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Two unhealthy dietary habits featuring a high fat content and a sucrose-containing beverage intake, alone or in combination, on inducing metabolic syndrome in Wistar rats and C57BL/6J mice

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Abstract

To establish animal models with diet-induced metabolic disorders similar to human metabolic syndrome, 2 unhealthy dietary habits featuring a high fat content and a sucrose-containing beverage intake, alone or in combination, were tested on Wistar rats and C57BL/6J mice. The 2 dietary habits were, respectively, simulated by feeding a high-fat diet (regimen A) or additionally providing 30% sucrose (wt/vol) in the drinking water (regimen B). Using a 2 × 2 factorial design, 4 groups of animals were fed chow diet plus plain water (group C), high-fat diet (30% [wt/wt] fat) plus plain water (group A), chow diet plus sucrose in drinking water (group B), and high-fat diet plus sucrose in drinking water (group AB) for 26 weeks. In Wistar rats, regimen B caused a significant increase in visceral fat; serum levels of lipids, glucose, insulin, and uric acid; insulin resistance; and blood pressure, whereas regimen A only caused a significant increase in visceral fat and serum insulin levels ($P < .05$). In contrast, regimen A induced a full array of metabolic syndrome in C57BL/6J mice; but regimen B only caused slight obesity and hyperlipidemia. In both Wistar rats and C57BL/6J mice, there were no additive effects of the 2 regimens, indicated by significant interactions between regimens A and B on the metabolic indexes measured. These results show that, in terms of inducing metabolic syndrome, Wistar rats are more responsive to sucrose water regimen, whereas C57BL/6J mice are more responsive to the high-fat diet regimen.

1. Introduction

Metabolic syndrome, indicated by the clustering of certain risk factors, including insulin resistance, central obesity, hypertension, and dyslipidemia, is a global health problem with a soaring morbidity [1,2]. The interaction of a polygenetic predisposition with environmental influences, such as a dietary pattern of excess fat or caloric intake and an increasingly sedentary lifestyle, is responsible for the prevalence of obesity and its sequels [3]. Recently, dietary fructose, mainly from sucrose or high-fructose corn syrup, has been found to be a key contributor to the epidemic of obesity and metabolic disorders [4,5]. In modern human life, a high-fat diet and the consumption of sugar-sweetened beverages are common. However, the relative importance of these 2 dietary habits, alone or in combination, in the pathology of metabolic disease is not clear.

High-sucrose (or fructose) diets and high-fat diets have been used to cause diet-induced metabolic syndrome in animal models and show different inducing effects [6-8]. The distinct phenotypes of sensitivity to high-fat diet– or high-sucrose diet–induced metabolic disturbances may depend on the genetic background. The inbred C57BL/6J mouse is prone to obesity and diabetes in response to a high-fat diet [9,10] and has been suggested to be resistant to sucrose treatment when this disaccharide isocalorically replaces starch in the feed [6,8]. Studies on sucrose have yielded conflicting results in terms of its ability to induce obesity and insulin resistance in rodents [11,12]; and this depends not only on the species or strain of animals used, but is further

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complicated by the way the sucrose is provided. In Wistar rats fed a normal–fat content chow diet, addition of sucrose to the drinking water (30%) as an extra caloric source has been shown to be a successful way of inducing symptoms associated with metabolic syndrome, including abdominal obesity, hypertension, hyperlipidemia, and hyperinsulinemia [13-15]. However, whether sucrose-containing drinking water induces symptoms in other species is unclear.

To establish animal models with diet-induced metabolic disorders similar to human metabolic syndrome, 2 dietary treatment regimens were tested. One used a high-fat diet (regimen A) and the other provided sucrose (30% wt/vol) in the drinking water (regimen B), which represent the 2 unhealthy dietary habits commonly seen in modern human life. The individual as well as the combined effects of the 2 dietary regimens on inducing metabolic disturbances were investigated using a 2 × 2 factorial design. Wistar rats and C57BL/6J mice were both used in this study to demonstrate the differential susceptibility to the 2 regimens on eliciting metabolic derangements due to genetic factor.

2. Materials and methods

2.1. Animals and diets

Forty male C57BL/6J mice and forty male Wistar rats were purchased from the National Applied Research Laboratories (Taipei, Taiwan) at 7 weeks of age. After 1 week of acclimation to a standard rodent chow diet (6 g of water, 51 g of crude carbohydrate, 23.5 g of crude protein, 4.5 g of crude lipid, 6 g of crude fiber, and 9 g of ash per 100 g diet; Fwusow Industry, Taichung, Taiwan), the mice and rats were each divided into 4 groups on the basis of a 2 × 2 factorial design and received either chow diet (groups C and B) or a high-fat diet (30% [wt/wt] fat; groups A and AB) with either plain water (groups C and A) or 30% sucrose in water (groups B and AB) as drinking water. The composition of the high-fat diet (16 g of corn starch, 16 g of sucrose, 26 g of casein, 29 g of butter, 1 g of soybean oil, 6 g of cellulose, 4.2 g of AIN-76 mineral mixture, 1.2 g of AIN-76 vitamin mixture, 0.3 g of methionine, and 0.2 g of choline per 100 g diet) was that used by Hsu and Huang [16]. The animals were kept in a room maintained at 23°C ± 2°C on a controlled 12-hour light/dark cycle with free access to food and drinking water. Body weight was recorded weekly. The protocols for animal care and handling were approved by the Institutional Animal Care and Use Committee of the China Medical University.

