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Changes in α-glucosidase activities along the jejunal-ileal axis of normal rats by the α-glucosidase inhibitor miglitol

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Abstract

Miglitol, an α-glucosidase inhibitor that inhibits postprandial hyperglycemia by delaying carbohydrate digestion and absorption along the jejunal-ileal axis, has recently been approved for use in patients with type 2 diabetes mellitus. Miglitol treatment may lead to increased α-glucosidase activities toward the ileum because carbohydrate flow toward the ileum increases. However, it is not yet known if miglitol treatment alters the α-glucosidase activities along the jejunal-ileal axis. In this study, we examined the effects of miglitol supplementation for 3 or 7 days on α-glucosidase activities along the jejunal-ileal axis of Wistar rats. Supplementation with miglitol for 3 or 7 days in rats increased tissue weights of the lower jejunum and ileum, but did not alter tissue weights of the upper jejunum and cecum or the contents of the cecum. Furthermore, supplementation with miglitol for 7 days reduced the activities of isomaltase and maltase in the upper jejunum and increased the activities of sucrase, isomaltase, and maltase in the lower jejunum and ileum. These results suggest that the delay in carbohydrate digestion and absorption along the jejunal-ileal axis by miglitol supplementation in rats is associated with increased α-glucosidase activities toward the ileum.

1. Introduction

α-Glucosidase inhibitors, which are oral antidiabetic agents, delay carbohydrate digestion along the jejunal-ileal axis by inhibiting the intestinal activities of α-glucosidases such as sucrase, isomaltase, and maltase. This then results in a decrease in postprandial hyperglycemia. So far, 3 drugs (ie, acarbose, voglibose, and miglitol) have been approved for use in patients with type 2 diabetes mellitus. Acarbose, a pseudotetrasaccharide, has been reported to be a competitive inhibitor of sucrase, isomaltase, and glucoamylase [1-4]. Voglibose, an N-substituted valiolamine derivative, has been reported to be a strong inhibitor of maltase and sucrase [5]. Miglitol, a 1-deoxynojirimycin derivative, is another compound selected for development as an antihyperglycemic drug [6]. It is a strong inhibitor of sucrase, isomaltase, and glucoamylase [7]. These drugs have been shown to inhibit postprandial hyperglycemia in diabetic patients [8,9]. Occasional adverse effects include digestive symptoms such as diarrhea, which is caused by an increased flow of carbohydrates toward the ileum and colon due to the delay in carbohydrate digestion and absorption in the jejunum.

We have previously demonstrated that feeding rats a diet high in amylose starch, which is more slowly digested than amylopectin, for 14 days led to a decrease in α-glucosidase activities in the upper jejunum and an increase in α-glucosidase activities in the lower jejunum and upper ileum [10]. Treating normal rats and streptozotocin-induced diabetic rats with acarbose for 12 days led to reduced α-glucosidase activity and reduced sucrase protein levels in the jejunum and ileum [11], whereas treating diabetic mice with acarbose for 84 days induced sucrase activity in the ileum, but not in the jejunum [12]. These results indicate

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Table 1
Diet composition

	Control	Miglitol (/100 g diet)	
		40 mg	80 mg
α-Corn starch (g)	35	34.96	34.92
Sucrose (g)	30	30	30
Corn oil (g)	5	5	5
Casein (g)	20	20	20
AIN^{76}-M mix (g)	3.5	3.5	3.5
AIN^{76}-V mix (g)	1	1	1
Choline bitartrate (g)	0.2	0.2	0.2
DL-Methionine (g)	0.3	0.3	0.3
Cellulose (g)	5.0	5.0	5.0
Miglitol (g)	–	0.04	0.08
Total (g)	100	100	100

that treatment with drugs or food components capable of suppressing carbohydrate digestion and absorption leads to changes in α-glucosidase activities along the jejunal-ileal axis. This may indicate an adaptation of the small intestine to improve digestion and absorption of carbohydrates toward the ileum and prevent digestive symptom such as diarrhea. Miglitol can be administered in much higher doses than other inhibitors because it is largely absorbed by the jejunum and therefore causes fewer digestive symptoms [13,14]. It is likely that miglitol treatment not only leads to increased carbohydrate flow toward the ileum, but also increases α-glucosidase activities toward the ileum to aid the absorption of these carbohydrates. However, it is not yet known if miglitol supplementation alters α-glucosidase activities along the jejunal-ileal axis.

