Suppressive Effect of Cellulose on Osmotic Diarrhea Caused by Maltitol in Healthy Female Subjects

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Summary Using a single-group time-series design, we determined that osmotic diarrhea caused by maltitol ingestion was suppressed by the addition of not only soluble but also insoluble dietary fiber in healthy humans. We then clarified that cellulose delayed gastric emptying in rats. Twenty-seven healthy volunteers ingested maltitol step-wise at doses of 15, 20, 25, 30, 35, 40 and 45 g from small to large amounts. Within that range of ingested amounts, 22 out of 27 subjects experienced osmotic diarrhea from maltitol ingestion, and the minimal dose level of maltitol that induced osmotic diarrhea (MMD) was established for each subject. When 5 g of cellulose was added to the MMD, osmotic diarrhea was suppressed in 13 out of 19 subjects (68.4%), while partially hydrolyzed alginate-Na (PHA-Na), a soluble dietary fiber, suppressed osmotic diarrhea in 10 out of 20 subjects (50.0%). When a mixed solution of cellulose and maltitol was administered to rats, the gastric emptying of maltitol was significantly delayed at 30 and 60 min after administration (p=0.019, p=0.013), respectively. PHA-Na also significantly delayed gastric emptying at 30 min (p=0.013). In conclusion, cellulose can suppress the osmotic diarrhea caused by maltitol ingestion in humans and delay the gastric emptying of maltitol in rats. A new physiological property of cellulose was clarified in this study.

Key Words cellulose, osmotic diarrhea in humans, maltitol, partially hydrolyzed sodium alginate, gastric emptying in rats

Cellulose, which consists of plant cell walls, is an insoluble dietary fiber of glucose polymers with β-1,4 linkages (1). Ingestion of cellulose increases stool weight and alleviates constipation. In addition, cellulose can displace energy density, or increase the time of mastication (2). Cellulose and its derivatives, methylcellulose and cellubiose, which are produced from cellulose using specific bacterial enzymes, are broadly used in food manufacture and in the formulation of tablets (1, 3). However, cellulose has no viscosity or gel-forming capability. Although some beneficial health effects such as lowering plasma cholesterol and suppressing postprandial hyperglycemia are associated with the viscosity of soluble dietary fiber (1, 2, 4–7), cellulose is generally recognized to be rather inert with regard to these health effects. However, Takahashi et al. reported that crystalline cellulose reduces plasma glucose concentration in rats (8), so it is likely that cellulose has other physiological functions in gastrointestinal tracts.

In a previous study, we reported that the addition of 5 and 10 g of partially hydrolyzed guar gum (PHGG) to the minimal dose level of maltitol that induced osmotic diarrhea (MMD) suppressed diarrhea in 23 out of 28 subjects (82.1%) (9). In addition, PHGG improved the diarrhea caused by tube feeding of enteral nutrition in the elderly (10, 11) and treated acute diarrhea with infection in children (11, 12). Washington et al. reported that diarrhea caused by lactulose ingestion in humans was suppressed by adding psyllium (13). These effects might be associated with the viscosity of soluble dietary fiber, which is an important determinant of gastric emptying (14–18) and small bowel transit (19), or with the fermentability of the dietary fiber (20, 21). It is not clear whether insoluble dietary fibers also suppressed osmotic diarrhea caused by maltitol ingestion.

Maltitol is one of the non-digestible sugar alcohols with good sweetness and beneficial health effects such as a prebiotic effect or a prevention against dental caries (20, 21), and it is widely used in functional foods and processed foods. The usual intake of maltitol from these foods does not cause osmotic diarrhea; however, if the consumer eats a combination of many processed foods containing maltitol and other sugar alcohols, the total amount of sugar alcohols may exceed the laxative threshold and osmotic diarrhea may occur (21–25). In addition, osmotic diarrhea may spoil the prebiotic effect of maltitol. The suppression of osmotic diarrhea is essential in the development of functional foods and processed foods using non-digestible oligosaccharides and sugar alcohol.