2.2. Blood pressure and heart rate

The diastolic and systolic blood pressure and heart rate were measured in rats after 20 weeks on the diets using a tail-cuff system (BP 2000; Visitech Systems, Apex, NC) that uses a photoelectric sensor to detect blood flow in the tail [17]. The rats were familiarized to the procedure for 7 consecutive days before blood pressure and heart rate recordings on day 8. For each rat, at least 1 set of 10 measurements with 9 or more successful readings was obtained.

2.3. Glucose tolerance and insulin sensitivity

After dietary treatment for 20 weeks, the glucose tolerance and insulin sensitivity of the rats and mice were assessed by the oral glucose tolerance test (OGTT) and insulin tolerance test (ITT). For the OGTT, animals were fasted overnight (only plain water was supplied); then tail blood was collected before (0 minute) and at 30, 60, 90, and 120 minutes after oral administration of a 2.5-mol/L glucose solution (1.5 g/kg body weight). For the ITT, the animals were fed for 3 hours after overnight fasting; then tail blood was collected before (0 minute) and at 30, 60, 90, and 120 minutes after intraperitoneal injection of a 0.1-U/mL solution of insulin (0.75 U/kg body weight). The area under the curve (AUC) for serum glucose over the 2 hours was calculated in both cases.

2.4. Tissue sampling and preparation

At the end of treatment (26 weeks), all animals were killed by carbon dioxide asphyxiation. Blood was collected from the orbital capillary. The liver, visceral fat (including epididymal and retroperitoneal fats), and gastrocnemius muscle were excised and weighed. A small portion of the liver and muscle was frozen at −20°C for lipid content analysis. Serum samples were obtained by centrifugation of

Table 1
Independent and interaction effects of the regimen A (the high-fat diet regimen) and regimen B (sucrose water regimen) in inducing metabolic syndrome

	Wistar rats			C57BL/6J mice		
	A	B	A × B	A	B	A × B
	P value					
Body weight gain	.0005*	.0006*	.0061*	<.0001*	.0151*	.0294*
Visceral fat accumulation	<.0001*	.0004*	.0012*	<.0001*	.0244*	<.0001*
Serum TG	.3084	<.0001*	.2833	.0116*	.0023*	<.0001*
Serum TC	.8801	.0137*	.0159*	<.0001*	<.0001*	.3797
Serum glucose	.2019	.0012*	.0091*	.0014*	.3200	.0451*
Serum insulin	.0053*	.0005*	.0048*	.0030*	.5697	.8894
AUC for the OGTT	.0925	.0183*	.9953	.0003*	.0019*	.0951
AUC for the ITT	.2908	.0061*	.0364*	<.0001*	.9265	.1555
Systolic blood pressure	.2330	.0004*	.4918			
Diastolic blood pressure	.2248	.0178*	.2662			
Serum uric acid	.8194	.0037*	.0039*			

P values for the high-fat diet regimen (A), sucrose water regimen (B), and their interaction (A × B) were analyzed by 2-way ANOVA.

* $P < .05$.

blood at 3000*g* for 10 minutes; then glucose was measured immediately, and the remaining serum was stored at −20°C for analysis of insulin, lipids, and adipocytokines. A 0.5-cm^3 cube of retroperitoneal fat was fixed in 10% formaldehyde for histochemical analysis.

2.5. Measurement of biomedical indices

Serum glucose and uric acid were measured using an enzymatic color-developing system (Randox Laboratories, Crumlin, Northland, United Kingdom). Enzyme-linked immunosorbent assays were used to measure serum insulin (Linco, St Charles, MO), adiponectin (R&D, Minneapolis, MN), and leptin (R&D). Lipids in liver and skeletal muscle were extracted by the method of Folch et al [18]. Triglyceride (TG) and total cholesterol (TC) in serum and tissue extracts were measured by enzymatic methods using commercial kits (Randox Laboratories).

2.6. Adipocyte cell size

The fixed retroperitoneal fat was dehydrated through a graded ethanol series, embedded in paraffin, cut into 10-μm sections, and examined under a light microscope (OLYMPUS I × 71) equipped with a SPOT RT color-2000 digital camera (Diagnostic Instruments, Sterling Heights, MI) to obtain images for cell size determination. Adipocyte cell size was estimated by counting the number of adipocytes in a microscopic field of known area using SPOT ADVANCED software (Diagnostic Instruments). For quantification, 3 animals in each group were used; and 3 fields were randomly chosen in each of 10 sections from each individual.

