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Maltose consumption exacerbates high-fat diet-induced overweight and related parameters in mice

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ABSTRACT

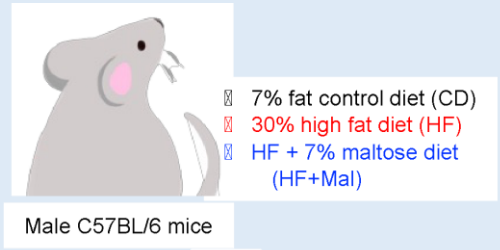
Background: Maltose is a disaccharide formed from two units of glucose. The amount of maltose in raw sweet potatoes reportedly increased by more than 40-fold after baking. We aimed to investigate the effects of maltose consumption on diet-induced obesity using a mouse model.

Methods: Male C57BL/6J mice were divided into three dietary groups: a control diet of American Institute of Nutrition (AIN)-93 (CD), an AIN-93-based 30% high-fat diet (HFD), or an HFD diet containing 7.0% maltose (HFD+Mal). After 13 weeks, body mass index, blood glucose, lipid parameters, including total cholesterol and triglyceride, and hepatic fatty acid content were evaluated.

Results: After 6 weeks on the special diet, weight gain was significantly higher in the HFD+Mal group than in the HFD group. The body mass index rose steadily and was significantly higher in the HFD+Mal group (5.03 ± 0.22), compared to the CD (3.32 ± 0.30) and HFD (4.57 ± 0.40) groups at 12 weeks. The relative liver weight per weight was also significantly higher in the HFD+Mal group than in the other two groups. The increases in blood glucose levels were more significant in the HFD+Mal group compared to the HFD group, as were the plasma levels of total cholesterol, high-density lipoprotein (HDL)-cholesterol and non-HDL-cholesterol. In the liver, levels of the following fatty acids increased in both the HFD and HFD+Mal groups relative to those in the CD group: C14:0 (myristic acid), C16:0 (palmitic acid), C18:0 (stearic acid), C18:1 (oleic acid), C18:2 (linoleic acid) and C18:3 (α-linolenic acid). Additionally, the C16:0 content in the HFD+Mal group was

significantly higher than that in the HFD group.

Conclusion: The results of this study suggest that daily consumption of maltose exacerbated the development of obesity and related parameters, including body mass index and plasma cholesterol levels, under the high-fat diet consumption. It is possible that the consumption of maltose-rich cooked sweet potatoes, as part of an overall HFD, might exacerbate HFD-induced overweight.



Main results. Changes *vs* CD group

	Body weight	Plasma	
		glucose	total cholesterol
HF	↑	↑	↑
HF+Mal	↑↑	↑↑	↑↑

Keywords: high-fat diet-induced obesity, maltose, mice, roasting, sweet potato

INTRODUCTION

The sweet potato (*Ipomoea batatas* L.) is one of the most important food crops worldwide. In comparison to other major food crops, the sweet potato has a diverse range of positive attributes, including high yield, nutritional value (vitamins, minerals, dietary fiber, and starch), wide geographic range of production, length of production cycle, as well as resistance to production stresses (e.g., high temperature, water deficit, insect and disease pressure, low fertility) [1]. Recently, many research groups conducting clinical studies, animal studies and *in vitro* studies have reported that sweet potato consumption might have the potential to prevent obesity and hyperglycemia [2-5]. These backgrounds imply that the sweet potato could become a functional food candidate, although there has yet to be a consensus on the definition of functional foods and therefore many institutions lack a comprehensive process for its classification [6-7]. Functional foods are not meant to take the place of conventional medicine, rather they can be used in conjunction with Western medicine and serve as an aid to health optimization for people with chronic diseases and prioritize the management of symptoms associated with those diseases [8].