The objectives of this study were to clarify that cellulose suppresses osmotic diarrhea caused by maltitol ingestion, to compare that with the suppressive effect of partially hydrolyzed sodium alginate (PHA-Na), a solu-
ble dietary fiber in humans, and to investigate the delaying effect of PHA-Na and cellulose on gastric emptying, using rats.

**MATERIALS AND METHODS**

**Materials.** We used a microcrystalline cellulose (Celolus FD-101®) with an average particle size of 50 μm, which was provided by Asahi Kasei Chemicals Corp. (Tokyo, Japan). Maltitol (Lesys®, purity > 98%) produced by the hydrogenation of maltose was provided by Towa Chemical Industry Co., Ltd. (Tokyo, Japan). PHA-Na (Solgin fiber®, average M.W. 55,000), which was hydrolyzed by acid from the extract of seaweed, was provided by Kaigen Co., Ltd. (Osaka, Japan).

**Subjects.** Twenty-seven female subjects participated in this study. None of the subjects had a history of gastrointestinal disease, carbohydrate malabsorption or disaccharidase deficiency, and none had been treated with antibiotics or laxatives within 2 wk before the experimental day. The average age was 22.3 ± 2.0 y, average body weight was 52.4 ± 10.4 kg and that of height was 159.4 ± 6.4 cm. The average body mass index was 20.5 ± 2.7. Each subject gave her written informed consent to participate in this study.

**Experimental protocol for the evaluation of a suppressive effect of cellulose on osmotic diarrhea caused by maltitol in humans.** The experimental protocol in humans is shown in Fig. 1. The protocol was carried out according to our previous study (9, 23–25) using a single-group time-series design.

Experiment 1: Measurement of the minimal dose level of maltitol that induces osmotic diarrhea: In a previous study, we clarified that the dose level of maltitol that induces osmotic diarrhea varied from person to person (9, 23–25). First, the minimal dose level of maltitol that would induce osmotic diarrhea was estimated in each subject. Each subject ingested 15, 20, 25, 30, 35, 40 and 45 g of maltitol step-wise from small to large amounts at intervals of 7 d. The ingestion of maltitol was stopped when osmotic diarrhea was induced by the ingestion of maltitol, and this maltitol level in each subject was set to be the minimal dose level of maltitol that induces osmotic diarrhea (MMD) for that subject. When a subject did not experience diarrhea from the ingestion of 45 g maltitol, the largest dose used in this experiment, she was excluded from the next trial, which attempted to determine the suppressive effect of dietary fiber on osmotic diarrhea.

Experiment 2: Evaluation of the suppressive effect of the cellulose on osmotic diarrhea caused by maltitol ingestion: To evaluate the suppressive effect of cellulose on osmotic diarrhea caused by maltitol ingestion, each subject was administered a mixed solution of 5 g of cellulose and MMD estimated in experiment 1. Thereafter, to compare the suppressive effect on osmotic diarrhea, each subject ingested a mixture of 5 g of PHA-Na and MMD. The test substance was dissolved in 150 mL of warm tap water, and the subjects were required to finish ingesting the solution within a few minutes. Each subject ingested the mixed solution of maltitol and dietary fiber at intervals of 7 d.

More than 1 wk after the suppressive effect of dietary fiber on osmotic diarrhea was evaluated, in order to confirm the repeatability and reliability of MMD, the 10 subjects that were selected by a random sampling were required to ingest the MMD again.

Restrictions placed on the subjects: Beginning 2 d prior to the experimental day, all of the subjects were...
required to avoid ingestion of foods and beverages containing non-digestible sugar substitutes and other non-digestible or fermentable ingredients. The subjects were required to avoid both eating and drinking 3 h before and after the administration of the test solution on the day of the experiment.

Data collection: Beginning 24 h after administration, episodes of osmotic diarrhea, fecal shape and side effects such as abdominal pain, borborygmus, distension and the onset time of defecation were recorded by the subjects themselves according to a prescribed form using a questionnaire (23–26). The fecal shapes were classified according to the following descriptors: very hard, hard, normal, soft, muddy, and watery (26). The defecation of muddy or watery stool was defined as diarrhea in this experiment.

