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Original

Promoting Effects of Sucrose-rich Diet on N-Nitrosobis (2-oxopropyl) amine-induced Pancreatic Carcinogenesis in Hamsters

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Abstract: It has been reported that there is an association between pancreatic cancer and obesity, impaired glucose metabolism and diabetes based on excess dietary fat and sugar intakes. A number of studies have suggested that a high-fat diet increases development of carcinomas in various organs and possible risk factors for pancreatic cancer. However, how an excess sugar intake promotes pancreatic carcinogenesis is still unknown. In the present study, we investigated the influence of an excess sugar intake on pancreatic carcinogenesis by administration of a sucrose-rich diet in which starch was replaced by sucrose in order to contain the same calories and other nutrients. Two similar experiments were performed. Six-week-old male Syrian golden hamsters were given N-nitrosobis (2-oxopropyl) amine (BOP) at a dose of 50 and 20 mg/kg body weight as a carcinogen in Week 0 and 1, respectively. In Week 2, the animals were divided into control and experimental groups. In experiment 1, 15 animals received a control diet or sucrose-rich diet in which 100% of the starch was replaced by sucrose, respectively. Since five animals fed on the sucrose-rich diet died by Week 12, the diet was changed to a sucrose-rich diet in which 50% of the starch was replaced by sucrose. In experiment 2, 15 animals received a control diet or sucrose-rich diet in which 50 or 20% of the starch was replaced by sucrose, respectively. All animals were sacrificed 25 weeks after the start of the experiment, and histological examination of the pancreas was performed. No significant difference was seen in the body weight at the end of the experiment. There were no significant differences in the glycosylated hemoglobin (HbA1c) and serum triglyceride, total cholesterol and HDL-cholesterol levels between the control and sucrose-rich diet groups in experiments 1 and 2. The incidence and number of carcinomas increased in hamsters fed the sucrose-rich diet compared with the control diet in experiments 1 and 2. These results suggest that an excess sucrose intake may promote the development of pancreatic cancer in hamsters. (J Toxicol Pathol 2010; **23**: 19–24)

Key words: sucrose-rich diet, pancreas, carcinogenesis, N-nitrosobis (2-oxopropyl) amine, hamster

Introduction

Despite recent diagnostic and therapeutic advances, pancreatic cancer shows the highest mortality among malignancies, with a 5-year survival rate of <5 %. Thus, prevention could play an important role in reducing pancreatic cancer-related mortality.

The risk factors for pancreatic cancer are not yet well-established, except for cigarette smoking[1]. About 80% of pancreatic cancer patients show impaired glucose metabolism, insulin resistance and frank diabetes. However, the correlation between type 2 diabetes and development of pancreatic cancer is still contravertial[2–4]. Experimental studies have reported that induction of peripheral insulin resistance by the administration of a high-fat diet promotes the development of pancreatic carcinoma in BOP-treated hamsters, which closely resemble their human counterparts[5–7]. Some epidemiological studies suggest that a high-fat diet and obesity, which causes peripheral insulin resistance, may induce compensatory islet cell proliferation and promote development of pancreatic cancers. And the inhibition of islet cell proliferation by streptozotocin and improvement of insulin resistance by metformin inhibit the development of pancreatic cancer in hamsters[8–12].

It has been shown that an excess dietary sugar intake may be associated with a greater risk of pancreatic

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Table 1. Composition of Experimental Diets (g/100 g)

Components	Control diet	Sucrose-rich diet		
		100S	50S	20S
Corn starch	50	–	25	40
α-starch	15	–	7.5	12
Sucrose	–	65	32.5	13
Milk casein	20	20	20	20
Soybean oil	5	5	5	5
Cellulose	5	5	5	5
Mineral mix	3.5	3.5	3.5	3.5
Vitamin mix	1	1	1	1
L-cystine	0.3	0.3	0.3	0.3
Choline bitartrate	0.25	0.25	0.25	0.25
Butylhydroquinone	0.0014	0.0014	0.0014	0.0014
Energy (kcal/g)	3.85	3.85	3.85	3.85

100S: 100% sucrose-rich diet. 50S: 50% sucrose-rich diet. 20S: 20% sucrose-rich diet.

cancer[13–15]. Insulin can act as a promoter of tumor development by inhibiting apoptosis and stimulating cell proliferation[16]. Therefore, impaired glucose metabolism, insulin resistance and hyperinsulinemia may be risk factors associated with pancreatic cancer. Furthermore, slightly elevated risks of pancreatic cancer, especially those associated with sucrose, have been obseved in overweight and obese people who may already have developed insulin resistance[13, 16]. However, few experimental studies have investigated the effects of dietary sugar intake and impaired glucose metabolism on pancreatic carcinogenesis.

