mass/Body Mass (mg/g)</th>
<th>Total LV Mass/Tibial Length (mg/cm)</th>
<th>Total RV Mass (mg)</th>
<th>Total RV Mass/Body Mass (mg/g)</th>
<th>Total RV Mass/Tibial Length (mg/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>11</td>
<td>476 ± 6</td>
<td>107 ± 6</td>
<td>1078 ± 20</td>
<td>2.26 ± 0.03</td>
<td>262 ± 10</td>
<td>214 ± 11</td>
<td>0.45 ± 0.03</td>
<td>52 ± 3</td>
</tr>
<tr>
<td>CC+S</td>
<td>7</td>
<td>435 ± 11*†</td>
<td>65 ± 10*</td>
<td>1280 ± 48*</td>
<td>2.94 ± 0.08*</td>
<td>315 ± 10*†</td>
<td>239 ± 16</td>
<td>0.55 ± 0.03*</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>FAT</td>
<td>10</td>
<td>495 ± 6</td>
<td>118 ± 6</td>
<td>1158 ± 30</td>
<td>2.34 ± 0.06</td>
<td>278 ± 6</td>
<td>236 ± 11</td>
<td>0.48 ± 0.02</td>
<td>57 ± 3</td>
</tr>
<tr>
<td>FAT+S</td>
<td>10</td>
<td>473 ± 10</td>
<td>95 ± 7*</td>
<td>1426 ± 33*</td>
<td>3.02 ± 0.07*</td>
<td>349 ± 9*</td>
<td>277 ± 17*</td>
<td>0.59 ± 0.04*</td>
<td>68 ± 5*</td>
</tr>
<tr>
<td>FRU</td>
<td>11</td>
<td>424 ± 9*</td>
<td>76 ± 7</td>
<td>897 ± 225</td>
<td>2.12 ± 0.05*†</td>
<td>218 ± 6§</td>
<td>204 ± 13</td>
<td>0.48 ± 0.03</td>
<td>50 ± 4</td>
</tr>
<tr>
<td>FRU+S</td>
<td>2 (90)</td>
<td>448 ± 31</td>
<td>60 ± 37</td>
<td>1423 ± 143*</td>
<td>3.17 ± 0.10*</td>
<td>343 ± 29*</td>
<td>271 ± 56*</td>
<td>0.60 ± 0.08</td>
<td>65 ± 12*</td>
</tr>
<tr>
<td>FRU+S</td>
<td>9 (47-90d)</td>
<td>417 ± 12</td>
<td>54 ± 10</td>
<td>1368 ± 31*</td>
<td>3.30 ± 0.08*†</td>
<td>332 ± 9*</td>
<td>256 ± 11*</td>
<td>0.62 ± 0.03</td>
<td>61 ± 3*</td>
</tr>
<tr>
<td>WES</td>
<td>10</td>
<td>424 ± 9†</td>
<td>65 ± 5§</td>
<td>898 ± 169</td>
<td>2.12 ± 0.03§</td>
<td>222 ± 5§</td>
<td>192 ± 9</td>
<td>0.45 ± 0.02</td>
<td>47 ± 2</td>
</tr>
<tr>
<td>WES+S</td>
<td>9</td>
<td>466 ± 11*</td>
<td>90 ± 10*</td>
<td>1355 ± 18*</td>
<td>2.94 ± 0.09*</td>
<td>327 ± 4*</td>
<td>238 ± 13*</td>
<td>0.57 ± 0.03</td>
<td>57 ± 3*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. Abbreviations as in text.

* P < .05 versus the same dietary group with low salt; † P < .05 versus FAT+S; ‡ P < .05 versus FAT; § P < .05 versus FAT and CC.
peak negative dP/dt in any of the groups fed low salt chow (Fig. 3, bottom panel). There was a decrease in peak negative dP/dt in FAT+S, FRU+S, and WES+S groups compared to the same dietary groups without the salt. Also, there was a further decrease in negative dP/dt in the FRU+S group compared to all other salt-added groups.