Experimental protocol for the evaluation of delaying effect of cellulose on gastric emptying of maltitol in rats. We investigated whether the ingestion of cellulose delayed gastric emptying of maltitol, similar to the effect of PHA-Na, using rats.

Animals: Seven-week-old male Wistar rats (CLEA Japan, Inc., Tokyo, Japan) were housed in air-conditioned cages (22–24°C, 50% humidity) and maintained on a 12 h light-dark cycle (light from 8:00 to 20:00). They were fed a standard solid diet (MF diets, Oriental Yeast Co., Ltd., Tokyo, Japan) and distilled water ad libitum.

Test solutions administered to rats: Test solutions were 300 mg of maltitol per milliliter solution as a control, a mixed solution containing 300 mg of maltitol and 75 mg of cellulose per milliliter, and a mixed solution containing 300 mg of maltitol and 75 mg of PHA-Na. The ratio of maltitol to cellulose in the test solution was 4 : 1, based on the human experiments in which the suppressive effect on diarrhea had been observed.

Collection of gastrointestinal digesta: Sixty rats were randomly assigned to 3 groups (20 rats in each group). One group was administered the maltitol solution as a control group, and the other 2 groups were administered the mixed solution of maltitol and cellulose, or the mixed solution of maltitol and PHA-Na. We administered 2 mL of the test solutions to each rat using a stomach sonde. After the administration of the test solutions, 5 rats from each of the 3 groups were sacrificed by decapitation at 0, 30, 60 and 120 min, respectively. The rats that were sacrificed immediately after the administration of the test solution were considered to have been killed at 0 min. After the decapitation, the stomachs and small intestines were removed from each rat. The gastric digesta and the small intestinal contents were collected from each rat by washing in 45 mL of physiological saline.

Preparation of sample solution for HPLC analysis: The collected digesta were heated at 100°C to inactivate the enzymes and centrifuged at 10,000 × g for 15 min at 20°C. The supernatants were used for HPLC analysis to measure the maltitol contents. The samples were stored at −20°C until HPLC analysis.

HPLC condition of maltitol analysis: The maltitol in the digesta was analyzed by the HPLC system (SCL-10A, Shimadzu Corp., Kyoto, Japan) with a refractive index detector (RID-10A, Shimadzu Corp.) using a Shodex SUGAR SC1011 column (8.0 mm ID × 300 mm L., Showa Denko Co., Ltd., Tokyo, Japan). The analysis was performed at a constant temperature of 80°C. The sample was eluted with deionized distilled water at a flow rate of 1.0 mL/min and the injection volume of the sample was 5 μL.

Calculation and statistical analysis. We used the chi-square test to compare the percentage of the subjects whose osmotic diarrhea was improved by ingesting cellulose, PHA-Na or PHGG (9). The amount of maltitol remaining in the rat stomach and the amount being transferred to the small intestine at each time point after administration were calculated in terms of means and standard deviations (SD), and we compared the amount among the maltitol group, the maltitol and cellulose group, and the maltitol and PHA-Na group using ANOVA and Tukey’s post hoc test. A p-value of less than 0.05 was considered to be significant. The statistical analysis was performed using SPSS version 11.0 for Windows, Japan (SPSS Inc., Tokyo, Japan) (27).

Ethics. The protocol of the human experiment was approved in accordance with the tenets of the Declaration of Helsinki and the ethical committees of Siebold University of Nagasaki. The rat experiment was performed according to the guidelines on the care and use of laboratory animals of Siebold University of Nagasaki and the standards relating to the care and management of experimental animals (Notification No. 6, March 27, 1980 of the Prime Minister’s Office). All of the experiments were carried out in the Laboratory of Public Health Nutrition of the Graduate School of Human Health Science, Siebold University of Nagasaki.

