Effect of Sucrose on Cisplatin-induced Fatigue-like Behavior in Mice: Comparison With Fructose and Glucose

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Abstract. Background/Aim: Fatigue is the most common symptom in patients with cancer undergoing radiation therapy or cancer chemotherapy. However, cancer-related fatigue remains undertreated and poorly understood. Materials and Methods: Mice were administered a single dose of cisplatin (10 mg/kg, intraperitoneally) or saline (as a control) and then treated with sucrose, fructose, glucose (each at 500 or 5,000 mg/kg, orally), or saline (control) daily for 4 days. cisplatin-induced fatigue-like behavior was investigated by assessment of running activity on a treadmill. The influence of glucose intake on tumor growth was also examined in Lewis lung carcinoma (LLC)-bearing mice. Results: Administration of sucrose and glucose improved cisplatin-induced fatigue-like behavior in mice, whereas administration of fructose showed only slight antifatigue effects. Although glucose-fed mice showed increased tumor growth, this was balanced out by the powerful cytotoxicity of cisplatin. Conclusion: Sucrose, and especially glucose, may improve patient quality of life during treatment with anticancer agents by preventing fatigue without interfering with the antitumor effects of cisplatin.

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Cisplatin, currently one of the most effective anticancer agents, is associated with side-effects, such as nausea, vomiting, and anorexia, which may lead to body weight loss. In a clinical report, body weight loss was shown to be the most important risk factor for compliance with adjuvant chemotherapy in patients with gastric cancer (1). Therefore, nutritional interventions for patients with cancer are recommended. The application of nutritional therapy in combination with cancer chemotherapy has been reported since the 1970s, at which time combined hyperalimentation and chemotherapy were reported to aid cancer patient management (2, 3).

Cancer-related fatigue is a common symptom experienced by patients with cancer (4); it is complicated by several factors, including those caused by tumors and cancer treatments and those associated with symptoms such as insomnia, depression, and pain. Improving nutrition addresses fatigue and is often easier to apply than other interventions (4). However, only preliminary studies exist on the effects of diet and dietary supplements in cancer survivors experiencing fatigue.

Glycogen stores in the liver and skeletal muscle are depleted by exercise (5) and depletion of endogenous carbohydrate stores is associated with fatigue. A previous report showed that carbohydrate intake during running exercise improves endurance and delays fatigue in humans and rodents (5); in other words, replenishment of glycogen stores in the liver and skeletal muscle affects running activity. Thus, glycogen replenishment seems to play an important role in recovery from fatigue.

Previously, we found that glucose prevented cisplatin-induced fatigue-like behavior in mice, whereas a similar preventive effect was not observed in mice given olive oil (6). Warburg et al. found that compared with normal cells,
most cancer cells rely more heavily on glycolysis than oxidative phosphorylation to produce energy, even under normoxic conditions (7). In other words, cancer cells are more dependent on glucose than normal cells and increased glucose uptake is important for tumor growth. In previous experiments with mouse models of lung adenocarcinoma, deletion of either glucose transporter 1 (Glut1) or Glut3, which are highly expressed in tumor cells, did not impair tumor growth, whereas combined deletion of these two transporters reduced tumor development (8). Overall, glucose is considered to prevent cisplatin-induced fatigue but potentially enhance tumor growth (9).

The aim of the present study was to determine whether sucrose or fructose might prevent cisplatin-induced fatigue-like behavior in mice in a similar manner to the administration of glucose. The influence of glucose intake on tumor growth was also examined in Lewis lung carcinoma (LLC)-bearing mice.

**Materials and Methods**

**Animals.** Male C57BL/6N mice (7 weeks old at the time of the experiments) were purchased from Japan SLC (Shizuoka, Japan). The animals were housed in groups of five or six per cage, and food and water were provided ad libitum. The room temperature was controlled at 23°C±1°C, and a 12 h light/12 h dark cycle was maintained (lights on from 8.00 am to 8.00 pm). All experimental protocols were approved by the Institutional Animal Care and Use Committee of Tokyo University of Science (approval numbers: Y19049 and Y20037), and all efforts were made to reduce the number of animals used and their suffering.