In this study, we treated normal Wistar rats with 2 oral doses of miglitol and determined α-glucosidase activities along the jejunal-ileal axis.

2. Materials and methods

2.1. Animals

Five-week-old male Wistar rats (Japan SLC, Shizuoka, Japan) were divided into 3 groups: a group fed a control diet, a group fed a low-dose miglitol diet (40 mg/100 g), and a group fed a high-dose miglitol diet (80 mg/100 g). The diets were provided ad libitum for either 3 or 7 days. The compositions of the diets are shown in Table 1. Miglitol was provided by Sanwa Kagaku Kenkyusho (Mie, Japan). At the end of feeding for 3 or 7 days, nonfasting rats were killed by decapitation between 10:00 and 11:00 AM; and the entire small intestine and cecum were collected. The experimental procedures used in this study conformed to the guidelines of the Animal Usage Committee of the University of Shizuoka.

2.2. Preparation of intestinal samples

The entire jejunoileum was removed and divided into 3 segments of equal length. The proximal third was considered to be the upper jejunum; the middle third, the lower jejunum; and the distal third, the ileum. The contents of the lumen were removed by injecting 0.9% NaCl after which the small intestine was opened longitudinally. The fluid in the small intestine was then rubbed and weighed. The cecum was weighed both with and without its content. The weight of the contents of the cecum was calculated as the difference between the weights of the cecum with and without its contents.

2.3. Enzyme assays

Mucosa was removed from the small intestine segments with 4 volumes of 10 mmol/L potassium-phosphate buffer (pH 7.0) and immediately used for α-glucosidase activity assays. Sucrase, isomaltase, and maltase activities were assayed as described by Dahlqvist [15] using 28 mmol/L sucrose, palatinose, and maltose as substrates, respectively. Protein was measured according to the method of Lowry et al [16].

2.4. Statistical analysis

Results were expressed as means ± SEM. Differences among groups were determined by Tukey multiple range test based on analysis of variance. P values $< .05$ were considered statistically significant.

Table 2
Effects of miglitol supplementation on body weight and food intake

		Control	Miglitol (/100 g diet)		
			40 mg	80 mg	
Supplementation with miglitol for 3 d					
Body weight	0 d (g)	121 ± 2	120 ± 3	120 ± 2	NS
	3 d after starting (g)	128 ± 2	124 ± 4	125 ± 3	NS
Food intake	(g/3 d per rat)	30.1 ± 5.6	27.1 ± 7.5	25.1 ± 3.6	NS
Supplementation with miglitol for 7 d					
Body weight	0 d (g)	121 ± 2	120 ± 3	120 ± 2	NS
	7 d after starting (g)	128 ± 2	124 ± 4	125 ± 3	NS
Food intake	(g/7 d per rat)	30.1 ± 5.6	27.1 ± 7.5	25.1 ± 3.6	NS

Values are means ± SEM for 6 animals. NS indicates no significant differences.

3. Results

3.1. Effects of miglitol supplementation on weights of the intestine and contents of the cecum

No differences in body weight or food intake were found among the treatment groups after either 3 or 7 days of treatment (Table 2). Weights of the tissue and mucosa of the upper jejunum and total protein in the mucosa of the upper jejunum were not different among groups after either 3 or 7 days of treatment (Table 3). Weights of the tissue and mucosa of the lower jejunum and total protein in the mucosa of the lower jejunum were increased by miglitol after both 3 and 7 days of supplementation in a dose-dependent manner. Weights of the tissue and mucosa of the ileum were increased by miglitol supplementation for 3 days in a dose-dependent manner, but total protein did not change significantly. Weights of the mucosa and total protein in the ileum were increased by miglitol supplementation for 7 days in a dose-dependent manner, but tissue weight did not increase significantly. No differences in tissue weight and contents of the lumen of the cecum were seen among the treatment groups after either 3 or 7 days of treatment. Digestive symptoms such as diarrhea were not observed in any of the groups.