RESULTS

Suppressive effect of cellulose on osmotic diarrhea caused by maltitol in humans

The MMD and the number of subjects whose osmotic diarrhea was improved by the addition of cellulose or PHA-Na are shown in Table 1.

The MMD in each subject. None of the subjects reported serious side effects during any of these experiments. Twenty-seven subjects completely finished the maltitol ingestions. Twenty-two out of 27 subjects (81.5%) experienced osmotic diarrhea following ingestion of doses from 20 to 45 g of maltitol, and we determined the MMD in each subject. The MMD in each subject thus varied from 20 to 45 g. No subject had osmotic diarrhea after the ingestion of 15 g of maltitol. Five subjects (18.5%) had no diarrhea even at the largest dose of 45 g maltitol, so they were excluded from the next trial, in which we attempted to determine the suppressive effect of dietary fiber on osmotic diarrhea.

Suppressive effect of cellulose on osmotic diarrhea induced by maltitol ingestion. Nineteen out of 22 subjects completely finished the experiment involving the mixture of maltitol and cellulose ingestion, and 20 out of 22 subjects completely finished the experiment involving the...
ingest the test solution. The calculation because they could not completely ingest the MMD.

Subjects of the PHA-Na experiment were excluded from subjects of the cellulose ingestion experiment and the 2 subjects of the ingestion of maltitol and PHA-Na. The remaining 3 subjects of the cellulose ingestion in human subjects. To evaluate the suppressive effect on diarrhea, 5 g of cellulose or PHA-Na was added to MMD.

The addition of 5 g of cellulose to the MMD suppressed osmotic diarrhea in 13 out of 19 subjects (68.4%) in whom diarrhea was induced by the ingestion of maltitol and dietary fiber. MMD: the amount of maltitol that induced osmotic diarrhea in each subject. To evaluate the suppressive effect on diarrhea, 5 g of cellulose or PHA-Na was added to MMD.

The addition of 5 g of cellulose to the MMD suppressed osmotic diarrhea in 13 out of 19 subjects (68.4%) in whom diarrhea was induced by the ingestion of maltitol alone. PHA-Na suppressed osmotic diarrhea in 10 out of 20 subjects (50.0%). When the ratio of the number with suppressed osmotic diarrhea was compared between cellulose and PHA-Na, the difference was not significant using the chi-square test ($p=0.242$). Although the MMD varied from 20 to 45 g, the suppression of osmotic diarrhea was not related to the dose level of maltitol ingestion.

In order to confirm the repeatability and reliability of MMD, 10 subjects were randomly selected, and were required to ingest the MMD again. All of these subjects experienced osmotic diarrhea following ingestion of MMD.

### Table 1. Suppressive effect of adding 5 g of cellulose or PHA-Na to test solution on osmotic diarrhea caused by maltitol ingestion in human subjects.

| Sample No. | MMD (g) | Suppressive effect | Cellulose (5 g) | PHA-Na (5 g) |
|------------|---------|-------------------|----------------|-------------|
| 1          | 20      | ○                 | ○              | ●           |
| 2          | 20      | ○                 | ○              | ×           |
| 3          | 25      | ○                 | ○              | ○           |
| 4          | 30      | ○                 | ○              | ○           |
| 5          | 30      | ○                 | ○              | ●           |
| 6          | 35      | ○                 | ○              | ○           |
| 7          | 35      | ○                 | ○              | ○           |
| 8          | 40      | ○                 | ○              | ○           |
| 9          | 40      | ○                 | ○              | ○           |
| 10         | 45      | ○                 | ○              | ○           |
| 11         | 45      | ○                 | ○              | ○           |
| 12         | 45      | ○                 | ○              | ●           |
| 13         | 45      | ○                 | ○              | ●           |
| 14         | 25      | ●                 | ●              | ●           |
| 15         | 35      | ●                 | ●              | ○           |
| 16         | 35      | ●                 | ●              | ○           |
| 17         | 40      | ●                 | ●              | ●           |
| 18         | 40      | ●                 | ●              | ●           |
| 19         | 45      | ●                 | ●              | ●           |
| 20         | 35      | ×                 | ×              | ●           |
| 21         | 35      | ●                 | ●              | ×           |
| 22         | 35      | ×                 | ×              | ×           |

- ○: suppressed osmotic diarrhea; ●: still experienced diarrhea; ×: did not completely ingest the mixed solution of maltitol and dietary fiber.