**Drugs.** The drugs used in the present study were purchased from the following manufacturers: cisplatin solution for injection (0.5 mg/ml) from Pfizer Japan Inc. (Tokyo, Japan); sucrose and D(-)-fructose from FUJIFILM Wako Pure Chemical Industries (Osaka, Japan); and glucose from FUSO Pharmaceutical Industries, Ltd. (Osaka, Japan). Sucrose, fructose, and glucose were dissolved in distilled water. All drugs were administered at a volume of 10 ml/kg, except cisplatin (20 ml/kg).

**Treatment.** Mice were administered a single dose of cisplatin (10 mg/kg, intraperitoneally) or saline (0.9% sodium chloride as a control). Subsequently, mice were administered a saline control or treatments of sucrose, fructose, or glucose (each at 500 or 5,000 mg/kg) once daily per os (p.o.) for 4 days. Body weights were recorded daily for 5 days. The effects of cisplatin and carbohydrates were examined while referring to their pharmacological potency as described previously (6).

**Treadmill fatigue test.** To measure fatigue, we modified a previously reported method (6). The percentage of running performance was measured between the pretest running potential (i.e., the pre-value) and the running potential after cisplatin treatment (i.e., the post-value). The treadmill fatigue test protocol was performed as previously described (6). Briefly, 2 weeks before the treadmill fatigue test, mice were subjected to the protocol (Table 1), and only animals that ran more than 460 m (26 m/min × 5 min) and less than 750 m (30 m/min × 5 min) were selected for use in the present study (the collected data comprised the pre-values). At 24 h after the final dose of saline, sucrose, fructose, or glucose, fatigue-like behavior was assessed again in the tested mice using treadmill exercise as an index of whole-body exercise capacity (the collected data comprised the post-values). During the treadmill test, each mouse was forced to run on a motor-driven treadmill (TMS-2; Melquest, Toyama, Japan). The running performance percentage [(post-value running distance/pre-value running distance) + (post-value running time/pre-value running time) ×0.5×100] was calculated for each animal.

**Measurement of liver glycogen content.** Liver glycogen content was measured in different animals from those used in the treadmill fatigue test. At 24 h after the final dose of saline, sucrose, fructose, or glucose, nonfasted mice were killed under deep isoflurane anesthesia. Then their livers were removed and weighed (wet weight). Liver glycogen content was measured as previously described (6). Liver tissue (600 mg) was ground in preparation for extraction. For hydrolysis of glycogen, 1.0 ml of the extract was heated with 1.2 ml of concentrated HCl for 2 h at 100°C. After neutralization of the HCl with alkali and adjustment of the volume to 2.5 ml with water, the resulting glucose in solution was measured using a glucose sensor (Precision Xceed; Abbott Japan Co., Ltd., Chiba, Japan).

**Blood analysis.** Blood was analyzed in different animals from those used in the treadmill fatigue test. At 24 h after the final dose of saline, fructose (5,000 mg/kg), or glucose (5,000 mg/kg), blood samples were extracted from the tail veins of 2-h fasted mice. From these samples, blood glucose and ketone (β-hydroxybutyrate) levels were measured using a Precision Xceed blood glucose and ketone monitoring system (Abbott Japan Co., Ltd., Chiba, Japan).

In addition, 24 h after the final dose of saline, fructose (5,000 mg/kg), or glucose (5,000 mg/kg), blood was collected from 2-h fasted mice under 3% isoflurane anesthesia; blood samples were sent to Nagahama LSL (Shiga, Japan) for measurement of serum levels of total cholesterol, triglyceride, and non-esterified fatty acid (NEFA).

**Tumor cells.** LLC cells (Riken Cell Bank, Tsukuba, Japan) were cultured in Dulbecco’s modified Eagle’s medium containing low glucose, L-glutamine, phenol red (FUJIFILM Wako Pure Chemical Industries), 10% fetal bovine serum (Capricorn Scientific GmbH, Dayton, OH, USA) for 2 weeks in the presence of 10% fetal bovine serum; the cells were then cultivated to 95% confluence. The cells were used in the present study (the collected data comprised the pre-values). At 24 h after the final dose of saline, sucrose, fructose, or glucose, fatigue-like behavior was assessed again in the tested mice using treadmill exercise as an index of whole-body exercise capacity (the collected data comprised the post-values). During the treadmill test, each mouse was forced to run on a motor-driven treadmill (TMS-2; Melquest, Toyama, Japan). The running performance percentage [(post-value running distance/pre-value running distance) + (post-value running time/pre-value running time) ×0.5×100] was calculated for each animal.