2.7. Statistical analysis

Data are expressed as the mean ± SD. To test the significance of the effects of the high-fat diet regimen (regimen A) or sucrose water regimen (regimen B) and their interaction (A × B), the data for the 4 groups were analyzed by 2-way analysis of variance (ANOVA). The significance of differences among the 4 groups was also analyzed statistically by 1-way ANOVA and Duncan multiple range test. Data were transformed to log values for the statistical analysis if the variances were not homogeneous. The General Linear Model of the SAS package (SAS Institute, Cary, NC) was used for both statistical analyses, and differences were considered significant at $P < .05$.

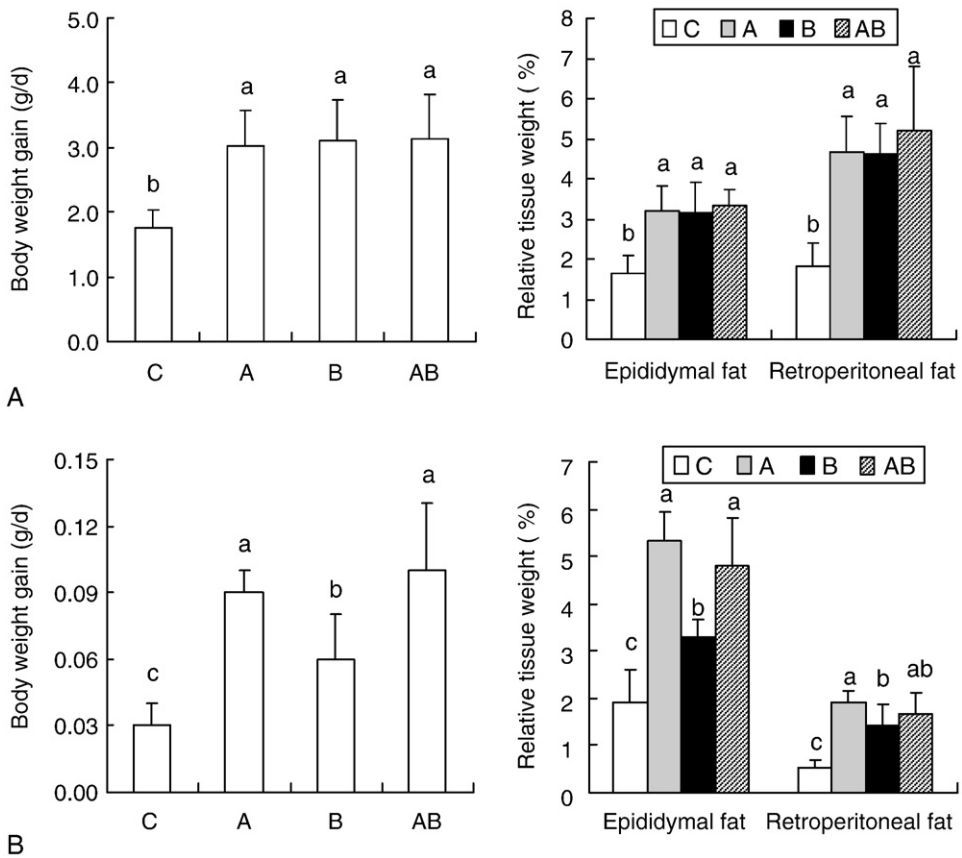


Fig. 1. Body weight gain and relative visceral fat weight in Wistar rats (A) and C57BL/6J mice (B) fed chow diet plus plain water (group C), a high-fat diet plus plain water (group A), chow diet plus sucrose water (group B), or the high-fat diet plus sucrose water (group AB). The values are the mean ± SD (n = 10). The significance of differences among groups was analyzed by 1-way ANOVA and Duncan multiple range test. Values not sharing a superscript letter between groups are significantly different ($P < .05$).

3. Results

3.1. Induction of obesity

In both species, it was noticeable that, when sucrose was added to drinking water as an extra caloric source, solid food intake decreased markedly, whereas the total energy intake (the sum of the energy from the solid food and drinking water) increased compared with group C (data not shown).

Regardless of the animal strain used, 2-way ANOVA shows that both dietary regimens A and B significantly increased body weight gain and visceral fat accumulation (retroperitoneal and epididymal fats) (Table 1 and Fig. 1). However, the 2 dietary regimens also had significant interaction in that animals fed with both regimens (group AB) did not show additive increases compared with either dietary regimen alone (Table 1 and Fig. 1). Whereas the body weight gain and relative visceral fat weight of Wistar rats were comparable between groups A, B, and AB (Fig. 1A), those of C57BL/6J mice of the group B were significantly lower than groups A and AB (Fig. 1B).

3.2. Induction of hyperlipidemia

In Wistar rats, only the regimen B, but not regimen A, significantly increased serum levels of TG and TC. Besides, a significant interaction between regimens A and B was observed for serum cholesterol (Table 1 and Fig. 2A). Serum TC levels of group B, but not group AB, were significantly higher than those of group C ($P < .05$, Fig. 2A).

In C57BL/6J mice, the 2 regimens significantly increased the serum lipids; but an interaction effect was only observed for serum TG (Table 1 and Fig. 2B). Whereas serum TG levels of both groups A and B were significantly higher than those of group C, serum TG of group AB was not different from that of group A but was significantly lower than that of group B (Fig. 2B).