**Metabolic Results**

Plasma glucose levels were increased in the low salt FRU and WES groups compared to the low salt CC group (Table 3), and were reduced in the FRU+S and WES+S groups compared to the same diets with low salt. In addition, the FRU+S group had lower glucose levels compared to FAT+S. Plasma insulin was significantly reduced in the FRU+S group compared to FRU and the CC+S groups. Terminal samples indicate that plasma fatty acid and plasma triglyceride levels were elevated in the FAT and WES groups with either high or low salt compared to all other groups. The WES group has higher tissue triglyceride levels than CC, and the FAT+S and WES+S had lower tissue triglyceride levels compared to the same diets with low salt (Table 3).

**Discussion**

The primary finding of this study was that a diet high in fructose increased mortality in hypertensive rats compared to either a high fat, high starch, or a mixed “western” diet (Fig. 2). All rats on a high salt diet displayed the same levels of hypertension despite the diet (Fig. 1). Although previous studies have established that hypertension results in increased mortality in the DSS rat, the results of the present study illustrate that mortality can be profoundly affected by dietary macronutrient composition. The large mortality in the FRU+S group makes it impossible to draw strong conclusions with regard to LV function at the termination of the study. However, the two surviving FRU+S animals had greater relative LV wall thickness, increased MPI, and decreased positive and negative dP/dt compared to all other hypertensive animals, which is con-

**Left Ventricular Pressure**

There were no differences in peak positive dP/dt among any of the groups fed low salt chow (Fig. 3, top panel); however, the FRU+S group had a dramatic decrease in peak positive dP/dt compared to the FRU group, as well as all other salt-added groups. There was no difference in peak negative dP/dt in any of the groups fed low salt chow (Fig. 3, bottom panel). There was a decrease in peak negative dP/dt in FAT+S, FRU+S, and WES+S groups compared to the same dietary groups without the salt. Also, there was a further decrease in negative dP/dt in the FRU+S group compared to all other salt-added groups.

![FIG. 3. Peak positive (top) and peak negative dP/dt (bottom) measured by left ventricular catheterization during the terminal surgery. Filled bars represent diets with low salt, open rectangles represent diets with salt (+S). Data are the mean ± SEM. *P < .05 compared to the same dietary group with low salt. †P < .05 compared to all other diets with salt.](Image)

Table 3. Plasma glucose and insulin concentration taken at 9 weeks, and plasma FFA and triglyceride, and cardiac triglyceride measurements taken from terminal samples

<table>
<thead>
<tr>
<th>Group</th>
<th>Glucose (mM)</th>
<th>Insulin (pM)</th>
<th>Free Fatty Acids (µM)</th>
<th>Plasma TG (mg/mL)</th>
<th>Cardiac TG (µmol/g wet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>8.26 ± 0.13</td>
<td>405 ± 60</td>
<td>0.28 ± 0.02</td>
<td>1.77 ± 0.16</td>
<td>2.74 ± 0.37</td>
</tr>
<tr>
<td>CC+S</td>
<td>8.32 ± 0.26</td>
<td>299 ± 72</td>
<td>0.22 ± 0.04</td>
<td>0.91 ± 0.15</td>
<td>2.07 ± 0.27</td>
</tr>
<tr>
<td>FAT</td>
<td>8.84 ± 0.24</td>
<td>276 ± 60</td>
<td>0.60 ± 0.03†</td>
<td>2.65 ± 0.20†</td>
<td>3.22 ± 0.32</td>
</tr>
<tr>
<td>FAT+S</td>
<td>9.22 ± 0.35</td>
<td>150 ± 23</td>
<td>0.53 ± 0.06‡</td>
<td>3.33 ± 0.45‡</td>
<td>3.00 ± 0.28</td>
</tr>
<tr>
<td>FRU</td>
<td>9.63 ± 0.53**</td>
<td>355 ± 64</td>
<td>0.38 ± 0.04</td>
<td>2.45 ± 0.21</td>
<td>3.41 ± 0.33</td>
</tr>
<tr>
<td>FRU+S</td>
<td>7.75 ± 0.23†</td>
<td>116 ± 16*†</td>
<td>0.24 ± 0.06</td>
<td>1.83 ± 0.19</td>
<td>2.16 ± 0.55*</td>
</tr>
<tr>
<td>WES</td>
<td>9.99 ± 0.38**</td>
<td>236 ± 33</td>
<td>0.65 ± 0.05‡</td>
<td>3.37 ± 0.31‡</td>
<td>3.97 ± 0.31**</td>
</tr>
<tr>
<td>WES+S</td>
<td>8.81 ± 0.38*</td>
<td>134 ± 13</td>
<td>0.46 ± 0.07‡</td>
<td>3.57 ± 0.64‡</td>
<td>2.31 ± 0.31*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM.