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Subcutaneous tumor model. LLC-bearing mice were produced as previously described (10). Briefly, LLC cells were suspended in 0.1 ml of D-PBS (pH 7.4) at a density of 1×10^6 cells and then mixed with 0.1 ml of Corning Matrigel® Growth Factor Reduced Basement Membrane Matrix (Catalog #354230; Corning, NY, USA). This suspension mixture (0.2 ml) was transplanted subcutaneously into the right flank of anesthetized (3% isoflurane) mice. After the implantation of LLC cells, the animals were individually housed. Subsequently, tumor volume (length × width × height)/2 was measured at 8, 10, 12, 14, and 16 days using a caliper.

To evaluate the effects of glucose on tumor growth, high-glucose groups were presented with a 30% glucose solution instead of water on day 0 to 16 after the implantation of LLC cells. In addition, to evaluate antitumor effects, mice were treated with a single dose of cisplatin (10 mg/kg, intraperitoneally) or saline on day 8 after the implantation of LLC cells. Hydration with saline (10 ml/kg, p.o.) was started together with cisplatin and applied once daily for 4 days.

**Statistical analysis.** Results are expressed as the mean ± standard error of the mean (SEM). Differences were evaluated by one-way or two-way analysis of variance (ANOVA) followed by Tukey’s multiple comparison tests. A p-value of less than 0.05 was considered significant. All statistical analyses were performed in Prism 8 for macOS (GraphPad Software, San Diego, CA, USA).

**Results**

**Treadmill fatigue test.** Figure 1A shows the experimental timeline. The running activity during the treadmill test was significantly reduced in the cisplatin–saline group compared with that in the saline–saline (control) group (Figure 1B; one-way ANOVA, F[3, 20]=17.43, p<0.0001; Tukey’s test, p<0.005 vs. control group). However, these reductions were dose-dependently and significantly improved in the cisplatin–sucrose–treated group (50 or 5,000 mg/kg) groups (Figure 1B; Tukey’s test, p<0.05 vs. cisplatin–saline group). Administration of sucrose (50 or 5,000 mg/kg) slightly ameliorated cisplatin-induced fatigue-like behavior in a dose-dependent manner, although not to a statistically significant extent (Figure 1C; one-way ANOVA, F[3, 20]=7.77, p=0.0012; Tukey’s test, p<0.005 vs. control group). In contrast, administration of glucose (500 or 5,000 mg/kg) exhibited a significant preventive effect against cisplatin-induced fatigue-like behavior (Figure 1D; one-way ANOVA, F[3, 20]=10.40, p=0.0002; Tukey’s test, p<0.005 vs. control group; p<0.05 and p<0.01 vs. cisplatin–saline group).

**Cisplatin-induced body weight loss.** Cisplatin administration led to a decrease in the body weight of mice (Table II). Daily administration of sucrose, fructose, or glucose slightly but not sufficiently restored the body weight loss caused by cisplatin (Table II).

**Liver weight and liver glycogen content.** In the cisplatin–saline group, the liver weight of mice significantly decreased compared with that of mice in the control group; liver weight also decreased in the cisplatin–sucrose–treated groups (Figure 2A; one-way ANOVA, F[3, 20]=3.61, p=0.0313; Tukey’s test, p<0.05 vs. control group). Similarly, cisplatin administration significantly reduced liver glycogen content (Figure 2B; one-way ANOVA, F[3, 20]=22.98, p<0.0001; Tukey’s test, p<0.005 vs. control group). In both cases, cisplatin–sucrose treatments significantly restored liver weight and glycogen content (Figure 2B; Tukey’s test, p<0.05 and p<0.005 vs. cisplatin–saline group). In contrast, although the cisplatin–saline group showed a significant reduction of liver weight (Figure 2C; one-way ANOVA, F[3, 20]=5.16, p<0.0083; Tukey’s test, p<0.05 vs. control group) and liver glycogen (Figure 2D; one-way ANOVA, F[3, 20]=47.98, p<0.0001; Tukey’s test, p<0.005 vs. control group) compared to the control group, administration of fructose did not improve cisplatin-induced liver weight reduction (Figure 2C) or liver glycogen depletion (Figure 2D). Similarly to our previous results (6), administration of glucose did not significantly improve the reduction in liver weight caused by cisplatin (Figure 2E; one-way ANOVA, F[3, 20]=5.42, p=0.0068; Tukey’s test, p<0.001 vs. control group; not significant vs. cisplatin–saline group), but it did improve the cisplatin-induced reduction in liver glycogen content (Figure 2F; one-way ANOVA, F[3, 20]=38.46, p<0.0001; Tukey’s test, p<0.005 vs. control group; p<0.01 and p<0.005 vs. cisplatin–saline group).