3.3. Induction of hyperglycemia and insulin resistance

In Wistar rats, the serum levels of glucose and insulin as well as the AUC for the OGTT and ITT were significantly affected by regimen B, but not regimen A, except for serum insulin (Table 1). There was a significant interaction effect of the 2 regimens on serum glucose, insulin, and AUC for the ITT (Table 1). Whereas comparable hyperinsulinemia was observed in groups A, B, and AB, hyperglycemia was only seen in group B ($P < .05$, Fig. 3A). The results of the OGTT and ITT indicated that glucose intolerance and insulin resistance developed in group B because the AUC over 2 hours for both the OGTT and ITT was significantly increased in group B compared with group C ($P < .05$, Fig. 4A).

In C57BL/6J mice, the serum levels of glucose and insulin as well as the AUC for the OGTT and ITT were significantly affected by regimen A, but not regimen B, except for AUC for the OGTT. There was a significant interaction effect of the 2 regimens on serum glucose

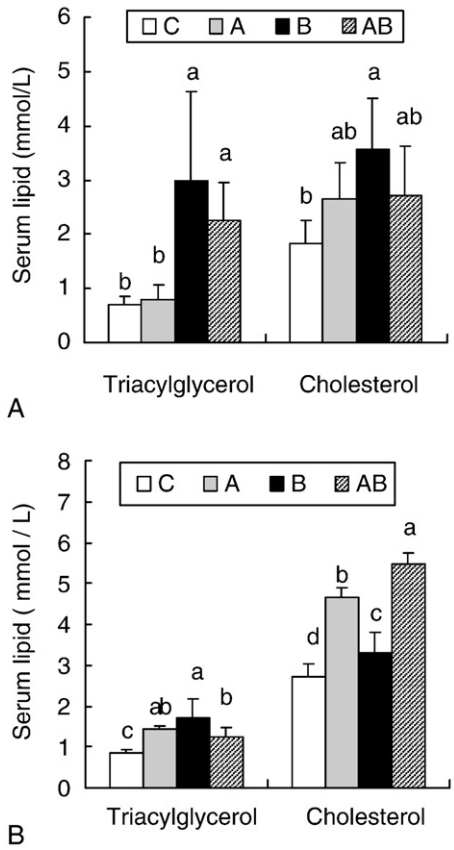


Fig. 2. Serum levels of lipids in Wistar rats (A) and C57BL/6J mice (B) fed chow diet plus plain water (group C), a high-fat diet plus plain water (group A), chow diet plus sucrose water (group B), or the high-fat diet plus sucrose water (group AB). The values are the mean ± SD (n = 10). The significance of differences among groups was analyzed by 1-way ANOVA and Duncan multiple range test. Values not sharing a superscript letter between groups are significantly different ($P < .05$).

(Table 1). Therefore, hyperinsulinemia was observed in groups A and AB ($P < .05$), whereas hyperglycemia was only seen in group A ($P < .0001$) but not group AB (Fig. 3B). The OGTT and ITT showed that glucose intolerance was only observed in group A, whereas insulin resistance developed in groups A and AB ($P < .0001$, Fig. 4B). Regimen B seems to reduce the AUC of OGTT because the index in groups B and AB was decreased compared with groups C and A, respectively.

3.4. Induction of hypertension and hyperuricemia in Wistar rats

Blood pressure and serum uric acid levels were measured only in Wistar rats and not in C57BL/6J mice. Again, regimen B, but not regimen A, significantly increased blood pressure and uric acid levels. A significant interaction of both regimens was seen in serum uric acid levels (Table 1 and Fig. 5). Serum uric acid levels were significantly increased in group B, but not in group AB ($P < .005$, Fig. 5).