3.2. Effects of miglitol supplementation on α-glucosidase activities along the jejunal-ileal axis

Supplementation with miglitol for 3 days reduced total isomaltase activity in the upper jejunal section and isomaltase activity per milligram of protein in the upper jejunum (specific activity) (Fig. 1A). Miglitol increased specific and total activities of isomaltase in the ileum. Total activities of isomaltase and maltase in lower jejunum were also increased by 3-day supplementation.

Supplementation with miglitol for 7 days reduced specific and total activities of isomaltase in the upper jejunum in a dose-dependent way (Fig. 1B). Total and specific activities of sucrase in the lower jejunum and the ileum were increased by 7-day miglitol supplementation. Supplementation with miglitol for 7 days increased specific

Table 3
Effects of miglitol supplementation on weights of intestine and content of cecum

	Control	Miglitol (/100 g diet)		
		40 mg	80 mg	
Supplementation with miglitol for 3 d				
Upper jejunum				
Tissue weight (g)	0.95 ± 0.03	0.95 ± 0.03	1.02 ± 0.03	NS
Mucosa weight (g)	0.59 ± 0.01	0.56 ± 0.02	0.61 ± 0.03	NS
Total protein (mg)	87.5 ± 4.4	87.5 ± 5.9	96.5 ± 3.2	NS
Lower jejunum				
Tissue weight (g)	0.98 ± 0.03^{a}	1.11 ± 0.06^{ab}	1.19 ± 0.04^{b}	
Mucosa weight (g)	0.58 ± 0.03^{a}	0.68 ± 0.04^{ab}	0.73 ± 0.02^{b}	
Total protein (mg)	51.7 ± 5.9^{a}	69.5 ± 4.3^{b}	77.8 ± 3.1^{b}	
Ileum				
Tissue weight (g)	0.64 ± 0.03^{a}	0.70 ± 0.04^{ab}	0.78 ± 0.03^{b}	
Mucosa weight (g)	0.39 ± 0.01^{a}	0.47 ± 0.03^{b}	0.47 ± 0.03^{b}	
Total protein (mg)	43.6 ± 1.7	47.6 ± 3.5	52.7 ± 2.5	NS
Cecum				
Tissue weight (g)	1.01 ± 0.08	1.15 ± 0.09	1.16 ± 0.11	NS
Contents in lumen (g)	0.43 ± 0.03	0.39 ± 0.02	0.40 ± 0.02	NS
Supplementation with miglitol for 7 d				
Upper jejunum				
Tissue weight (g)	1.24 ± 0.15	1.03 ± 0.04	1.07 ± 0.05	NS
Mucosa weight (g)	0.63 ± 0.02	0.62 ± 0.03	0.63 ± 0.03	NS
Total protein (mg)	72.5 ± 3.4	76.5 ± 3.3	83.0 ± 4.2	NS
Lower jejunum				
Tissue weight (g)	1.07 ± 0.04^{a}	1.16 ± 0.04^{ab}	1.26 ± 0.04^{b}	
Mucosa weight (g)	0.58 ± 0.02^{a}	0.67 ± 0.02^{b}	0.76 ± 0.02^{c}	
Total protein (mg)	73.3 ± 3^{a}	83 ± 3^{ab}	103 ± 4^{b}	
Ileum				
Tissue weight (g)	0.68 ± 0.03	0.75 ± 0.04	0.80 ± 0.03	NS
Mucosa weight (g)	0.37 ± 0.01^{a}	0.41 ± 0.03^{ab}	0.48 ± 0.02^{b}	
Total protein (mg)	38.9 ± 1.2^{a}	44.3 ± 2.9^{ab}	52.3 ± 2.4^{b}	
Cecum				
Tissue weight (g)	1.33 ± 0.08	1.22 ± 0.08	1.22 ± 0.10	NS
Contents in lumen (g)	0.39 ± 0.02	0.43 ± 0.01	0.40 ± 0.01	NS

Values are means ± SEM for 6 animals. Values not sharing a common superscript differ significantly ($P < .05$) from one another.