In the present study, the effect of excess sugar intake on pancreatic carcinogenesis was investigated using a sucrose-rich diet, in which starch was replaced at rates of 20, 50 and 100% by sucrose in order to administer the same levels of calories and the other nutrients, in a hamster-based experimental model for pancreatic adenocarcinomas.

Materials and Methods

Animals

Five-week-old male Syrian golden hamsters weighing approximately 90 g were obtained from Japan SLC (Shizuoka, Japan) and acclimated to the laboratory for one week. They were housed three or four per plastic cage in an air-conditioned room at 24°C and 60% humidity, with a daily 12-hour alternating cycle of light and dark. Body weights were measured weekly, and food consumption was measured twice a week.

Diets

All feed was obtained from CLEA Japan, Inc. (Osaka, Japan). The animals in the control group received a semipurified diet containing 65% starch (50% corn starch and 15% α-starch), 20% milk casein, 5.0% soybean oil, 5.0% cellulose, 3.5% mineral mix and 1.0% vitamin mix (control diet). The animals in sucrose-rich diet group received the same semipurified diet except that 20, 50 or 100% of the starch was replaced by sucrose (20S, 50S and 100S diets, respectively). The compositions of the diets are shown in Table 1. All diets provided approximately 3.85 kcal/g of chow, and the animals had free access to food and water for 25 weeks.

Study design

Two similar experiments were performed according to the following protocol. In experiment 1, thirty hamsters at 6 weeks of age were used. BOP (Nacalai Tesque, Kyoto, Japan) at a dose of 50 or 20 mg/kg body weight was administered subcutaneously in Weeks 0 and 1, respectively. The animals were randomized into two dietary groups of 15 animals each at in Week 2. They subsequently received a control or 100S diet. Since five animals fed on the 100S diet died by Week 12, the diet was changed to a 50S diet starting in Week 14. In experiment 2, forty-five hamsters at 6 weeks of age were used. BOP at a dose of 50 or 20 mg/kg body weight was administered subcutaneously in Weeks 0 and 1, respectively. The animals were randomized into three dietary groups of 15 animals each in Week 2. They subsequently received a control, 20S or 50S diet.

In experiments 1 and 2, animals were sacrificed at 25 weeks after the start of the experiment. Animals were fasted for at least 15 hours before autopsy. Blood samples were collected from the inferior vena cava under pentobarbital anesthesia. Serum were stored at –80°C until being assayed for triglycerides and total and HDL cholesterol, and blood cell-precipitates were stored at 4°C until assayed for glycosylated hemoglobin (HbA1c;immunoagglutination methods by SEKISUI MEDICAL Co., Ltd, Tokyo, Japan). In experiment 2, serum were assayed for glucose and insulin (ELISA methods by Shibayagi Co., Ltd, Gunma, Japan) in addition to the items examined in experiment 1. At autopsy, the pancreas, liver and adipose tissue (epididymal fat) were totally removed and weighed. The pancreas was fixed in 10% phosphate-buffered formalin (pH 7.4) after spreading on filter paper, processed for histology by conventional

methods, and embedded in paraffin wax. It was then sectioned and stained with hematoxylin and eosin for histopathological examination.

All experiments were conducted in accordance with guidelines for Animal Experiments at Nara Medical University, which are in line with other guidelines and laws concerning animal rights.

Statistical analysis

The experimental data, except for the incidence of lesions, are expressed as the mean ± SD. Statistical significance between groups was compared using the Student's t-test for mean data and the Fisher's exact test for incidence data in experiment 1 and using the Tukey's HSD test for mean data and the chi-square test for incidence data in experiment 2.