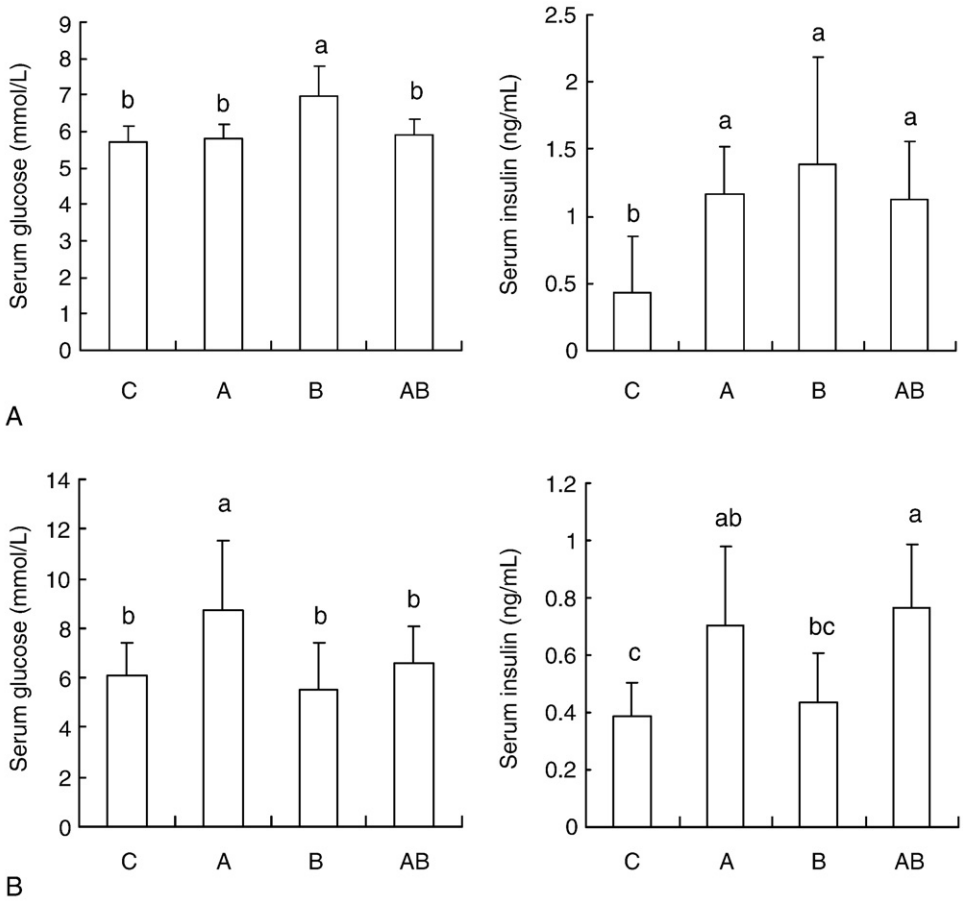


Fig. 3. Serum levels of glucose and insulin in Wistar rats (A) and C57BL/6J mice (B) fed chow diet plus plain water (group C), a high-fat diet plus plain water (group A), chow diet plus sucrose water (group B), or the high-fat diet plus sucrose water (group AB). The values are the mean ± SD (n = 10). The significance of differences among groups was analyzed by 1-way ANOVA and Duncan multiple range test. Values not sharing a superscript letter between groups are significantly different ($P < .05$).

3.5. Lipotoxicity and adipocyte hypertrophy in Wistar rats

To explore the mechanisms underlying regimen B–induced metabolic syndrome in Wistar rats, lipid accumulation in the liver and muscle was measured because lipotoxicity (ie, overloading adipose tissue beyond its storage capacity, which leads to deposition of lipids in nonadipose tissues) is believed to be involved in the pathogenesis of insulin resistance [19,20]. There were significantly increasing effects of the 2 regimens on liver TG and TC, but the interactions were also significant (Table 1 and Fig. 6A). The liver lipids were higher in groups A, B, and AB than in group C ($P < .0001$), but were comparable among these 3 groups (Fig. 6A). Muscle TG was increased only by regimen B without interaction (Table 1 and Fig. 6A).

We also measured adipocyte size in the retroperitoneal fat. As shown in Fig. 6B, the 2 regimens, with significant independent and interaction effects, resulted in adipocyte hypertrophy. Whereas the mean adipocyte diameter of group B was significantly higher than the remaining 3 groups ($P < .0001$), that of groups A and AB were comparable.

Hypertrophic adipocytes might modify levels of circulating adipocytokines that are involved in energy homeostasis and glucose metabolism [21]. Serum levels of leptin and adiponectin were measured because the former is a good indicator of fat mass [22] and the latter is the only known adipocytokine that can increase insulin sensitivity [23]. As shown in Fig. 6C, serum leptin levels were significantly increased by both regimens A and B; despite that, there was also a significant interaction of the two. Groups B and AB had comparable serum leptin value. In contrast, neither independent nor interaction effect was seen in adiponectin levels. Adipose tissue messenger RNA (mRNA) levels for leptin and adiponectin (data not shown) agreed with their serum protein levels.

4. Discussion

In this study, our intention was not to compare 2 dietary components (sucrose and fat), but to compare the 2 unhealthy dietary habits in terms of inducing metabolic syndrome in Wistar rats and C57BL/6J mice. Regimen A

