Effects of a High-sucrose Diet on Body Weight, Plasma Triglycerides, and Stress Tolerance

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We examine the effects of feeding a high-sucrose diet on body weight gain, plasma triglycerides, and stress tolerance in rats. Feeding a high-sucrose (60%) diet for 2 weeks did not induce a greater body weight gain compared with that of standard diet when caloric intake was similar in ventromedial hypothalamic–lesioned obese and sham-operated lean animals. The high-sucrose diet elevated plasma triglycerides by increasing the triglyceride secretion rate and decreasing the fractional catabolic rate in both groups. In response to stress, feeding a high-sucrose diet for one week induced enhanced gene expressions of heat shock proteins (HSP 70 and 27) and suppressed NOX production in the brain, whereas the standard diet did not. Results suggest that feeding a high-sucrose diet does not induce obesity in lean rats or enhance weight gain in obese rats, if caloric intake is appropriate. The diet does elevate plasma triglycerides in lean and obese rats, but it may have the potential to improve stress tolerance.

Key words: high-sucrose diet, weight gain, plasma triglycerides, heat shock protein

A diet high in sucrose, which is a common food constituent in developed countries, is presumed to induce obesity.1–4 It is not clear, however, whether obesity is due to sucrose per se or to high caloric intake associated with sucrose intake; sucrose-containing foods are usually taken as desserts at the end of meals or as snacks between meals. The substitution of polysaccharides with high amounts of sucrose in the diet enhances plasma triglycerides (TG) in human5 and animal studies.6 A high-sucrose diet increases triglyceride secretion rate (TGSR),7,8 but little is known about plasma TG clearance. The mechanism by which a high-sucrose diet induces hypertriglyceridemia has not yet been clarified.

Bilateral lesions of the ventromedial nuclei in the hypothalamus (VMH) can produce obesity in rats.9 These rats shows several characteristic abnormalities, such as hyperphagia, hypertriglyceridemia, and hyperinsulinemia, neural-mediated hyperinsulinemia being the main cause of obesity.9,10

Humans and rodents sometimes overeat under physiologic stress, a condition termed stress-induced hyperphagia. Overeating is observed during mild tail pinch in rodents,11 and it is enhanced in the presence of a high-sucrose diet.12 These findings suggest that sucrose feeding may attenuate stress. Because the brain is vulnerable to a stressful environment, it induces several gene expressions and/or proteins related to protection of the stressor or as defenses to stress. The brain is the most important site where glucose is used. If a massive amount of glucose is consumed in the brain during stress, therefore, it is possible that feeding a high-sucrose diet contributes to counteracting stress. In the following, we report the results from studies of the effects of feeding a high-sucrose diet (60% by weight) on body weight gain, plasma triglycerides, and stress tolerance in lean and obese rats.

Effects of a High-sucrose Diet on Body Weight Gain in Lean and Obese Rats

There are three types of animal models of obesity: hypothalamic (central), genetically transmitted, and dietary-induced obesity. Dietary-induced obesity is usually produced by feeding a combination of high-fat and
high-sucrose diets.\textsuperscript{13–15} This mixed diet is called a “cafeteria diet”\textsuperscript{16} or “supermarket diet.”\textsuperscript{17} In this case, both high caloric intake and enhanced lipogenesis contribute to the development of obesity. Feeding of a high-fat diet alone is also used to produce of diet-induced obesity based on energy density.\textsuperscript{18–20} In the case of high-fat diet feeding, even isocaloric intake (i.e., the same caloric intake as the standard diet) can produce obesity.\textsuperscript{21,22} However, investigators debate whether feeding a high-sucrose diet alone can produce diet-induced obesity in animal studies. Kaga et al.\textsuperscript{23} reported that a high-sucrose diet induced obesity in mice with transiently increased caloric intake that overexpressed the neuropeptide Y (NPY) gene. Toida et al.\textsuperscript{24} and Russell et al.\textsuperscript{25} reported that no difference in body weight gain was observed by feeding an isocaloric high-sucrose diet to lean rats and to JCR:LA corpulent, one of five distinct strains incorporating the corpulent (\textit{CP}) gene first isolated by Koletsky rats, which are obese, hypertensive, and atherosclerotic rats. On the other hand, Franco-Colin et al.\textsuperscript{26} and Goodson et al.\textsuperscript{27} reported that feeding a high-sucrose diet induced less weight gain in lean rats with isocaloric and high caloric intake, respectively.