Interestingly, the beneficial health effects of sweet potatoes vary remarkably, depending on the processing

and cooking methods used. For example, in a clinical study using non-diabetic subjects, Bahado-Singh et al. reported that the glycemic index (GI) response was significantly higher in the groups consuming roasted (GI value: 79-93) or baked (82-94) sweet potatoes, compared to boiled sweet potatoes (41-50) [9]. One explanation for these differences might be the formation of maltose from starch that is broken down during cooking. Indeed, Chan et al. reported that the maltose content in sweet potatoes increases dramatically during the baking process, resulting in maltose becoming the major component of baked sweet potatoes [10]. The actual amount of maltose in fresh, raw sweet potatoes ranges from 0.01% to 0.13%, and increases by more than 40-fold after baking (2.86%–5.43%). These amounts correspond to 9.1%–18.2% of dry matter weight. In contrast, the amount of maltose generated during steaming is only approximately 70% of that found in baked sweet potatoes [11]. Therefore, consumption of baked sweet potatoes results in a much larger intake of maltose compared to other processing methods.

Maltose is a disaccharide formed from two units of glucose joined with an α (1 → 4) bond. Maltose–similar to glucose--is a reducing sugar and is digested to glucose by maltase, which is located in the brush border of the small intestine [12-13]. The glucose monosaccharides are then transported into the cells of the body, together with Na^+, by a brush border transporter protein [14]. According to the report by Luo et al., approximately 63% of maltose was hydrolyzed to glucose during 60 minutes of perfusion using an *in vivo* rat model [15]. Interestingly, the absorption of glucose from maltose has been reported to be significantly higher than that absorbed from an equivalent amount of glucose itself [16]. This suggests that daily consumption of high amounts of maltose, which comprises two glucose molecules bound together, might exert a different physiological effect than consumption of glucose alone, or maltose in the form of starch. Currently, information about the effects of maltose consumption on human health remains limited.

In this study, we investigated the physiological effects of daily consumption of a high-fat diet (HFD) containing 7% maltose in mice, which equates to a daily diet containing 20% baked sweet potatoes.

METHODS

Materials Cellulose, α-cornstarch, β-cornstarch, and sucrose were purchased from Oriental Yeast Co., Ltd., (Tokyo, Japan). Casein, t-butylhydroquinone, L-cysteine, D (+)-maltose monohydrate (> 98%), and soybean oil were obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). American Institute of Nutrition (AIN) formulations for vitamins (AIN-93-VX) and minerals (AIN-93G-Mix and AIN-93M-Mix), and lard were from MP Biomedicals, LLC (Irvine, CA, USA). All other reagents were of the highest grade available.

Institutional approval of the study protocol This study was conducted in accordance with the guidelines of the Japanese Law for the Humane Treatment and Management of Animals (Law No. 105, 1973) and was approved by the Institutional Animal Care and Use Committee of the University of Miyazaki, Japan (protocol code no. 2019-016-2, approved on March 24, 2020).

Animal housing, diets, and experimental methods Male C57BL/6J mice (age: 4 weeks, body weight: 18.9 ± 0.7) were obtained from Japan SLC (Shizuoka, Japan). The animals were housed three per cage (W 235 mm × L 165 mm × H 125 mm) with paper bedding (Alpha-dri Certified, EPS Ekishin Co., Tokyo, Japan) in an air-conditioned animal housing room (23 ± 2°C temperature; 55 ± 5% humidity; light period from 9:00 AM to 9:00 PM) with free access to deionized water and a powdered AIN-93G diet (Table 1). The individual fatty acid compositions of the lard and soybean oil used in this study are shown in

Figure 1. In order to accurately measure the quantity of food consumption, the powdered diet was stocked in a bait box (Roden CAFÉ Type M, Oriental Yeast Co., Ltd., Tokyo, Japan). All animals were observed once daily for mortality and clinical signs. During the investigation, any abnormal findings were not observed.

Table 1. Compositions of the AIN-93 powder-based experimental diets (%) in the three study groups