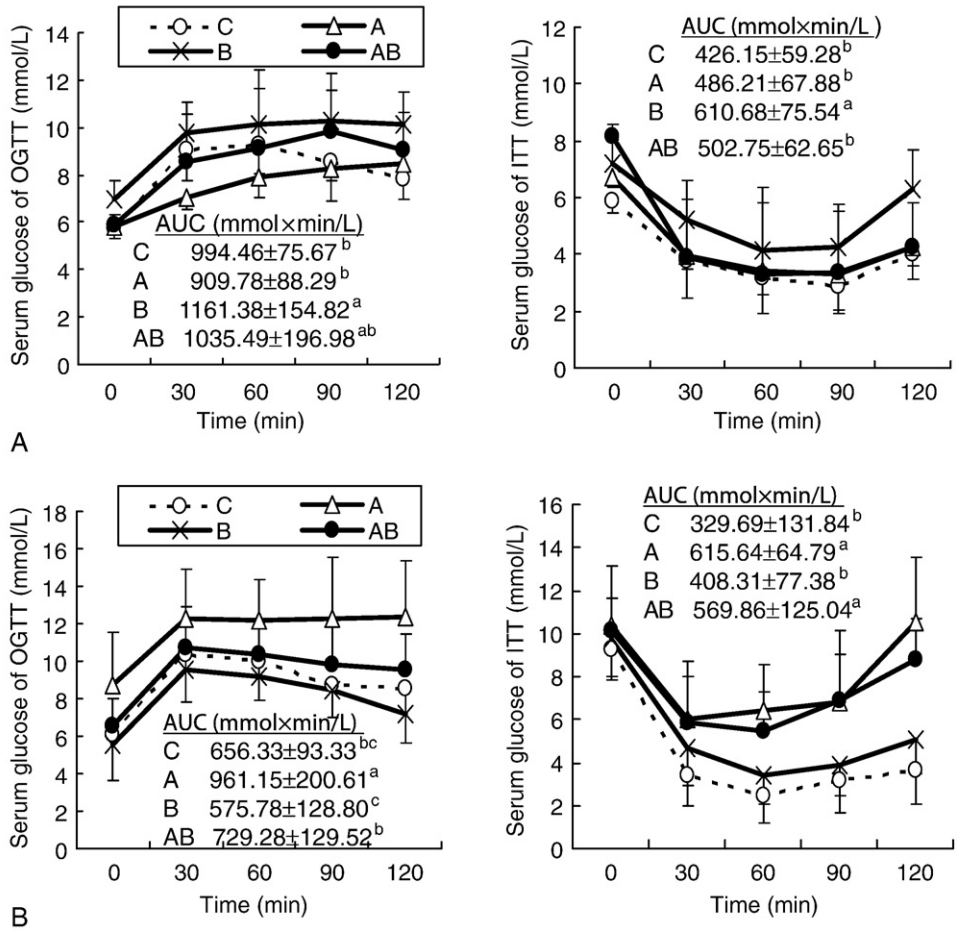


Fig. 4. Oral glucose tolerance test and ITT performed on Wistar rats (A) and C57BL/6J mice (B) fed chow diet plus plain water (group C), a high-fat diet plus plain water (group A), chow diet plus sucrose water (group B), or the high-fat diet plus sucrose water (group AB). The AUC over 2 hours was calculated, and the results are expressed as the mean ± SD (n = 10). The significance of differences among groups was analyzed by 1-way ANOVA and Duncan multiple range test. Values not sharing a superscript letter between groups are significantly different ($P < .05$).

simulates a high-fat dietary pattern, whereas regimen B simulates habitual consumption of sucrose-containing beverages. The individual and combined effects on eliciting metabolic derangements were demonstrated in the 2 × 2 factorial design, and data were statistically analyzed by 2-way ANOVA. Group C, which received chow diet plus plain

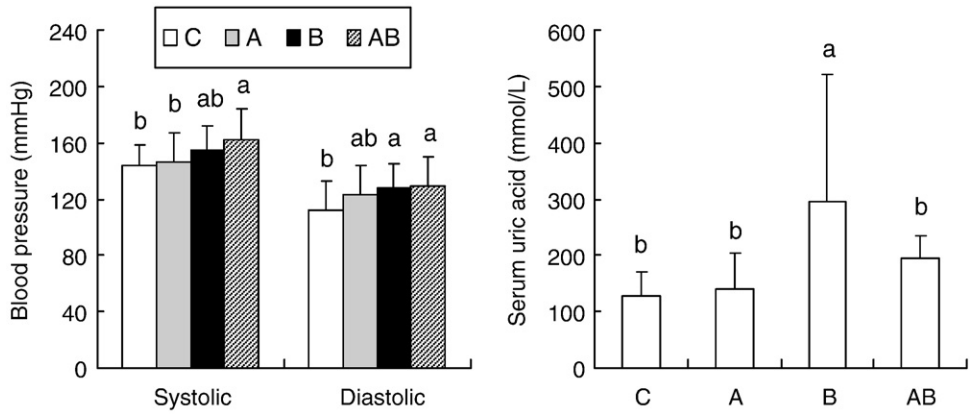
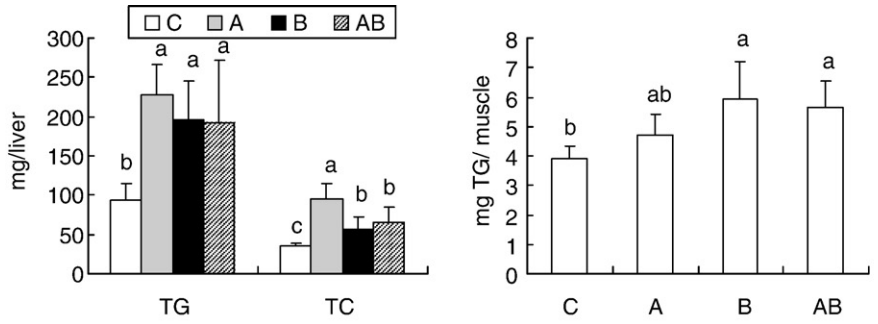
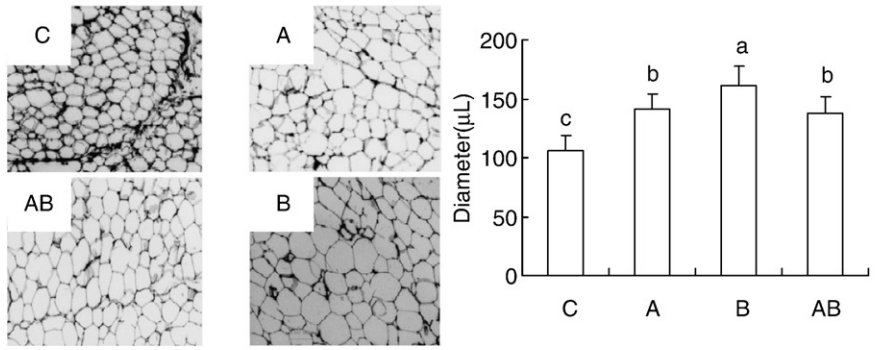