We postulated that these different results depended on caloric intake and that the effects of sucrose would be best described by isocaloric feeding of a high-sucrose diet. We therefore investigated the effects of a high-sucrose diet on body weight gain by comparing it with the effects of a high-fat diet fed to sham-operated lean and VMH-lesioned obese rats.\textsuperscript{28} Diets were either high in sucrose (60% sucrose by weight), high in fat (60% fat by weight), or standard (55% starch by weight).

All three groups of VMH-lesioned rats were heavier than the three groups of sham-operated rats 2 weeks after VMH lesions. Body weight gain in the high-fat diet–fed VMH-lesioned group was greater than the standard diet–fed VMH-lesioned and the high-sucrose diet–fed VMH-lesioned groups. No difference in body weight gain was observed between the latter two groups. Similar results in body weight gain were seen among the three sham-operated lean groups (Figure 1).

Total energy intake during the 2-week experiment in all three VMH-lesioned obese groups was greater than that in three sham-operated lean groups. Total energy intake in the high-fat diet–fed VMH-lesioned group was much higher than total energy intake in the standard diet–fed and high-sucrose diet–fed VMH-lesioned groups, whereas there was no difference in total energy intake between the latter two groups. Similar results were seen among sham-operated lean rat groups (Figure 2). Therefore, when the amount of caloric intake was similar, a high-sucrose diet, even if it contains 60% sucrose by weight, did not induce obesity in lean rats and did not enhance body weight gain in obese rats. This harmonizes with the results of Toida et al.\textsuperscript{24} and Russell et al.,\textsuperscript{25} who showed that isocaloric intake of a high-sucrose diet elicited no different body weight gain compared with body weight gain of standard diet–fed rats.

These results demonstrated that a high-sucrose diet does not induce obesity in lean animals or induce more weight gain in obese animals if the food intake is isocaloric. Sugar, therefore, which is found mainly in desserts or snack foods, does not induce obesity if total energy intake is appropriate. On the other hand, a high-fat, high-calorie diet induced obesity in lean rats and en-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Body weight gain in VMH-lesioned and sham-operated rats fed a standard, high-fat or high-sucrose diet. The number of rats in each group was six. VMH = ventromedial hypothalamus, Sham = without VMH lesion. Data adapted from Table 1 of Xue et al.\textsuperscript{28} ** $p < 0.01$ vs. rats fed a standard diet.}
\end{figure}
Enhanced weight gain in obese rats, consistent with previous results.18–20

**Effects of a High-sucrose Diet on Plasma Triglycerides**

Many reports have indicated that feeding a high-sucrose diet induces an increase in plasma TG in human and animals.8,29–32 Feeding high-fat diets also induce increased plasma TG in humans and animals.34–38 However, the precise mechanism by which hypertriglyceridemia is induced has not yet been elucidated.

Elevated plasma TG levels have been related to increased hepatic TG secretion, decreased TG removal, or both. There is evidence of the effects of high-sucrose diets and high-fat diets on TGSR; increased TGSR is indicated in rats fed a high-sucrose diet, whereas decreased or normal TGSR have been observed in rats fed a high-fat diet.37,38 Few reports describe the effect of high-sucrose and high-fat diets on post-heparin plasma lipoprotein lipase (LPL) in rats. None have examined simultaneously the effects of high-sucrose and high-fat diets on TG secretion and removal in VMH-lesioned obese and sham-operated lean rats.

Tissue LPL determines the fate of TG in the plasma, which enters adipocytes to be stored in adipose tissue, is used as fuel in muscle tissues, or remains in the blood leading to hypertriglyceridemia. Tissue LPL could be determined by heparin releasable LPL in the plasma.39 Little information is available about heparin releasable LPL in rats fed a high-sucrose diet.

We explored the mechanisms of hypertriglyceridemia induced by high-sucrose and high-fat diets by determining the TGSR and post-heparin plasma LPL activity in both VMH-lesioned obese and sham-operated lean rats.28 In VMH-lesioned obese and sham-operated lean rats, TG concentrations were much higher in the high-sucrose diet–fed groups than in the corresponding high-fat diet–fed or standard diet–fed groups. TG concentrations in the high-fat diet–fed groups were significantly higher than in the corresponding standard diet–fed groups (Figure 3).