	AIN-93G base[1]			AIN-93M base[1]		
	CD	**HFD**	**HFD+Mal**	**CD**	**HFD**	**HFD+Mal**
β-Cornstarch	39.8	16.8	9.8	46.6	20.6	13.6
α-Cornstarch	13.2	13.2	13.2	15.5	15.5	15.5
Casein	20.0	20.0	20.0	14.0	14.0	14.0
Soybean oil	7.0	7.0	7.0	4.0	4.0	4.0
Lard	0.0	23.0	23.0	0.0	26.0	26.0
Sucrose	10.0	10.0	10.0	10.0	10.0	10.0
Maltose	0.0	0.0	7.0	0.0	0.0	7.0
Cellulose	5.0	5.0	5.0	5.0	5.0	5.0
Vitamin mixture	1.0	1.0	1.0	1.0	1.0	1.0
Mineral mixture	3.5	3.5	3.5	3.5	3.5	3.5
L-Cystine	0.3	0.3	0.3	0.18	0.18	0.18
Choline bitartrate	0.25	0.25	0.25	0.25	0.25	0.25
t-Butylhydroquinone	0.0014	0.0014	0.0014	0.0008	0.0008	0.0008
Energy (kcal/g)	3.95	5.10	5.10	3.80	5.10	5.10
Protein (%)	20.0	20.0	20.0	14.0	14.0	14.0
Carbohydrate (%)[2]	63.0	40.0	40.0	72.1	46.1	46.1
Fat (%)	7.0	30.0	30.0	4.0	30.0	30.0
Dietary fiber	5.0	5.0	5.0	5.0	5.0	5.0

[1]Mice received an AIN93-G-based diet through the 11th week of age, and an AIN-93M-based diet thereafter. [2]Carbohydrate: total of β-cornstarch, α-cornstarch, sucrose and maltose. CD, control diet; HFD, 30% high-fat diet; Mal, maltose.

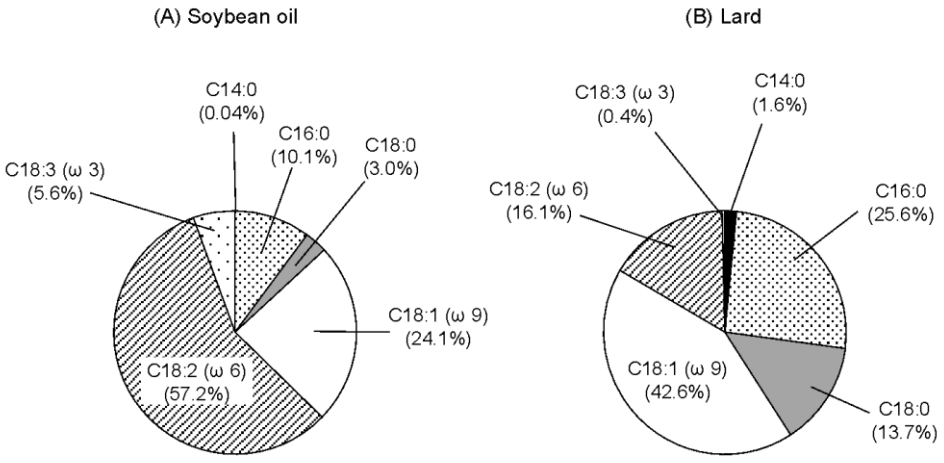


Figure 1. Fatty acid composition of the soybean oil (A) and lard (B) used in this study. Individual fatty acid content was analyzed by gas chromatography, as described below.

After 1 week of acclimation, the mice were divided into three groups: the control group was given a diet of AIN-93G (CD); the second group was given an HFD of 30% fat in an AIN-93G (HFD); and the third group was given an HFD with 7.0% maltose (HFD+Mal). The amount of maltose supplementation was determined as follows. Briefly, the amount of maltose in a baked sweet potato, excluding water, is 34.8% [11]. We calculated that a diet comprising 20% baked sweet potatoes would contain 7% maltose. At the 7th week of feeding (age: 12 weeks), the AIN-93G-based diet in all three groups was changed to a group-specific AIN-93M composition as shown in Table 1, as recommended by the AIN to accommodate the nutritional demands of mice and rats during growth and maintenance periods [17]. Total available carbohydrate (the sum total of β-cornstarch, α-cornstarch, sucrose and maltose) was 40.0% for the AIN-93G-based HFD groups, and 46.1% for the AIN-93M-based HFD groups.