Number of trials: 19; 20
Number of salutary effects: 13; 10
% of improvement: 68.4; 50.0

**Fig. 2. Effect of adding cellulose or PHA-Na to a maltitol solution on gastric emptying in rats.**

| Sample No. | MMD (g) | Suppressive effect | Cellulose (5 g) | PHA-Na (5 g) |
|------------|---------|-------------------|----------------|-------------|
| 1          | 20      | ○                 | ○              | ●           |
| 2          | 20      | ○                 | ○              | ×           |
| 3          | 25      | ○                 | ○              | ○           |
| 4          | 30      | ○                 | ○              | ○           |
| 5          | 30      | ○                 | ○              | ●           |
| 6          | 35      | ○                 | ○              | ○           |
| 7          | 35      | ○                 | ○              | ○           |
| 8          | 40      | ○                 | ○              | ○           |
| 9          | 40      | ○                 | ○              | ○           |
| 10         | 45      | ○                 | ○              | ○           |
| 11         | 45      | ○                 | ○              | ○           |
| 12         | 45      | ○                 | ○              | ●           |
| 13         | 45      | ○                 | ○              | ●           |
| 14         | 25      | ●                 | ●              | ●           |
| 15         | 35      | ●                 | ●              | ○           |
| 16         | 35      | ●                 | ●              | ○           |
| 17         | 40      | ●                 | ●              | ●           |
| 18         | 40      | ●                 | ●              | ●           |
| 19         | 45      | ●                 | ●              | ●           |
| 20         | 35      | ×                 | ×              | ●           |
| 21         | 35      | ●                 | ●              | ×           |
| 22         | 35      | ×                 | ×              | ×           |

- ○: suppressed osmotic diarrhea; ●: still experienced diarrhea; ×: did not completely ingest the mixed solution of maltitol and dietary fiber.

Number of trials: 19; 20
Number of salutary effects: 13; 10
% of improvement: 68.4; 50.0

**Effect of cellulose on gastric emptying of maltitol in rats.**

The total amount of maltitol in the digesta from the stomach and the small intestine at 0 min after administration was 520.4 mg, and 86.7% of the maltitol administered was recovered.

**Effect of adding cellulose or PHA-Na to maltitol solution on the remaining maltitol in rat stomach.**

The differences in the amount of maltitol remaining in the rat stomach between the solution of maltitol, the mixed solution of maltitol and cellulose, and the mixed solution of maltitol and PHA-Na are shown in Fig. 2. The amount of maltitol remaining in the stomach was 128.5±41.5 and 79.3±19.7 mg at 30 and 60 min after administration, respectively. The maltitol content remaining in the stomach was significantly greater following the addition of cellulose than that of controls at 30 min ($p=0.019$) and 60 min ($p=0.013$) after administration, respectively, by ANOVA and Tukey’s post hoc test. In the mixed solution of maltitol and PHA-Na, the amount of maltitol remaining in the stomach was 268.3±57.4 mg at 30 min after administration. Maltitol content remain-
ing in the stomach was also significantly greater after the administration of the mixture of maltitol and PHA-Na than that of the control (p = 0.013).

Effect of adding cellulose or PHA-Na on transference of maltitol from the stomach to the small intestine in rats. The effects in rats of adding cellulose or PHA-Na on the transference of maltitol from the stomach to the small intestine are shown in Fig. 3. The maltitol transferred into the small intestine following the addition of cellulose and PHA-Na were significantly less than that of controls at 30 min (p = 0.008, and p = 0.022) after administration, respectively, by ANOVA and Tukey’s post hoc test.