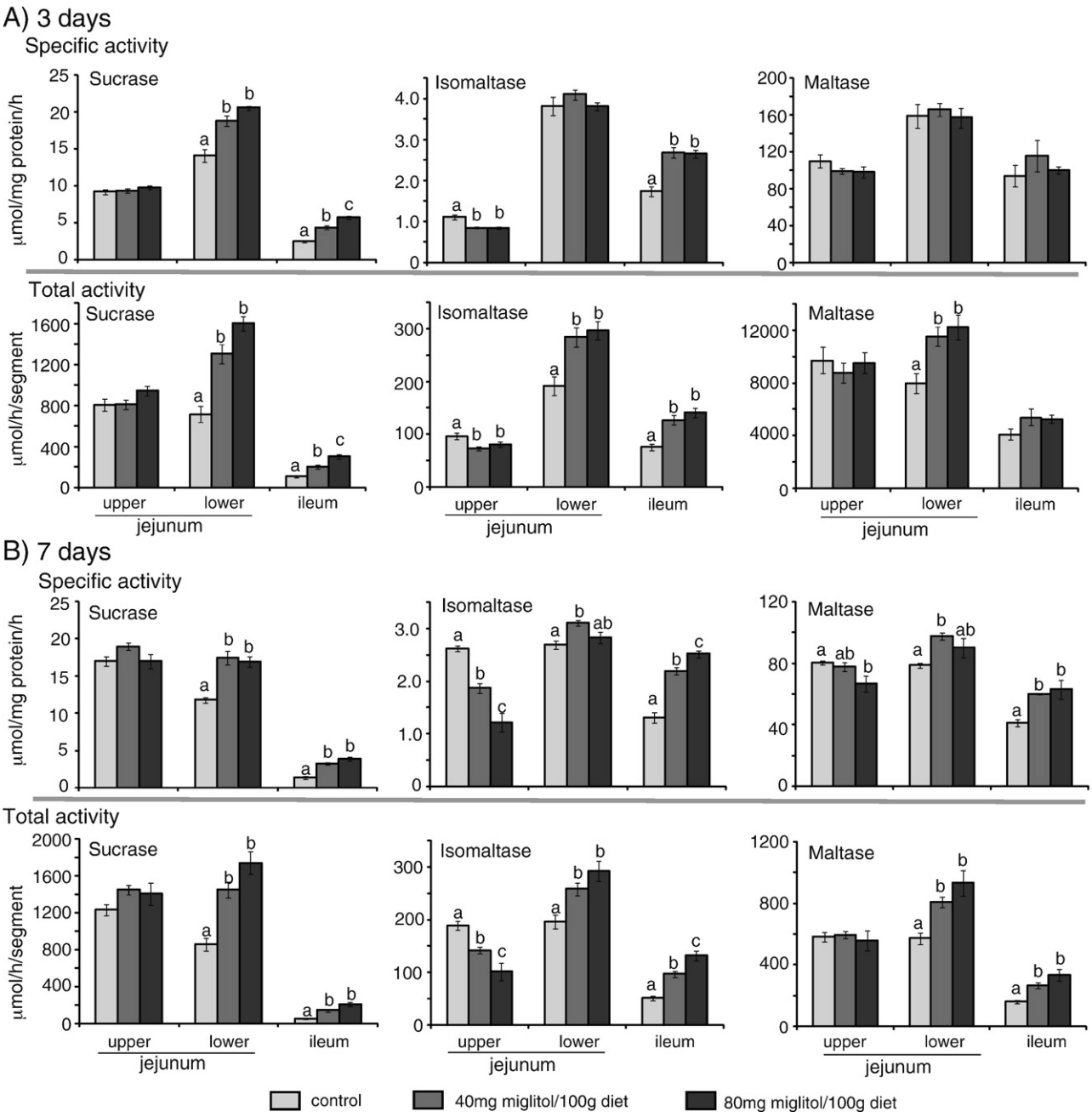

Fig. 1. α-Glucosidase activities along the jejunal-ileal axis in rats fed a diet with or without miglitol at 40 or 80 mg/100 g diet. A, Supplementation with miglitol for 3 days. B, Supplementation with miglitol for 7 days. Values are means ± SEM for 6 animals. Values not sharing a common superscript differ significantly ($P < .05$) from one another.

and total activities of isomaltase and maltase in the ileum. Significant differences were observed between the low-miglitol diet and the control diet in specific activity, and between both the low- and high-miglitol diets and the control diet in total activity. Specific and total activities of sucrase, isomaltase, and maltase in the ileum were also increased by miglitol supplementation for 7 days (Fig. 1). Overall, miglitol supplementation for 3 or 7 days in Wistar rats reduced isomaltase activity in the upper jejunum and increased sucrase, maltase, and isomaltase activities in the lower jejunum and ileum.