**Effect of glucose on tumor growth in LLC-bearing mice.** Figure 3A shows the experimental timeline. As shown in Figure 3B, intake of 30% glucose solution significantly enhanced tumor growth in LLC-bearing mice when compared with that observed in control (saline–water-treated) mice (Figure 3B; two-way ANOVA: column factor, p<0.0001; time factor, p<0.0001; interaction, p<0.0001). Tukey’s test, p<0.05 and p<0.01 vs. control group). No significant difference in body weight was observed between the two groups (Figure 3C). In the saline–glucose-treated group, mice drank 5.6±0.20 ml of 30% glucose solution per day. Conversely, when cisplatin was administered on day 8, tumor growth was suppressed compared with the growth observed in control mice (Figure 3B; Tukey’s test, p<0.05, p<0.01, and p<0.005 vs. control group). Interestingly, no significant difference was found in tumor growth between the cisplatin–glucose-treated and the cisplatin–water-treated groups (Figure 3B). Cisplatin-induced weight loss was observed in both the cisplatin–glucose and cisplatin–water groups, but this was recovered by day 16 (Figure 3C). In the cisplatin–glucose-treated group, mice drank 4.9±0.68 ml of 30% glucose solution per day.
Figure 1. Experimental timeline (A). Effects of sucrose (B), fructose (C), and glucose (D) in mice subjected to a treadmill fatigue test after treatment with cisplatin (CDDP). Each column represents the mean±standard error of the mean for six mice. Statistical analyses were performed with one-way analysis of variance followed by Tukey's multiple comparisons tests. Significantly different at: ***p<0.005 vs. the control group; #p<0.05, ##p<0.01, and ###p<0.005 vs. the CDDP–saline group.
inhibition of phosphorylase by fructose 1-phosphate (13). However, an even earlier report indicated that the administration of glucose rather than fructose increases liver glycogen depletion. Moreover, it is converted to glyceraldehyde and dihydroxyacetone phosphate by fructose 1-phosphate via fructokinase and then to cotransporter 1 and that of fructose is mediated by GLUT5 for carbohydrate and lipid metabolism, include a shift in the balance from oxidation to esterification of NEFA (12).

Discussion

Both our previous report (6) and the current study confirmed that the administration of glucose produces antifatigue effects associated with the prevention of liver glycogen depletion. Similar to the effects of glucose, administration of sucrose produced antifatigue effects in mice subjected to a treadmill fatigue test. Sucrose, a disaccharide consisting of one glucose and one fructose molecule, is digested by sucrase. We confirmed that the antifatigue effect of sucrose was attenuated by co-administration of acarbose (800 mg/kg, p.o.), which is an alpha-glucosidase inhibitor (data not shown). In contrast to glucose, administration of fructose produced only a slight antifatigue effect. These results indicate that in the antifatigue effects induced by sucrose, the contribution of glucose is greater than that of fructose.

Intestinal glucose absorption is mediated by sodium–glucose cotransporter 1 and that of fructose is mediated by GLUT5 (11). Both glucose and fructose are transported into the blood vessels via GLUT2 (11). Fructose, which exhibits different metabolic properties from those of glucose, is mainly delivered to and metabolized in the liver. Moreover, it is converted to fructose 1-phosphate by fructokinase and then to glyceraldehyde and dihydroxyacetone phosphate by fructose 1-phosphate aldolase (12). These steps, which have consequences for carbohydrate and lipid metabolism, include a shift in the balance from oxidation to esterification of NEFA (12).