After *ad libitum* feeding for 13 weeks, the mice were fasted for 12 hours and anesthetized with isoflurane (1.5%). Body length (from tail root to nose) was measured as described previously [18] by an operator who was blinded to the diet that each animal had consumed. Body weight just before dissection was used to determine the body mass index using the following formula (1):

$$\text{Body mass index} = \text{body weight (g)} / \text{length (cm}^2\text{)} \quad (1).$$

After measuring the body length and weight, blood samples were drawn from the abdominal vein and blood glucose levels were measured using a Medisafe FIT Blood Glucose Meter with the exclusive Test TIP (Terumo Medical Corp., Tokyo, Japan). The remaining blood was transferred to EDTA-coated tubes (Microtainer Tube with EDTA and Microgard Closure, BD, Mississauga, ON, Canada), then separated by centrifugation at 2000 × g for 90 seconds at 15°C. The plasma fraction was stored at −80°C for later plasma biochemical analysis. The liver, kidneys, spleen, thymus, lungs, heart, and visceral fat (epididymal fat + perirenal fat) were weighed. One liver section was flash-frozen in liquid nitrogen and stored at −80°C for later lipid analysis.

Blood biochemical parameters and hepatic lipid analysis Plasma biochemical parameters (triglycerides, total cholesterol, and high-density lipoprotein [HDL]-cholesterol) were analyzed using a Dri-Chem 4000v chemistry analyzer (Fujifilm Co., Tokyo, Japan) and an individual cartridge slide. Hepatic lipid levels were determined as described in our previous report [19].

Hepatic fatty acid analysis Hepatic fatty acid compositions were analyzed as described in our previous study [18]. Briefly, liver samples (200 mg) were homogenized with 1 mL of 50 mM sodium acetate, and then extracted using a chloroform-methanol mixture (2:1 [vol/vol]). Aliquots of the extracts (20 mg sample equivalent) were then methyl-ester-derivatized using a Fatty Acid Methylation kit (Nacalai Tesque, Inc., Kyoto, Japan) per the manufacturer's instructions. Methyl-ester-derivatized fatty acids were reconstituted with 200 µL of hexane for subsequent analysis.

Fatty acids were analyzed using a gas chromatography-flame ionization detector (GC-2010, Shimadzu Co., Kyoto, Japan). The SUPELCOWAX^{TM} 10 capillary column (30-m length × 0.32-mm inner diameter × 0.25-µm film thickness; Sigma-Aldrich, St. Louis, MO, USA) was used to separate the fatty acids. The column oven temperature was elevated from 170°C to 225°C, and the separated fatty acid methyl esters were detected using the flame ionization detector. A standard mixture of fatty acid methyl esters (Supelco 37 Component FAME Mix) was obtained from Sigma-Aldrich.

Statistical analysis Data are presented as the mean ± standard deviation. Statistical analyses were conducted

using StatView for Windows (version 5.0, SAS Institute, Cary, NC, USA). Statistical significance among groups was determined using two-way analysis of variance (ANOVA), followed by Fisher's PLSD *post-hoc* test. For comparisons within groups, the alpha value was set to 0.05.

RESULTS

Effects of dietary maltose on food intake, and body and organ weights: After 5 weeks on the special diets, the HFD group exhibited significantly higher body weight gain than the CD group (Figure 2), a trend that persisted until the end of the study at 13 weeks. In the HFD+Mal group, the weight gain was significantly higher than that in the HFD group, but only for the period from weeks 8 to 12. Growth parameters and organ weight measurements in the three groups are shown in Table 2. During the experiment, the HFD group consumed significantly higher amounts of dietary energy (18.0 kcal/mouse/day) than both the CD (12.2 kcal/mouse/day) and HFD+Mal (14.6 kcal/mouse/day) groups. The body mass index of the HFD+Mal group at 13 weeks (5.03 ± 0.22) was significantly higher than those of the CD (3.32 ± 0.30) and HFD (4.57 ± 0.40) groups, despite the similarities in body length. The relative weight of the liver in the HFD+Mal group was significantly heavier than that in the other two groups. The relative weights of the kidneys, heart, lungs and visceral fat in both the HFD and HFD+Mal groups were significantly heavier than those in the CD group, but there were no significant differences between the HFD and HFD+Mal groups. Spleen and thymus weights were similar among the three groups.