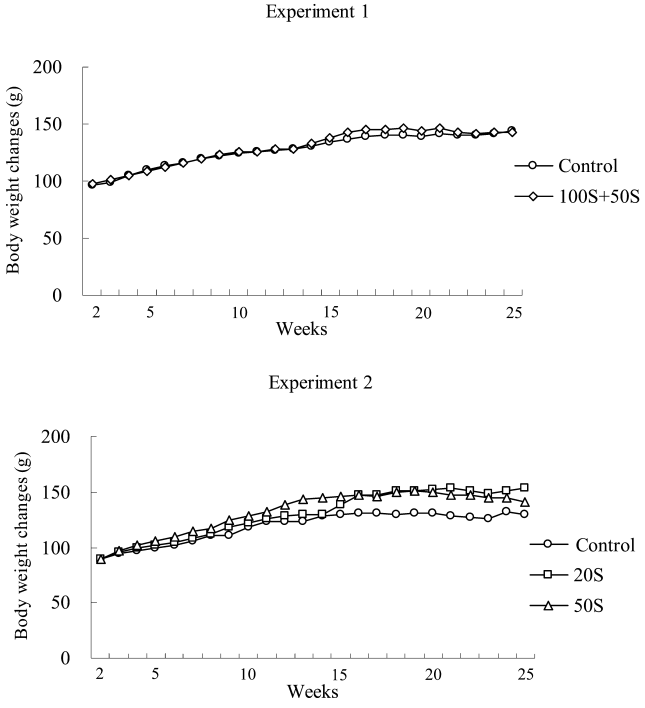

Fig. 1. Mean body weight changes in hamsters fed sucrose-rich diets.

Results

Clinical signs and survival

In experiment 1, five animals fed the sucrose-rich diet lost weight rapidly and died by Week 12. At autopsy, liver nodules were observed in the dead animals, but the cause of death was not clear. After the diet was changed to a sucrose-rich diet in which 50% of the starch was replaced by sucrose, no deaths occurred in the animals during the period of experiment.

In experiment 2, there ware no adverse clinical signs or deaths.

Gross findings

In experiments 1 and 2, liver nodules were observed in all animals at the end of the experiment.

Body weight, relative organ weights and energy intake

In experiment 1, there were no significant differences in body weight between the control and sucrose-rich diet groups throughout the experiment period, whereas the energy intake in the sucrose-rich diet group was lower than that in the control diet group (21.4 ± 2.8 vs. 23.6 ± 3.5 kcal/day, $P<0.01$, respectively). In experiment 2, there were no significant differences in body weight between the control, 20S and 50S diet groups throughout the experiment period (Fig.1), whereas the energy intake in the 50S diet group was lower than that in the control and 20S diet groups (20.0 ± 3.9 vs. 22.8 ± 5.1 kcal/day, $P<0.01$ and 20.0 ± 3.9 vs. 22.1 ± 3.3 kcal/day, $P<0.05$, respectively). Body weight gain tended to increase in the 50S group, but there were no statistically significant differences. There were no significant differences in the relative weights of the pancreas, liver and

Table 2. Effects of Sucrose-Rich Diets on the Final Body Weight, Relative Organ Weights and Energy Intake

Experiment 1

Group	Effective No. of animals	Body weight (g)	Pancreas (%)	Liver (%)	Epididymal fat (%)	Energy intake (kcal/day)
Control	15	144 ± 25	0.58 ± 0.2	4.6 ± 0.5	2.4 ± 0.5	23.6 ± 3.5
100S+50S	10	142 ± 27	0.67 ± 0.2	5.4 ± 2.8	2.4 ± 0.7	21.4 ± 2.8**

Experiment 2

Group	Effective No. of animals	Body weight (g)	Pancreas (%)	Liver (%)	Epididymal fat (%)	Energy intake (kcal/day)
Control	8	129 ± 21	0.48 ± 1.2	4.4 ± 1.2	1.9 ± 0.3	22.8 ± 5.1
20S	9	153 ± 21	0.70 ± 0.2	4.6 ± 0.8	2.3 ± 0.5	22.1 ± 3.3
50S	11	141 ± 24	0.58 ± 0.1	4.4 ± 0.7	2.3 ± 0.5	20.0 ± 3.9**$^{\#}$

Values are expressed as the mean ± SD. Organ weights are expressed as a percentage of body weight. **: $P<0.01$ compared with the control group. $^{\#}$: $P<0.05$ compared with the 20S diet group.