In 1987, Youn et al. reported that administration of fructose inhibits the degradation of liver glycogen via allosteric inhibition of phosphorylase by fructose 1-phosphate (13). However, an even earlier report indicated that the administration of glucose rather than fructose increases liver glycogen content in rats (14). In the present study, administration of fructose did not sufficiently increase liver glycogen levels following cisplatin-induced liver glycogen depletion. Instead, administration of fructose increased the blood NEFA level (Table III). Major pathways of fructose metabolism involve conversion to glucose and lipids. Usually, the majority of fructose is metabolized by the Hers pathway as glucose and the remaining amount as fructose (11).

However, excessive consumption of fructose would result in increased endogenous glucose production and fatty acid synthesis in the liver (11). Fructose supplementation has been reported to uniquely up-regulate sterol regulatory element-binding protein and expression of downstream fatty acid synthesis genes (15). In the present study, administration of high doses of fructose likely led to most fructose accumulating in the liver. Additionally, these fructose doses may have increased the NEFA level via fatty acid synthesis. However, we did not evaluate these pathways, nor did we determine whether fructose up-regulated sterol regulatory element-binding protein in our mice; these are limitations of our study that should be the focus of future research.

Although both carbohydrates and lipids provide energy for exercise, glucose availability is regulated directly in relation to exercise intensity, whereas the regulation of fat metabolism seems to be more complex (16). Both administration of fructose and glucose improved cisplatin-induced fatigue-like behavior in the current study. Nevertheless, the effects were stronger with glucose than with fructose, suggesting that liver glycogen synthesis by glucose may be more efficient than fatty acid synthesis by fructose for maintaining running activity.

We showed that sucrose and particularly glucose can improve cisplatin-induced fatigue-like behavior in mice. The effect of glucose in this respect may be partly associated with a reduction in cisplatin cytotoxicity. Therefore, determining whether continuous administration of glucose affects the antitumor effect of cisplatin was necessary. Glucose intake has been shown to increase tumor growth (9). Indeed, intake of 30% glucose solution in our study increased tumor growth in LLC-bearing mice. In a previous report, C57BL/6 mice were shown to consume greater amounts of sucrose solution at 8% and 16%, followed by 32% (17); we expected that mice would drink too much of 8% and 16%, but not 32%. Based on this report, we used a 30% glucose solution to examine extreme effects. The tested mice drank approximately 5 ml of 30% glucose solution daily (equivalent to about 60 g/kg). This dose was >10-fold higher than the highest glucose dose (5,000 mg/kg, p.o.) that showed

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**Table II. Cisplatin (CDDP)-associated loss of body weight in mice (g) (n=6; mean±standard error of the mean).**

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline + saline (control)</td>
<td>21.8±0.35</td>
<td>21.6±0.47</td>
<td>22.0±0.31</td>
<td>21.9±0.37</td>
<td>21.9±0.46</td>
</tr>
<tr>
<td>CDDP + saline</td>
<td>23.5±0.47</td>
<td>22.8±0.47</td>
<td>21.9±0.47</td>
<td>20.9±0.41</td>
<td>20.4±0.40</td>
</tr>
<tr>
<td>CDDP + sucrose (500 mg/kg)</td>
<td>22.6±0.67</td>
<td>21.6±0.53</td>
<td>21.2±0.55</td>
<td>21.0±0.57</td>
<td>20.8±0.55</td>
</tr>
<tr>
<td>CDDP + sucrose (5,000 mg/kg)</td>
<td>23.1±0.56</td>
<td>21.9±0.51</td>
<td>21.4±0.54</td>
<td>21.2±0.64</td>
<td>21.1±0.69</td>
</tr>
<tr>
<td>CDDP + fructose (500 mg/kg)</td>
<td>21.4±0.34</td>
<td>20.3±0.20</td>
<td>19.7±0.14</td>
<td>18.9±0.18</td>
<td>18.7±0.23</td>
</tr>
<tr>
<td>CDDP + fructose (5,000 mg/kg)</td>
<td>23.1±0.57</td>
<td>21.7±0.58</td>
<td>21.2±0.66</td>
<td>21.0±0.74</td>
<td>20.8±0.79</td>
</tr>
<tr>
<td>CDDP + glucose (500 mg/kg)</td>
<td>22.5±0.50</td>
<td>21.7±0.52</td>
<td>21.0±0.49</td>
<td>20.6±0.46</td>
<td>20.4±0.47</td>
</tr>
<tr>
<td>CDDP + glucose (5,000 mg/kg)</td>
<td>22.5±0.43</td>
<td>22.1±0.35</td>
<td>21.4±0.43</td>
<td>21.1±0.35</td>
<td>20.7±0.38</td>
</tr>
</tbody>
</table>
antifatigue effects. However, the increased tumor growth induced by glucose in mice was balanced out by the powerful cytotoxicity of cisplatin. It was also a concern that the effect of glucose on cisplatin-induced fatigue-like behavior might be due to the attenuation of the cytotoxicity of cisplatin, but these results confirm that this was not the case.