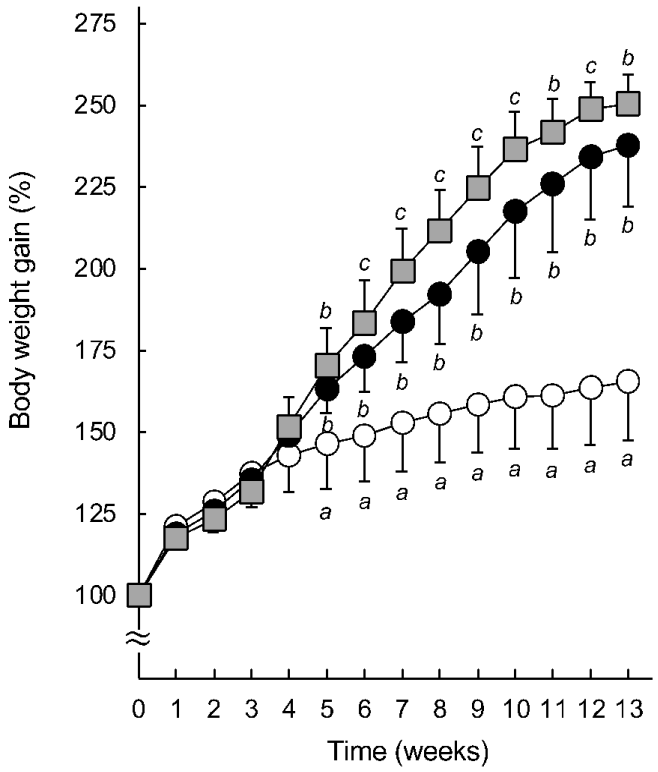


Figure 2. Effects of maltose consumption on body weight gain in mice consuming a high-fat diet (HFD). Mice were divided into three groups: control diet (CD, ○), 30% HFD (HFD, ●), and HFD+Maltose (HFD+Mal, ■). Data is expressed as mean ± standard deviation (n = 9). Different alphabetical superscript letters indicate significant differences ($p < 0.05$ in Fisher's PLSD test). The groups did not show differences until week 4.

Table 2. Effects of maltose consumption on growth parameters and organ weights.

	CD	HFD	HFD+Mal
Body weight (g)			
week-0	19.9 ± 1.1	19.8 ± 0.8	20.1 ± 0.7
week-13	31.1 ± 3.7 [a]	45.1 ± 4.6 [b]	47.8 ± 1.8 [b]
Food intake (g/day)	3.28 ± 0.2 [ab]	3.53 ± 0.4 [a]	2.86 ± 0.1 [b]
Energy intake (kcal/day)	12.2 ± 0.9 [a]	18.0 ± 2.2 [b]	14.6 ± 0.6 [a]
Body length (cm)	9.42 ± 0.26	9.71 ± 0.23	9.59 ± 0.19
Body mass index (g/cm^2)	3.32 ± 0.30 [a]	4.57 ± 0.40 [b]	5.03 ± 0.22 [c]
Relative organ weights (g/100 g body weight)			
liver	3.33 ± 0.22 [a]	3.29 ± 0.60 [a]	4.11 ± 0.35 [b]
Kidney	1.18 ± 0.20 [a]	0.86 ± 0.10 [b]	0.81 ± 0.06 [b]
Spleen	0.29 ± 0.03	0.25 ± 0.06	0.22 ± 0.01
Thymus	0.15 ± 0.03	0.15 ± 0.05	0.14 ± 0.03
Heart	0.53 ± 0.10 [a]	0.37 ± 0.05 [b]	0.34 ± 0.03 [b]
Lung	0.57 ± 0.06 [a]	0.39 ± 0.06 [b]	0.37 ± 0.03 [b]
visceral fat	3.07 ± 1.66 [a]	7.22 ± 0.81 [b]	6.74 ± 0.78 [b]

CD, control diet; HFD, 30% high-fat diet; Mal, maltose. Data expressed as the mean ± standard deviation (n = 9). Different alphabetical superscript letters indicate significant differences ($p < 0.05$ in Fisher's PLSD test).

Effects of maltose on plasma biochemical parameters

After 13 weeks on the special diets, blood glucose levels were significantly higher in the HFD group compared with the CD group (Figure 3A). The increase in blood glucose levels in the HFD+Mal group was even more significant than that in the HFD group, as were the changes in total cholesterol, HDL-cholesterol, and non-HDL-cholesterol levels in plasma (Figure 3B–D). The levels of plasma triglyceride in both the HFD and HFD+Mal groups were significantly higher than those in the CD group, but there was no difference between the two HFD groups.

Effects of maltose on hepatic lipid levels There were no significant changes in hepatic lipid parameters (total cholesterol, triglyceride, and phospholipids) among the three groups after 13 weeks on the special diets (Figure 4A–C).