Fig. 5. Blood pressure and serum levels of uric acid in Wistar rats fed chow diet plus plain water (group C), a high-fat diet plus plain water (group A), chow diet plus sucrose water (group B), or the high-fat diet plus sucrose water (group AB). The values are the mean ± SD (n = 10). The significance of differences among groups was analyzed by 1-way ANOVA and Duncan multiple range test. Values not sharing a superscript letter between groups are significantly different ($P < .05$).



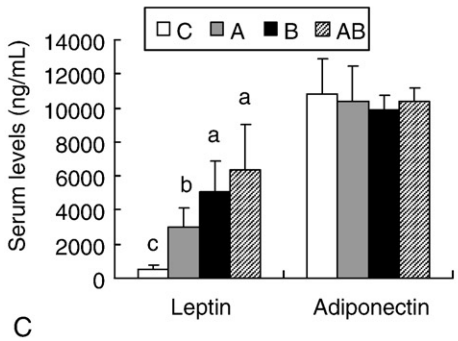
	P values		
	A	B	A×B
Liver TG	0.0003*	0.0018*	0.0032*
Liver TC	<0.0001*	0.0314*	0.0004*
Muscle TG	0.4453	0.0019*	0.1829

A



	P values		
	A	B	A×B
Adipocyte diameter	<0.0001*	<0.0001*	<0.0001*

B



	P values		
	A	B	A×B
Leptin	<0.0001*	<0.0001*	0.0049*
Adiponectin	0.9475	0.6459	0.6022

C

Fig. 6. Liver lipids and muscle TG (A), adipocyte size (B), and serum levels of leptin and adiponectin (C) in Wistar rats fed chow diet plus plain water (group C), a high-fat diet plus plain water (group A), chow diet plus sucrose water (group B), or the high-fat diet plus sucrose water (group AB). The values are the mean ± SD (n = 10). The significance of differences among groups was analyzed by 1-way ANOVA and Duncan multiple range test. Values not sharing a superscript letter between groups are significantly different ($P < .05$).

water, was assumed to be metabolically healthy. Consequently, genetic differences in the susceptibility to the metabolic effects of the 2 dietary regimens were observed, as Wistar rats were more responsive to metabolic syndrome induced by the sucrose water regimen, whereas C57BL/6J mice were more responsive to the high-fat diet regimen.

In Wistar rats, symptoms associated with metabolic disease were all observed in group B. The sucrose water regimen significantly increased visceral fat accumulation; serum concentrations of lipids, glucose, insulin, and uric acid; the AUC of the OGTT and ITT; and blood pressure. In contrast, the high-fat diet regimen only increased visceral fat

accumulation and serum insulin levels. On the contrary, the high-fat diet regimen elicited a full array of metabolic disturbances in C57BL/6J mice, but not the sucrose water regimen. Results of 2-way ANOVA indicated that the high-fat diet regimen had significant effects in increasing the values of all parameters measured (ie visceral fat accumulation; serum concentrations of lipids, glucose, and insulin; and the AUC of the OGTT and ITT), whereas the sucrose water regimen only had significant effects in increasing visceral fat and serum lipids and, unexpectedly, decreasing AUC of the OGTT. This is in accordance with the notion that C57BL/6J mice are more sensitive to a high-fat diet than a high-sucrose diet in terms of the development of obesity and insulin resistance [6,8-10]. The obesogenic and diabetogenic effects of the high-fat diet used in this study were verified in the C57BL/6J mice.

Oliart et al [13] first described success in the use of sucrose water to elicit symptoms similar to human metabolic syndrome in Wistar rats, and this strategy has been applied in many studies [14,15,24-26]. However, it is rarely used in C57BL/6J mice, a species suggested to be resistant to sucrose treatment. On replacing starch with an equal amount of sucrose in solid food with a normal fat content, Surwit et al [6] and Sumiyoshi et al [8] failed to induce obesity and hyperinsulinemia in C57BL/6J mice. In the present study, sucrose was introduced as an extra caloric source by addition to the drinking water. As a result, induction of obesity was seen; but insulin resistance was not elicited in sucrose water–treated C57BL/6J mice.

