A Genetic non-insulin dependent diabetic mice, KK-Ay mice, is elevated alpha-glucosyldisaccharide digestive/absorptive capacity in small intestine

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ABSTRACT

The alpha-glucosyldisaccharide digestive/absorptive capacity was studied in normal and KK-Ay mice, an animal model of non-insulin dependent diabetes mellitus (NIDDM). KK-Ay mice with hyperglycemia exhibited significantly increased maltose and sucrose digestive/absorptive capacity in small intestine ($P < 0.05$) when compared with that of normal mice. However, lactose digestive/absorptive capacity was not changed between them.

Increased glucose uptake in small intestine has been known as one of the major pathogenetic factors of non-insulin dependent diabetes mellitus, together with the insulin resistance in peripheral tissues and the impairment of glucose-induced insulin secretion from pancreatic beta cells. Recently, the therapeutic agents to inhibit the alpha-glucosidase of small intestine have been used for the treatment of NIDDM patients (2, 3, 4, 5, 7, 9, 12, 13). However, a few studies have been conducted concerning the comparison of alpha-glucosyldisaccharide digestive/absorptive capacity in normal and diabetic mice. On the other hand, *in vivo* studies related to the alpha-glucosyldisaccharide digestive/absorptive capacity have rarely been performed in normal and diabetic mice. Therefore, we examined the alpha-glucosyldisaccharide digestive/absorptive capacity using various disaccharides in both normal and diabetic mice, *in vivo*.

Materials. Maltose, sucrose and lactose were purchased from Wako Pure Chemical Industries Co. Ltd. (Osaka, Japan).

Animals. Adult male ddY mice (SLC, Shizuoka, Japan) weighing 22-25 g and KK-Ay mice (Clea, Tokyo, Japan) weighing 42-48 g were used. The mice were housed in an air-conditioned room at $22 \pm 2^\circ\text{C}$ with a 12 hours light and 12 hours dark cycle. The animals were kept in the experimental animal room for 7 days with free access to food and water. For the determination of blood glucose levels, blood samples were withdrawn from the cavernous sinus with a capillary. Three to seven animals were used for each group.

Oral disaccharide tolerance test. After overnight (20 h) fasting, the mice were orally given sugar (maltose, sucrose, or lactose, 2 g/kg body weight) solution. Blood samples were collected before the administration of sugar, and 0.5, 1 and 2 h later.

Disaccharase activity. After overnight (20 h) fasting, maltose, sucrose or lactose (100 mM, 0.5 mL) solution was injected into a loop of small intestine. After 0.5 h, the inside of small intestine was washed by 5 mL of saline solution, and disaccharide content was determined for the evaluation of alpha-glucosyldisaccharide digestive/absorptive capacity, as described below.

Determination of blood glucose, insulin and disaccharides in small intestine. Blood glucose levels in mice were determined by glucose oxidase

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method (11) and insulin was measured by a double-antibody immunoassay (1). The maltose, sucrose, and lactose content in small intestine was measured by means of the anthrone- H_2SO_4 method (6). All the data were expressed as mean $\pm$ S.E.M. and Student's *t* test was used for the statistical analysis. The values were considered to be significantly different when the *P* value was less than 0.05.

Blood glucose and plasma insulin level. The mean levels of blood glucose and insulin are shown in Table 1. The blood glucose and plasma insulin levels of KK-Ay mice are significantly higher than those of normal mice.

Oral disaccharide tolerance test. The mean blood glucose levels of ddY or KK-Ay mice at various time intervals after oral administration of maltose, sucrose or lactose are shown in Fig. 1 (ddY mice) and Fig. 2 (KK-Ay mice). In normal mice, the blood glucose in maltose tolerance is higher than that in sucrose or lactose. In KK-Ay

mice, the blood glucose in sucrose is higher than that of lactose.

The blood glucose of normal mice in sucrose tolerance is higher than that of KK-Ay mice (Fig. 3).

Alpha-glucosylidisaccharides Digestive/Absorptive Capacity. The maltose digestive/absorptive capacity 30 min after the oral administration of maltose is shown in Fig. 4. The values were compared to those found in normal mice group. Maltose digestive/absorptive capacity of KK-Ay mice was higher than that of normal mice ($P < 0.05$). The sucrose digestive/absorptive capacity 30 min after the oral administration of sucrose are shown in Fig. 4. Sucrose digestive/absorptive capacity of KK-Ay mice was increased when compared with that of normal mice ($P < 0.05$). On the other hand, no effect on lactose digestive/absorptive capacity is shown in both normal and KK-Ay mice (Fig. 4).

The present study clearly shows that the alpha-

Table 1 *Body Weight, Blood Glucose and Plasma Insulin Level*

	Body weight (g)	Blood glucose (mM/L)	Plasma insulin ($\mu\text{U/mL}$)
Normal mice	24.0 $\pm$ 0.5	9.1 $\pm$ 0.6	34 $\pm$ 6
KK-Ay mice	44.6 $\pm$ 0.8***	29.2 $\pm$ 1.1***	254 $\pm$ 32**

Blood samples were taken at 11:00 am. Each value represents the mean $\pm$ S.E.M. from 5 mice. Significantly different from normal mice, ** $P < 0.01$, *** $P < 0.001$.

Fig. 1 Disaccharide Tolerance Test in Normal Mice.

Each value represents the mean $\pm$ S.E. from 3-4 mice.

Fig. 2 Disaccharide Tolerance Test in KK-Ay Mice.

Each value represents the mean $\pm$ S.E.M. from 3 mice.

Fig. 3 Sucrose Tolerance Test in Normal and KK-Ay Mice

Each value represents the mean $\pm$ S.E.M. from 3 mice. Significantly different from corresponding normal mice, * $P < 0.05$, ** $P < 0.01$.

Fig. 4 Disaccharide Digestive/Absorptive Capacity in Normal and KK-Ay Mice.

Each value represents the mean $\pm$ S.E.M. from 3–4 mice. Significantly different from corresponding normal mice, * $P < 0.05$, N. S.; not significant.

glucosyldisaccharides digestive/absorptive capacity is increased in KK-Ay mice. We examined time-course (0, 30, 60, 120 min) of blood glucose levels after the administration of maltose, sucrose or lactose, and found that they exhibited hyperglycemia at 30 min and thereafter. When calcu-

lated the disaccharase activity in hyperglycemic KK-Ay mice, Maltase and sucrase activities of small intestine were significantly higher than those of normal mice. Hopfer (8), have reported that glucose absorption in experimental diabetic rats was twice as high as that in normal rat, and these findings indicate that the relative increase of glucose absorption was due to activation of Na^+ -glucose transporter by changing the Na permeability. In addition, Madara *et al.* (10) have reported that sucrase-isomaltase activity in experimental diabetic rats was significantly elevated when compared with normal rats. Our findings of the increment of sucrose and maltose digestive/absorptive capacity in KK-Ay mice could also be related with the increment of Na^+ -glucose transporter activity. However, no significant change in lactose digestive/absorptive capacity was observed. The oligosaccharidases have been known to be composed of two classes; the beta-galactosidases such as lactase (hydrolyse lactose to glucose and galactose) and the alpha-glucosidases such as maltase, isomaltase, glucoamylase and sucrase. It is suggested in the present study that the increase of alpha-glucosyldisaccharide digestive/absorptive capacity in KK-Ay mice is selective to the alpha-glucosidases. This report will provide useful information for future studies on the treatment of NIDDM.

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