Table 3. Effects of Sucrose-Rich Diets on the Serum Glucose, Insulin, Triglyceride, Cholesterol and Glycosylated Hemoglobin Levels

Experiment 1

Group	Effective No. of animals	HbA1c (%)	TG (mg/dL)	T-CHO (mg/dL)	HDL-C (mg/dL)
Control	15	4.1 ± 3.7	307 ± 84	195 ± 38	44 ± 29
100S+50S	10	4.1 ± 3.9	332 ± 101	196 ± 49	42 ± 25

Experiment 2

Group	Effective No. of animals	GLU (mg/dL)	INS (ng/mL)	HbA1c (%)	TG (mg/dL)	T-CHO (mg/dL)	HDL-C (mg/dL)
Control	8	90 ± 17	7.5 ± 5.5	2.8 ± 0.4	127 ± 54	176 ± 28	107 ± 17
20S	9	105 ± 31	7.7 ± 4.4	3.3 ± 0.9	157 ± 49	185 ± 16	108 ± 24
50S	8	112 ± 22	5.9 ± 5.2	3.4 ± 0.6	179 ± 48	169 ± 25	97 ± 19

Values are expressed as the mean ± SD. HbA1c: glycosylated hemoglobin. TG: triglycerides. T-CHO: total cholesterol. HDL-C: high-density lipoprotein cholesterol. GLU: glucose. INS: insulin.

Table 4. Effects of Sucrose-Rich Diets on the Number and Incidence of BOP-Induced Pancreatic Lesions in Hamsters

Experiment 1

Group	Effective No. of animals	AH	AC
Control	15	0.6 ± 0.7	0.1 ± 0.3 (6.7)
100S+50S	10	1.2 ± 0.8	0.6 ± 0.7* (50.0*)

Experiment 2

Group	Effective No. of animals	AH	AC	AH + AC
Control	8	0.6 ± 0.7	0 (0)	0.6 ± 0.7 (50.0)
20S	9	1.4 ± 1.7	1.0 ± 1.3$^{\#}$ (44.4$^{\#}$)	2.4 ± 2.7 (66.7)
50S	11	1.3 ± 1.1	0.2 ± 0.4 (18.2)	1.5 ± 0.9 (90.9$^{\#}$)

AH: atypical hyperplasia. AC: adenocarcinoma. The number of lesions is expressed as the mean ± SD, and the incidence (%) of lesion is shown in parentheses. *: $P<0.05$ compared with the control group. $^{\#}$: $P<0.05$ compared with the other groups.

epididymal fat between the control and sucrose-rich diet groups in both experiments 1 and 2 (Table 2).

Serum glucose, insulin and glycosylated hemoglobin

In experiment 1, there were no significant differences in the HbA1c levels of both groups. In experiment 2, there were no significant differences in the HbA1c and serum glucose and insulin levels between groups (Table 3).

Serum triglycerides and cholesterol

In experiments 1 and 2, there were no significant differences in the serum triglyceride, total cholesterol and HDL-cholesterol levels between groups (Table 3).

Incidence and number of pancreatic adenocarcinomas

In this study, proliferative ductal lesions of the pancreas were classified into atypical hyperplasia and adenocarcinoma. Proliferative ductal lesions were diagnosed according to well-established criteria that have been described previously[17]. In experiment 1, the incidence and number of pancreatic adenocarcinomas increased in the sucrose-rich diet group compared with the control group (50.0 vs. 6.7% and 0.6 ± 0.7 vs. 0.1 ± 0.3/animal, $P<0.05$, respectively). In experiment 2, the incidence and number of adenocarcinomas were higher in the 20S diet group compared with the control and 50S diet groups (44.4 vs. 0 and 18.2%, $P<0.05$, and 1.0 ± 1.3 vs. 0 and 0.2 ± 0.4/animal, $P<0.05$, respectively). In addition, the incidence of proliferative ductal lesions including atypical hyperplasia and adenocarcinoma increased in the 50S groups compared with the control and 20S diet groups (90.9 vs. 50.0 and 66.7%, $P<0.05$, respectively; Table 4).