**DISCUSSION**

In this study, one of the newly discovered physiological properties of cellulose was clarified. Cellulose suppressed the osmotic diarrhea caused by maltitol ingestion in human subjects, and the addition of cellulose delayed the gastric emptying of maltitol in an experiment using rats. These results demonstrated that the addition of not only soluble but also insoluble dietary fibers to maltitol solution alleviated osmotic diarrhea, and one of the factors of these suppressive effects was related to the delaying of gastric emptying.

In the present study, the ratios of the number of the subjects with suppressed osmotic diarrhea were 68.4% for 5 g of additional cellulose, and 50.0% for 5 g of PHA-Na, respectively, but it was not significant. In our previous study, the suppressive effect of 5 g of additional PHGG was 35.7% (9). These results demonstrate that the osmotic diarrhea caused by maltitol ingestion was suppressed effectively by the addition of not only soluble but also insoluble dietary fiber in healthy humans.

Although the MMD varied from 20 to 45 g, the suppressive effect for osmotic diarrhea was not related to the MMD. These results support the results in our previous study (9) and indicate that insoluble or soluble dietary fibers can suppress osmotic diarrhea caused by the ingestion of any amount of maltitol. The addition of 10 g of PHGG (82.1%) to maltitol solution strongly suppressed the osmotic diarrhea in comparison with the addition of 5 g of PHGG (35.7%) in our previous study. If the amount of cellulose and PHA-Na added to the maltitol solution is increased to 10 g or more, the suppressive effect should be great and clear.

The addition of 5 g of PHGG to the minimal dose level of lactitol (9) or fructooligosaccharides (data not shown) also suppressed osmotic diarrhea in our experiments. Likewise, the simultaneous ingestion of cellulose or PHA-Na with maltitol also suppressed the osmotic diarrhea induced by the ingestion of maltitol alone. These results suggest that the high rate of osmotic diarrhea caused by non-digestible sugar substitutes is non-specifically suppressed by any kind of dietary fiber. Dietary fiber functions as a useful ingredient in the design of functional foods and processed foods using non-digestible oligosaccharides and sugar alcohols, with beneficial health effects.

The alleviation of osmotic diarrhea appears to depend on decreasing the osmotic pressure in the lower intestine. When non-digestible sugar substitutes are simultaneously ingested with soluble dietary fiber, the sugar substitutes with small molecular size are incorporated in the gel of soluble dietary fiber with large molecular size. Therefore the osmotic pressure in the small and large intestine may decrease, thus alleviating the osmotic diarrhea. However, when the osmotic pressure of the mixtures of PHA-Na and maltitol or PHGG and maltitol was measured, it was not different from the total sum of osmotic pressure from the individual substances. Cellulose cannot decrease the osmotic pressure in the lower intestine, because it does not make a gel formation. These results demonstrate that the mechanism of the suppressive effect by dietary fiber against osmotic diarrhea is not the lowering of osmotic pressure that depends on the gel formation of dietary fiber.

Some reports have described the delaying of gastric emptying by soluble dietary fiber (14–18). Viscosity seems to be an important factor in gastric emptying and small bowel transit. However, in this study, the addition of cellulose as well as PHA-Na to a maltitol solution delayed the gastric emptying of maltitol in rats. The maltitol might be slowly transferred from the stomach to the small intestine by adding dietary fiber when maltitol is orally ingested in combination with dietary fiber. As a result, the osmotic pressure in the large intestine increases mildly, because maltitol gradually reaches the large intestine, where it is completely fermented by intestinal microbes.

In conclusion, osmotic diarrhea caused by maltitol...
ingestion was suppressed by the addition of not only soluble but also insoluble dietary fiber in human subjects. Cellulose as well as PHA-Na can delay the gastric emptying of maltitol in rats. The addition of dietary fiber to processed foods containing maltitol or other sugar alcohols can reduce the risk of osmotic diarrhea, and preserve the beneficial health effect. Thus, dietary fiber can contribute to the safety of functional foods and processed foods.

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