* P < .05 versus all other diets with low salt; † P < .05 versus the same dietary group with low salt; ** P < .05 versus CC; †† P < .05 versus FAT+S; †‡ P < .05 versus CC+S; †‡ P < .05 versus CC, CC+S, FRU, FRU+S.
persistent with impaired cardiac function as the potential cause of accelerated mortality.

Hypertension was not observed in animals fed a low salt complex carbohydrate (CC) diet. Significant hypertension was observed with the other low salt diets (FAT, FRU, and WES). Previous studies have noted that diets that are high in either fructose or saturated fat can trigger moderate levels of hypertension. However, this degree of hypertension was significantly less than what was observed on the high salt diets and no LVH was observed, suggesting the level of pressure overload was not sufficient to trigger a hypertrophic response. High dietary fat consumption has been shown to be an independent contributor to hypertension in animal and human studies. It has also been well-documented that fructose alone can be a contributor to hypertension in rats. However, because there were no differences among diets in systolic BP with high salt administration, it suggests that there may be a maximum effect of salt feeding in this model.

We recently observed that DSS rats fed an 8% salt diet for 6 weeks had the expected salt-induced increases in BP and LV mass when fed a standard high carbohydrate lab chow, but significantly less LVH when fed a high fat diet, despite similar levels of hypertension. Moreover, fat-fed animals had increased cardiac contractile performance. In the present study the FAT+S group had similar LVH to the other high salt groups. There are several differences between the two studies: particularly the duration of hypertension (6 v 13 weeks); the nutritional composition of the high carbohydrate chows (a standard lab chow with a mix of sucrose and starch versus primarily starch [CC] or fructose [FRU]); and the salt concentration in the chow (6% v 8%). One limitation of the present investigation is that standard rodents were not included in the protocol, but rather high controlled high starch and high fructose chows were used, thus future studies should incorporate treatments groups on standard commercial chow.

The mechanism for increased mortality with fructose feeding is not clear. One possibility is that fructose feeding triggers greater LVH due to greater insulin-induced cardiac protein synthesis. Recent studies in transgenic mice show that LVH involves activation of the serine–threonine kinase Akt and its downstream targets. Insulin, which is elevated by carbohydrate ingestion, also activates Akt and stimulates cardiac gene expression and growth; however, insulin levels in fed animals were not elevated in the present study (Table 3). This may also provide a potential reason for the lower LV masses observed in the FRU and WES groups compared to both CC and FAT groups (Table 2). The lack of elevated insulin levels with fructose feeding in the present study is in contrast with previous studies with similar high fructose diets. This lack of hyperinsulinemia could be due to an altered feeding pattern, especially with the high salt chows, as suggested by the reduced weight gain in the CC+S and FAT+S groups, and a greater weight gain in the WES+S diet compared to the respective low salt chows. To assess the role of the insulin signaling pathway, future studies should be conducted in other pressure-overload models to eliminate the potentially confounding effects of high dietary salt in the present study.

In conclusion, a high fructose diet increased LV wall thickness, decreased LV contractile function, and increased mortality in hypertensive rats compared to rats fed a high starch, high fat, or mixed diet. Although previous studies have established that hypertension increases mortality in the DSS rat, the present investigation demonstrates that mortality can be profoundly affected by dietary macronutrient composition.

Acknowledgments

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References