Because excess calorie intake is considered to be an important contributor to obesity or metabolic syndrome [3], the animals used in this study were fed ad libitum, rather than pair-fed isoenergetically. Regardless of the animal species examined, the sucrose water–fed animals consumed almost 50% less of the solid diet (and nutrients) than the controls (data not shown), but still had a significantly higher energy intake because of the energy content of the sucrose water. It is known that liquid carbohydrate (vs solid carbohydrate) elicits a weak compensatory dietary response and increases the risk of positive energy balance [27]. Accordingly, sucrose water drinking in Wistar rats provides a good model for studying metabolic syndrome because the rats are exposed to a similar environmental temptation to humans. In other words, the dietary effects of sucrose water drinking are similar to the overconsumption of sucrose-sweetened beverages (or empty-caloric foods) in modern human life, which results in a higher energy intake but lower nutrient value. It is possible that the adverse effects of a high sucrose intake might be accelerated by micronutrient inadequacy (eg, vitamin D deficiency, which had been linked to metabolic disease [28]), but this remains to be investigated. In addition, other concerns about this model, for example, water balance, including water intake and diuresis, need to be addressed and carefully evaluated in further studies.

For establishing animal models of metabolic syndrome, Oron-Herman et al [29] compared 2 commonly used models—sucrose water given to spontaneous hypertension rats (a model with a predominantly genetic spontaneous appearance of the metabolic syndrome) and a high-fructose diet (60% fructose in feed) given to Sprague-Dawley rats (an environmentally acquired metabolic syndrome model)—in terms of inducing metabolic syndrome. Because of the higher baseline values for blood levels of TG and insulin and blood pressure in the spontaneous hypertension rats, 12% sucrose water only had a mild exacerbating effect on insulin resistance and hypertension. In contrast, the high-fructose diet–fed Sprague-Dawley rats showed all the components of metabolic syndrome (glucose intolerance, hyperinsulinemia, hyperlipidemia, and hypertension), but were not obese.

It was also intriguing whether the combination of the 2 unhealthy dietary habits, each with independent adverse effects on metabolic health, resulted in an exacerbated condition. However, the expected additive or synergistic effects of the 2 dietary regimens were not observed in this study, except on serum cholesterol levels in C57BL/6J mice, for which no interaction was shown by 2-way ANOVA (Table 1). Most measured parameters of the group AB were comparable to either group A or group B. In addition, sucrose water–induced hypercholesterolemia, hyperglycemia, and insulin resistance (indicated by the AUC of ITT) were seen in Wistar rats consuming the chow diet (group B), but not in rats on the high-fat diet (group AB); and the high-fat diet–induced hyperglycemic effect was seen in C57BL/6J mice receiving plain water (group A), but not those receiving sucrose water (group AB). These interactions of the 2 diet regimens are interesting and worth further studies. A possible explanation for the interaction effects between the sucrose water and the high-fat diet regimens might be related to the fact that a high-fat diet has been shown to inhibit hepatic carbohydrate response element binding protein (ChREBP) expression in rats [30], thus slowing down the conversion of carbohydrate into fat (ie, de novo lipogenesis). In accordance with this, no further increase in lipid accumulation in tissues (liver and muscle) and adipocyte size (Fig. 6) was observed in group AB compared with groups A and B.

The genetic predisposition to sucrose water–induced metabolic syndrome might be associated with the sterol regulatory element binding protein-1c (*SREBP-1c*) gene. SREBP-1c, like ChREBP, is a transcription factor that plays a central role in up-regulating lipogenic and glycolytic gene expression [31,32]. It has been shown that susceptibility to fructose-induced hepatic lipogenesis is associated with a single nucleotide polymorphism at bp −468 in the promoter region of *SREBP-1c* [33]. In a study of 10 strains of inbred mice, C57BL/6J mice were found to be resistant to sucrose-/fructose-induced fatty liver because they have adenine instead of guanine at this site, which blunts the increase in liver SREBP-1c mRNA levels in response to a high-fructose diet [33]. With guanine at this site, ddY mice given sucrose water to drink show increased body weight gain and liver lipid accumulation accompanied by increased SREBP-1c

and ChREBP mRNA levels and mRNA levels of their target genes in the liver [34]. In this study, although we did not determine the single nucleotide polymorphism of the *SREBP* gene, sucrose water consumption resulted in increased SREBP-1c and ChREBP mRNA levels in the liver in Wistar rats (data not shown).

In conclusion, to establish animal models with diet-induced metabolic syndrome, 2 unhealthy dietary habits commonly seen in human society (ie, a high fat intake and a sucrose-containing beverage intake) were simulated by feeding a high-fat diet regimen or sucrose in drinking water regimen in Wistar rats and C57BL/6J mice. Our results suggest that Wistar rats are more responsive to sucrose water regimen, whereas C57BL/6J mice are more responsive to the high-fat diet regimen, in terms of eliciting a full array of metabolic syndrome. In both C57BL/6J mice and Wistar rats, the metabolic disturbances were not further aggravated by the combination of these 2 unhealthy dietary habits.

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