Other pancreatic lesions were not observed in ether experiment.

Discussion

Our present study demonstrated that a sucrose-rich diet in which starch was replaced by sucrose promoted BOP-induced pancreatic carcinogenesis in hamsters for 25 weeks, but did not induce hyperglycemia, hyperinsulinemia or hyperlipidemia. Under the experimental conditions employed in this study, there were no marked differences in the total calorie, lipid, protein or vitamin intakes among the groups, suggesting that excessive sucrose consumption promotes pancreatic carcinogenesis. In experiment 1, some animals in the 100S diet group died. However, the causes of death were unclear. In experiment 2, the pancreatic carcinogenesis-promoting effects of the 50S diet were less marked than those of the 20S diet. This was possibly because some other influence for promoter effect appeared when starch was replaced by sucrose at 50% or more.

Epidemiological studies have reported that high fructose and sucrose intakes are associated with a greater risk of pancreatic cancer[13–15]. A high intake of fructose and sucrose has a strong association with overweight and obesity in human and experimental animals[18–21]. In experiment 2, although the energy intake in the 50% sucrose-rich diet group was significantly lower than that in the control group, body weight gain tended to increase. The PFC rates indicate the percentages of calorie intake derived from protein (P), fat (F) and carbohydrates (C) of the total dietary calorie intake. Nutritionally, a P rate of 12 to 13%, F rate of 20 to 30%, and C rate of 57 to 68% are considered appropriate. The PFC rates of standard Japanese food are approximately 13, 29 and 58%, respectively, similar to the optimal rates. Internationally, dietary starch energy intake decreases with an increase in the national income, and animal protein, fat and sugar consumption increases. In the average Japanese diet, appropriate PFC ratios are still maintained. However, currently, fat and sugar intake has slightly increased in comparison with the period from 1955 to 1964[22]. The PFC rates of the 20S diet employed in this experiment were 20.8, 11.7 and 67.5% (sucrose: 13.5%), respectively. Extrapolation of this diet to human diet (2,000 kcal per day) shows that the calorie intake from sucrose is 270 kcal. This value corresponds to 67.5 g of sucrose, similar to the amount of sugar contained in approximately 500 ml of a soft drink. The results of this experiment support the fact that frequent consumption of favorite foods such as soft drinks, breads, cakes, ice cream and jam in daily life is a risk factor for pancreatic cancer.

These results indicate that, even when the calorie intake from carbohydrates is similar, an increase in calorie intake from sucrose, in comparison with that from starch, promotes the development of pancreatic cancer. Sucrose is more rapidly absorbed compared with starch, increasing the blood sugar level earlier. Therefore, the blood level of insulin is elevated. As a growth factor, insulin stimulates pancreatic cancer cell proliferation. The sucrose-rich diets may have promoted pancreatic carcinogenesis by transiently increasing the blood insulin level more markedly in comparison with the starch diet. In this experiment, there were no significant differences in the insulin level among the groups. However, this was possibly because the insulin level was measured after fasting. The relationship of the rate and duration of the postprandial increase in the insulin level with pancreatic carcinogenesis should be further investigated. On administration of 10% sucrose in the drinking water to hamsters for up to 24 weeks, the blood glucose levels of the hamsters remained within the normal range, while those of the rats did not[23–25]. The hamsters remained normoglycemic as a result of a neogenetic reaction of islet β-cells, while rats lack such a neogenetic reaction. In humans, hyperinsulinemia is observed in the initial phase of type 2 diabetes. However, when the condition persists, β cells are affected, reducing insulin secretion. Epidemiologically, the correlation between type 2 diabetes and pancreatic cancer development is still obscure. This may be because patients showing various insulin levels were enrolled in previous studies.

In conclusion, the sucrose-rich diets promoted pancreatic carcinogenesis without inducing obesity, diabetes or hyperlipidemia in hamsters. Sucrose at the level contained in the 20S diet can also be realistically ingested by humans, suggesting that the daily consumption of a large amount of sugar is a risk factor for pancreatic cancer.

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