Effects of maltose on hepatic fatty acid levels In the liver, the levels of the following fatty acids increased in both the HFD and HFD+Mal groups compared with the CD group: C14:0 (myristic acid), 16:0 (palmitic acid), C18:0 (stearic acid), C18:1 (oleic acid), C18:2 (linoleic acid) and C18:3 (α-linolenic acid) (Figure 5). Apart from the significantly higher level of C16:0 in the HFD+Mal group compared to the HFD group, there were no significant differences in fatty acid levels between these two groups.

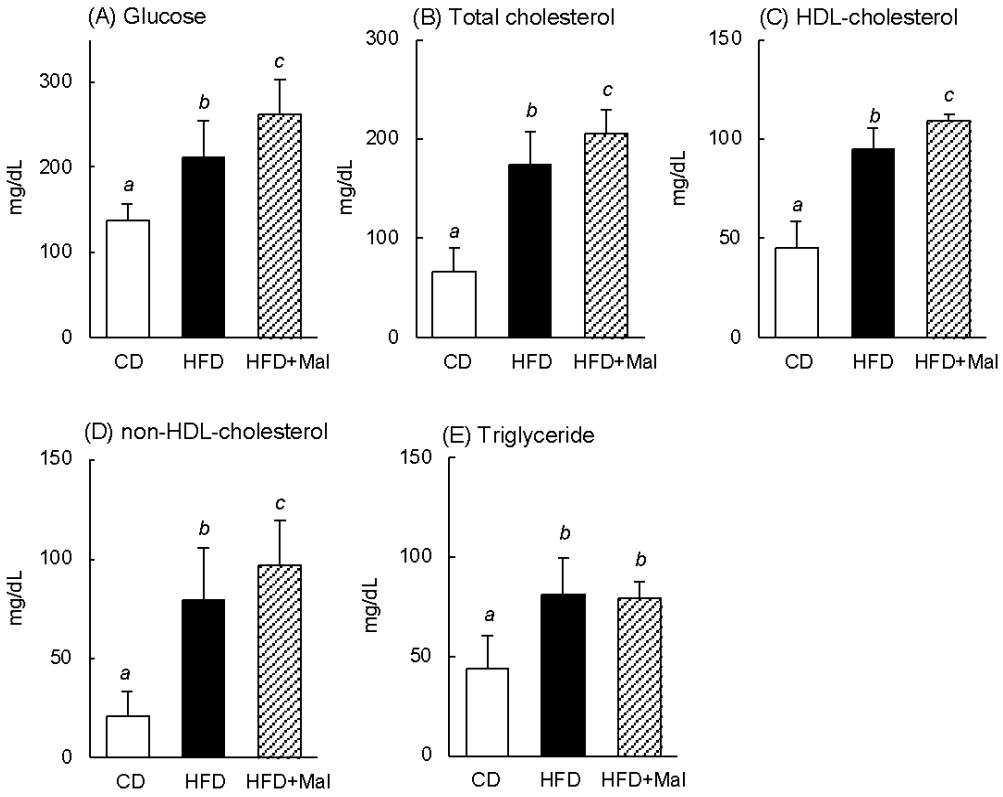


Figure 3. Effects of maltose consumption on plasma biochemical parameters: (A) glucose; (B) total cholesterol; (C) high-density lipoprotein (HDL)-cholesterol; (D) non-HDL-cholesterol; and (E) triglyceride. Data expressed as the mean ± standard deviation (n = 9). Different alphabetical superscript letters indicate significant differences ($p < 0.05$ in Fisher's PLSD test).