TGSR in the high-sucrose diet–fed VMH-lesioned obese and sham-operated lean groups was higher than in the corresponding high-fat or standard diet–fed VMH-lesioned obese and sham-operated lean groups, but there was no difference between the latter two groups in VMH-lesioned obese and sham-operated lean rats (Table 1).

In VMH-lesioned obese rats, post-heparin LPL in the high-sucrose diet–fed and the high-fat diet–fed groups was higher than in the standard diet–fed group. No difference in LPL was observed between the former two groups. In sham-operated lean rats, LPL in the high-fat diet–fed group was significantly higher than in the high-sucrose diet–fed or standard diet–fed group, and LPL in the high-sucrose diet–fed group was higher than in the standard diet–fed group (Table 1).

Besides heparin-releasable LPL, functional catabolic rate (FCR) is another indicator of TG removal.40 FCR in the standard diet–fed and high-fat diet–fed VMH-lesioned obese groups was the highest and lowest in the three VMH-lesioned obese groups, respectively. Similar results were observed in sham-operated lean rats (Table 1). FCR was decreased in rats fed the high-fat diet and the high-sucrose diet, implying that half-life of TG in these animals was prolonged.

These results indicated that a remarkably decreased FCR contributed to the increased fasting plasma TG in the high-fat diet–fed VMH-lesioned obese and sham-operated lean rats by prolonging the half-life of plasma...
TG. In addition to decreased TG removal in spite of increased post-heparin LPL, the increased TGSR contributed to much higher TG in the high-sucrose diet–fed VMH-lesioned obese and sham-operated lean rats than in the corresponding high-fat diet–fed rats. The results of high TGSR in the high-sucrose diet is consistent with the results of Sebokova et al.,\(^3\) who showed elevated hepatic lipogenesis by feeding a high-sucrose diet. And the results of reduced TG removal in the high-sucrose diet are consistent with the results of Grant et al.,\(^5\) who showed slow intravenous lipid clearance.

In summary, a high-sucrose diet induced marked hypertriglyceridemia by increasing TG production and reducing TG removal, while a high-fat diet induced mild hyperglycemia by reducing TG removal.

**Effects of a High-sucrose Diet on Stress-related Phenomena**

Heat shock protein (HSP) was initially identified as a protein induced by heat.\(^{41}\) Several subtypes exist in the HSP family. Over-expression of HSP genes is induced not only by thermal stress but also by environmental stress.\(^{42,43}\) HSPs are thought to assist in the maintenance of cellular integrity and viability, prevention of protein unfolding, and enhancement of cell survival.\(^{42}\) HSP70 is one of the most well studied HSPs. This protein helps cells in the repair process after environmental stressors such as heat, ischemia, ultraviolet irradiation, and oxidative stress, and can act as molecular chaperones.\(^{42,44,45}\) HSP27 is one of the small HSPs, which are abundant in

![Heat shock protein (cerebral cortex)](image)

**Figure 4.** HSP27 and HSP70 mRNA levels in cerebral cortex of standard diet–fed rats and sucrose diet–fed rats in immobilization stress. The number of rats in each group was five. Data adapted from Figure 1 of Kageyama et al.\(^{49}\) \(*P < 0.05\) significant difference by one-way ANOVA.

**Table 1.** TGSR, LPL, and FCR in VMH-lesioned Obese and Sham-operated Lean Rats Fed a Standard High-fat or High-sucrose Diet

<table>
<thead>
<tr>
<th></th>
<th>UD</th>
<th>Sham</th>
<th>HF</th>
<th>Sham</th>
<th>VMH</th>
<th>Sham</th>
<th>HS</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGSR (mmol/L/h)</td>
<td>5.71 ± 1.28</td>
<td>3.43 ± 0.70</td>
<td>5.24 ± 2.26</td>
<td>2.32 ± 0.76</td>
<td>11.06 ± 1.04*†</td>
<td>5.06 ± 0.18†‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPL (pmol/L)</td>
<td>129 ± 24</td>
<td>83 ± 32</td>
<td>197 ± 24*</td>
<td>160 ± 20*</td>
<td>190 ± 7*</td>
<td>110 ± 9*†</td>
<td></td>
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</tr>
<tr>
<td>FCR (min⁻¹)</td>
<td>0.072 ± 0.020</td>
<td>0.056 ± 0.008</td>
<td>0.037 ± 0.009*</td>
<td>0.018 ± 0.006*</td>
<td>0.052 ± 0.005*§</td>
<td>0.035 ± 0.006*†</td>
<td></td>
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</tr>
</tbody>
</table>