4. Discussion

In this study, Wistar rats were treated with the α-glucosidase inhibitor miglitol at doses of 40 and 80 mg per 100 g diet. Digestive symptoms such as diarrhea were not

observed in any of the groups. We showed that the contents of the cecum and cecum weight were not increased by the treatments. These results suggest that the carbohydrate flow toward the cecum was not increased by the treatment with miglitol at doses of 40 and 80 mg per 100 g diet. We have previously demonstrated that treatment with 20 and 40 mg miglitol per 100 g diet of Goto-Kakizaki rats, an animal model for mild dysfunction of insulin secretion from juvenile stage without obesity [17], did not cause any digestive symptoms [13]. In addition, we have demonstrated that treatment with 80 mg miglitol per 100 g diet of Otsuka Long-Evans Tokushima Fatty rats, which exhibit obesity and late onset of chronic and slowly progressing hyperinsulinemia, hyperglycemia, and hyperlipidemia caused by overeating [18], and of streptozotocin-induced hyperglycemic rats, a model of severely impaired insulin secretion from β-cells, did not cause any digestive symptoms [19, 20]. Because treatment with miglitol in these animal models improved glycemic status, doses of 20 to 80 mg per 100 g diet are suitable in animal models for improving postprandial hyperglycemia without causing digestive symptoms.

Interestingly, supplementation with miglitol for 7 days reduces the specific activities of isomaltase and maltase in the upper jejunum and increases the activities of sucrase, isomaltase, and maltase in the lower jejunum and ileum. This tendency was also observed after supplementation for 3 days. Furthermore, because tissue weights and total protein in lower jejunum and ileum were also increased, the total activities of sucrase, isomaltase, and maltase in lower jejunum and ileum showed a more pronounced increase than the specific activities. These results suggest that miglitol treatment increases the capacity for carbohydrate digestion toward the lower jejunum and ileum. The alterations of α-glucosidases activities along the jejunal-ileal axis by the treatments with α-glucosidase inhibitors including miglitol appear to be temporary, because it was reported that the alteration of α-glucosidases activities in the small intestine by feeding rats a diet containing acarbose for 23 days was recovered by feeding the rats a regular diet without acarbose [21]. It should be noted that 12-day treatment of diabetic rats with acarbose did not enhance α-glucosidase activities in lower jejunum and ileum [11], whereas treatment with acarbose for 84 days enhanceed sucrase activity in the ileum, but not the jejunum [12]. In this study, we demonstrated that the changes in α-glucosidase activities in the lower jejunum and ileum are observed after as little as 3 days of miglitol treatment. This may indicate that α-glucosidase activities along the jejunal-ileal axis adapt more rapidly after miglitol treatment than after acarbose treatment because miglitol is absorbed by the jejunum and ileum, whereas acarbose is not. This suggests that the increase in α-glucosidase activities toward the ileum after high-dose miglitol treatment may lead to complete absorption of the carbohydrate by the end of the ileum, and this may reduce the incidence of digestive symptoms such as diarrhea. The process by which miglitol supplementation alters the α-glucosidase activities, mucosal weight, and total protein along the jejunal-ileal axis needs further investigation.

In conclusion, we have demonstrated that supplementation with miglitol in normal Wistar rats for 3 or 7 days reduces isomaltase activity in upper jejunum and increases sucrase, maltase, and isomaltase activities in the lower jejunum and ileum without occurrence of any digestive symptoms. This indicates that changes in α-glucosidase activities caused by miglitol supplementation are associated with a delay in carbohydrate digestion along the jejunal-ileal axis in rats.

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