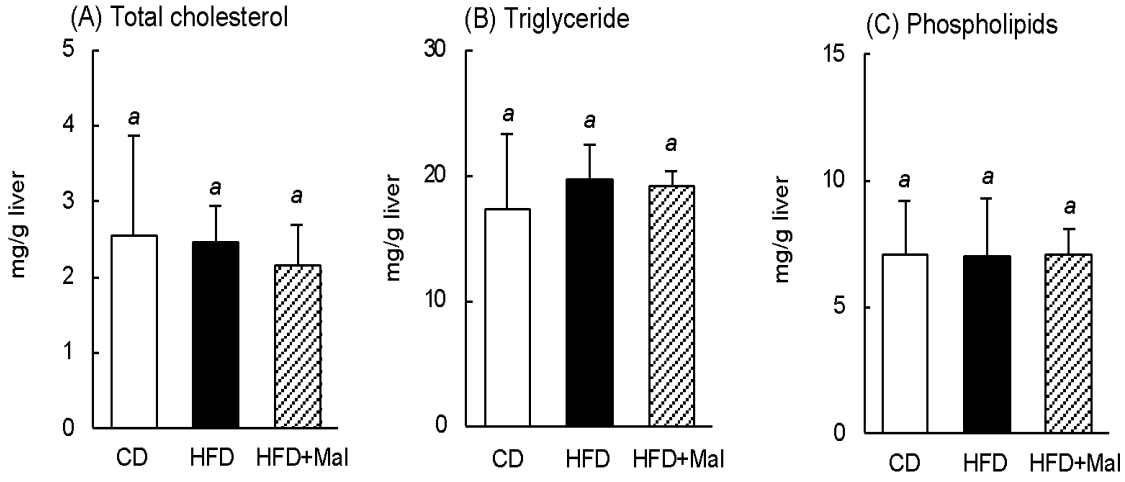


Figure 4. Effects of maltose consumption on lipid levels in the liver: (A) total cholesterol; (B) triglyceride; and (C) phospholipids. Data expressed as the mean ± standard deviation (n = 9). Different alphabetical superscript letters indicate significant differences ($p < 0.05$ in Fisher's PLSD test).

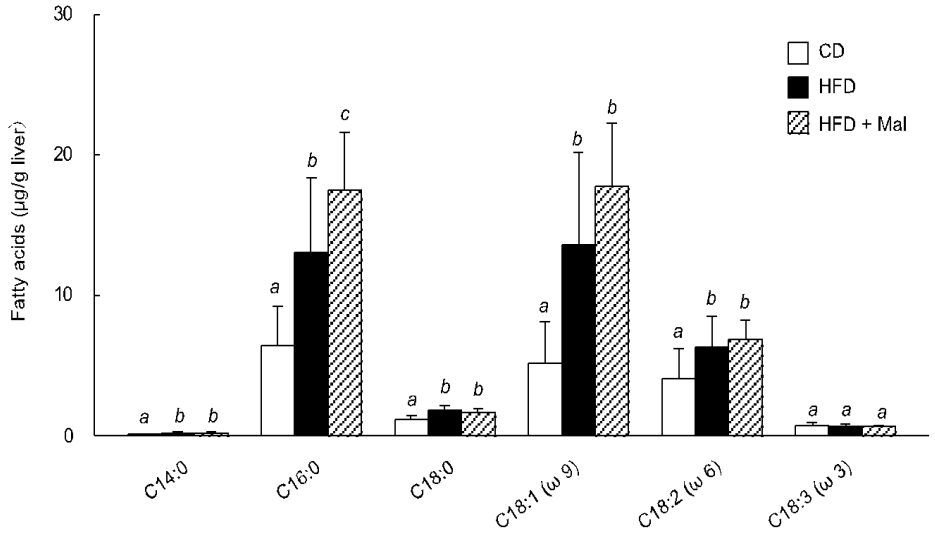


Figure 5. Effects of maltose consumption on fatty acid levels in the liver. Data is expressed as the mean ± standard deviation (n = 9). Different alphabetical superscript letters indicate significant differences ($p < 0.05$ in Fisher's PLSD test).

DISCUSSION: The starchy roots of different varieties of sweet potato display a wide range of colors, hold many nutrients, including anthocyanins, β-carotene, vitamins, minerals, dietary fiber and starch [20], and are widely consumed all around the world. Sweet potatoes are generally considered to have various preventive effects on lifestyle diseases, such as obesity and diabetes mellitus [2-5]. However, these health benefits are reportedly diminished by different cooking and processing methods [9], as demonstrated by remarkable changes in carbohydrate composition, maltose content, and carotenoid and ascorbic acid levels [10, 21-22]. Due the maltose content of a raw sweet potato increasing by approximately 40-fold after baking, we focused on the effects of maltose on diet-induced obesity in mice in this study.