The number of rats in each group was six. UD = standard diet, HF = high-fat diet, HS = high-sucrose diet, TGSR = triglyceride secretion rate, LPL = lipoprotein lipase, VMH = ventromedial hypothalamus, FCR = fractional catabolic rate.

Data adapted from Table 2 of Xue et al.\(^{28}\)

\(^*P < 0.05, \, *P < 0.01\) versus rats fed UD.

\(^\dagger P < 0.05, \, \dagger P < 0.01\) versus rats fed UF.
the brain, particularly in glial cells. Small HSPs may act as molecular chaperones or may protect against toxic chemicals or stress.\textsuperscript{46–48}

To explore the possibility that sucrose attenuates stress, we examined whether a sucrose diet alters HSP mRNA expression and nitrate and nitrite (NOx), hyperoxidant products, after immobilization stress by determining HSP27 and HSP70 mRNA and NOx concentrations in specific sites of rat brain.\textsuperscript{49} We also examined the effects a high-sucrose diet on stress-induced hyperglycemia.\textsuperscript{49}

The expression of HSP27 and HSP70 in the cerebral cortex was not induced in sucrose diet–fed rats without restraint stress. The expression of HSP70 mRNA increased with restraint stress in this tissue, but that of HSP27 mRNA did not. In standard diet–fed rats, on the

**Figure 5.** HSP27 and HSP70 mRNA levels in cerebellum of standard diet–fed and sucrose diet–fed rats in immobilization stress. Data adapted from Figure 2 of Kageyama et al.\textsuperscript{49} *$p < 0.05$ significant difference by one-way ANOVA.

**Figure 6.** HSP27 and HSP70 mRNA levels in hypothalamus of standard diet–fed and sucrose diet–fed rats in immobilization stress. Data adapted from Figure 3 of Kageyama et al.\textsuperscript{49} *$p < 0.05$ significant difference by one-way ANOVA.
other hand, neither the expression of HSP70 nor HSP27 mRNA was altered (Figure 4).

The expression of HSP70 mRNA in the cerebellum was significantly suppressed in sucrose diet–fed rats compared with that in standard diet–fed rats without restraint stress. The expressions of HSP70 and HSP27 were significantly enhanced by restraint stress in the cerebellum of sucrose diet–fed rats, whereas they were not enhanced by restraint stress in standard diet–fed rats (Figure 5).

The expressions of HSP27 and HSP70 mRNA in the hypothalamus were not induced in sucrose diet–fed rats without restraint stress. These expressions were significantly enhanced by restraint stress in the hypothalamus of sucrose diet–fed rats; however, no expressions were induced in all three tissues in standard diet–fed rats (Figure 6).

NOx concentrations in the cerebral cortex and cerebellum were not altered in the sucrose diet–fed or standard diet–fed rats after the immobilization stress; however, NOx concentrations were reduced in the hypothalamus in sucrose diet–fed rats. Fukudo et al. suggested that an increase in HSP by stress plays a protective role against stress in a vulnerable organ such as brain. NOx are the products of stress. Thus, our findings suggest that sucrose diets have the potential to attenuate stress.

No differences were observed in plasma glucose before and after the immobilization stress between rats fed a high-sucrose diet and rats fed a standard diet, although plasma glucose increased after the immobilization stress in standard diet–fed rats. Fukudo et al. thus, a high-sucrose diet did not modify stress-induced hyperglycemia.

Conclusion

The results of our studies suggest that a high-sucrose diet does not induce obesity in lean rats, and does not enhance weight gain in obese rats if caloric intake is appropriate, but does increase plasma TG. In rats under restraint stress, sucrose feeding has a favorable effect on modulating stress-related effects in the brain.