In conclusion, administration of sucrose improved cisplatin-induced fatigue-like behavior (associated with weight loss) in mice. Weight loss is considered one of the common side-effects of cancer chemotherapy, and anticancer agent-induced weight loss may cause fatigue. These results suggest the possibility that although carbohydrate supplementation failed to prevent...
loss of body weight, it may provide significant performance benefits in exercise, including reducing fatigue. The contribution of glucose to this effect was higher than that of fructose. Moreover, the use of liver glycogen might be more efficient than the use of blood NEFAs for the maintenance of running activity. Carbohydrate may improve the prognosis of patients treated with anticancer agents through preventing cancer-related fatigue, but not body weight gain.

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Figure 3. Experimental timeline (A). Effects of glucose or water intake with administration of cisplatin (CDDP) or saline on Lewis lung carcinoma (LLC)-bearing mice. Tumor volume was measured at 8, 10, 12, 14, and 16 days using a Vernier caliper. Tumor volume = length × width × width/2 (B). CDDP-treated mice showed a lower body weight relative to the body weight of control mice (C). Each point represents the mean±standard error of the mean for five mice. Statistical analyses were performed with two-way analysis of variance (ANOVA) followed by Tukey’s multiple comparisons test. Significantly different at: *p<0.05 and **p<0.01 vs. the control group.

Table III. Changes in blood biochemical analysis profile following cisplatin (CDDP) treatment (n=6; mean±standard error of the mean).

<table>
<thead>
<tr>
<th>Group</th>
<th>GLU (mg/dl)</th>
<th>β-OHB (mmol/l)</th>
<th>T-CHO (mg/dl)</th>
<th>TG (mg/dl)</th>
<th>NEFA (μEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline-saline (Control)</td>
<td>199±11.3</td>
<td>0.58±0.07</td>
<td>76.5±5.54</td>
<td>51.0±11.80</td>
<td>696.7±49.49</td>
</tr>
<tr>
<td>CDDP-saline</td>
<td>159±6.7</td>
<td>0.85±0.06</td>
<td>87.7±6.06</td>
<td>35.7±6.34</td>
<td>652.2±29.25</td>
</tr>
<tr>
<td>CDDP-fructose (5000 mg/kg)</td>
<td>189±8.2</td>
<td>0.65±0.05</td>
<td>86.2±5.19</td>
<td>39.2±5.53</td>
<td>878.5±74.41</td>
</tr>
<tr>
<td>CDDP-glucose (5000 mg/kg)</td>
<td>163±9.6</td>
<td>0.85±0.11</td>
<td>103.8±4.79</td>
<td>30.7±4.38</td>
<td>682.3±26.46</td>
</tr>
</tbody>
</table>

GLU: Glucose; β-OHB: β-hydroxybutyrate; T-CHO: total cholesterol; TG: triglyceride; NEFA: non-esterified fatty acid.
Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors’ Contributions

K.Y. designed the experiments and wrote the article. R.K., H.S., E.I., and H.N. conducted some of the in vivo studies. N.F., H.S., and K.N. provided scientific and technical advice. All of the Authors discussed the results and commented on the manuscript. All Authors critically reviewed the content and approved the final version submitted for publication.

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References


17 Ackroff K and Scalfani A: Maltodextrin and sucrose preferences in sweet-sensitive (C57BL/6J) and subsensitive (129 P3/J) mice revisited. Physiol Behav 165: 286-290, 2016. PMID: 27526998. DOI: 10.1016/j.physbeh.2016.08.012

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