Mice that consumed an HFD containing 7% maltose (HFD+Mal) showed a steady increase in body weight during the course of the experiment that was remarkably higher than that in mice on a typical HFD, although the difference was not significant at the very end of the study (13 weeks; Figure 2 and Table 2). Additionally, the body mass index and liver weight were significantly higher in the HFD+Mal group compared to the HFD group (Table 2). While the daily energy intake of the HFD+Mal group was significantly lower than that of the HFD group, the total amount of available carbohydrate (the sum of β-cornstarch, α-cornstarch, sucrose and maltose) was equal in both diets (Table 1), indicating that higher maltose consumption may have exacerbated the diet-induced obesity.

There is a sufficient amount of evidence on the effects of monosaccharides and disaccharides, including glucose, sucrose and fructose, on overweight caused by HFDs [23-29]. Briefly, Lozano et al. reported that consumption of a high-fructose beverage exacerbated the overweight induced by HFD in a rat model, but that the high-fructose beverage alone did not cause overweight [23]. Interestingly, glucose consumption has been reported to exacerbate HFD-induced overweight to a greater degree than fructose [26]. Furthermore, the absorption of glucose derived from maltose (the

disaccharide formed from two units of glucose) is reportedly higher than that from an equivalent amount of glucose [16], indicating that the effect of maltose consumption on body weight might extend beyond its glucose composition. Sucrose has also been shown to exacerbate HFD-induced overweight in C57BL/6J mice [29].

The plasma levels of glucose and cholesterol in the HFD+Mal group were significantly higher than those in the HFD group (Figure 3), and the HFD group also showed significant increases in five fatty acids (C14:0, C16:0, C18:0, C18:1 [ω 9] and C18:3 [ω 6)]), compared to the CD group (Figure 5). In this study, the soybean oil-containing AIN-93 diet was used for the control group and the lipid content of the HFD group was increased to 30% with lard. These results can be explained by the fatty acid composition of lard (Figure 1). Interestingly, the amounts of C16:0 and C18 (ω 9) increased in the HFD+Mal group, with the increase in C16:0 being significant. A few research groups have suggested that fructose and sucrose consumption may lead to an adaptive response in the physiological fatty acid profile, in association with the development of the metabolic syndrome [30-31]. The results of this study implied that maltose consumption may affect lipid metabolism and consequently, exacerbate diet-induced overweight. We intend to elucidate this possibility in future research.

On the other hand, any significant changes in hepatic total cholesterol and triglyceride levels were not observed among the three groups (Figure 4). In this study, liver samples were removed from C57BL/6 mice under fasting for 12 hours. Hepatic levels of total cholesterol and triglyceride are decreased during the fasting. Nishikawa et al examined the effects of fasting on hepatic lipid accumulation using C57BL/6 and BALB/c mice [32]. They reported that both C57BL/6 and BALB/c mice showed moderate hepatic steatosis after high-fat diet consumption, but the hepatic lipid accumulation was markedly decreased in C57BL/6, but not in BALB/c mice after 24 hours fasting. Additionally, they speculated that fatty acid synthesis in C57BL/6 mice decreased during fasting, and therefore induces a decrease of triglyceride synthesis, followed by less hepatic lipid accumulation. The reasons why hepatic total cholesterol and triglyceride levels on HFD group were similar to CD group imply because of the effects of fating period before sacrifice.

CONCLUSION: In this study, we mimicked the effects of human consumption of high-GI baked sweet potatoes in a mouse model of HFD-induced obesity using 7% maltose supplementation. Our results clearly indicate that daily consumption of maltose exacerbated the development of overweight and related parameters, including body mass index and plasma cholesterol levels, under the high-fat diet consumption. To date, it has been difficult to discern whether the exacerbating effect of maltose on overweight induced by an HFD differs from that of other sugars, such as glucose and fructose. The results of this study point to the possibility that the consumption of maltose-rich roasted or baked sweet potatoes, as part of an overall HFD, may exacerbate HFD-induced overweight.

Abbreviations: CD: control diet, HFD: 30% high-fat diet, Mal: maltose

Authors Contributions: NS, YS and HS designed the research; NS, WT, HM, HK and KO performed the animal study; NS and WT analyzed the data; NS, YS, DY and HS prepared the manuscript.

Competing Interests: None of the authors have any financial interests or conflict of interests to report.

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