DISACCHARIDASE ACTIVITIES IN SMALL INTESTINAL MUCOSA OF ALLOXAN–DIABETIC MICE

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ABSTRACT

Increased activities of maltase and sucrase of small intestinal mucosa were found in alloxan-diabetic mice.

Adrenalectomy did not affect the activities of the enzymes in normal mice, but lowered those of alloxan-diabetic mice as well as blood sugar level. Administration of glucocorticoid raised the enzyme activities in normal mice, non-diabetic adrenalectomized mice and adrenalectomized alloxan-diabetic mice.

Positive correlation was noted between blood sugar level and the activities of both enzymes.

Lactase activity did not undergo any change under these conditions.

Adrenal hyperfunction seems to play an important role in the increase of these enzyme activities. Significance of these findings in alloxan-diabetes was also discussed.

INTRODUCTION

Enhancement of hexose absorption in the small intestine was found in *in vivo* or *in vitro* in experimental alloxan-diabetic rat, in anti-insulin serum-treated rat or in juvenile-onset diabetes mellitus[1~4]

Since little monosaccharide is contained in foods, studies on absorption of carbohydrates in diabetes were directed to disaccharidases, enzymes of the small intestinal mucosa. Hossain *et al.*[5] reported on an increase in maltase activity in small intestinal mucosa of alloxan-diabetic rats in 1970, Olsen *et al.*[6] on an increase in sucrase activity in 1971 and Younoszai *et al.*[7] on an increase in activities of lactase, sucrase and maltase in 1972. The mechanism of increase in activities of these enzymes remains unknown, although Caspary[8),9)] suggested in 1973 that an insulin deficiency would play a role in the increase of disaccharidase activities in experimental diabetes mellitus.

The present paper deals with variations in the activities of disaccharidases and the hormonal regulatory mechanism of the activities of enzymes in the small intestinal mucosa of alloxan-diabetic mice, as revelaed by influence of adrenalectomy and administration of glucocorticoid on the disaccharidase activities.

MATERIALS AND METHODS

Animals: SMA strain male mice of 3 to 6 months of age, weighing 25 to 35 g were used. The animals were fed with mouse food (MF) manufactured by Oriental Yeast Co. Japan and water *ad libitum.*

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Alloxan diabetes: Alloxan was dissolved in physiological saline; 0.2 ml of 1.125 per cent alloxan solution (75 mg/kg) was injected into the tail vein once. Three days and five days after the injection, urine sugar was tested with Tes-Tape(Ames).

Adrenalectomy: Under anesthesia with intraperitoneal injection of 1.5 mg of Nembutal, the adrenals were extirpated by the bilateral subcostal incision. After adrenalectomy the mice were supplied with physiological saline instead of water, until they were used for experiment.

Administration of glucocorticoid: Prednisolone hemisuccinate was dissolved in physiological saline; 0.1 ml of 0.5 per cent prednisolone hemisuccinate solution (0.5 mg) was injected subcutaneously into each mouse once a day for three successive days. Four hours after the final injection, the animals were sacrificed.

Assay of enzyme activities of small intestinal mucosa: After having been fasted for four hours, mice were sacrificed by decapitation. The small intestine excluding the duodenum was excised and flushed with ice cold saline. Proximal two thirds of the small intestine were cut open longitudinally and then washed with ice cold physiological saline. Moisture on the surface of the small intestinal mucosa was blotted thoroughly with filter paper. The mucosal tissue was scraped off with a slide glass and was stored at $-20°C$ till it was used for enzyme assay. Just before measurement, the mucosal tissue was homogenized in a small quantity of distilled water; the homogenate diluted suitably with distilled water was used as enzyme solution.

Activities of lactase (β-D-galactoside galactohydrolase, EC 3.2.1.23), sucrase (β-D-fructofuranoside fructohydrolase, EC 3.2.1.26) and maltase (α-D-glucoside glucohydrolase, EC 3.2.1.20) were determined by the method described by Dahlqvist.[10] Enzyme activity was expressed as micromoles of substrate hydrolyzed per minute at 37°C per g of mucosal tissue protein (I.U.).

Determination of protein content: The protein content of homogenates was determined by the method of Lowry[11] using bovine serum albumin (Dai-ichi Pure Chemical Co., Ltd.) as the standard.

Determination of the blood sugar level: The blood sugar level was determined by the anthrone method of Roe[12] on blood obtained when the animals were sacrificed.

RESULTS

I. Disaccharidase Activities in Small Intestinal Mucosa of Alloxan-diabetic Mice and Blood Sugar Level

Of the 26 mice injected with alloxan, 21 showing a blood sugar level of 200 mg/dl or more were designated as the alloxan-diabetic group.

A) Blood sugar level

The blood sugar level of the alloxan-diabetic group was 308.0 ± 53.7 (mean ± S.E.) mg/dl. Control group consisting of 10 mice was injected with 0.2 ml of physiological saline into the tail vein. The blood sugar level of the control was 84.1 ± 6.1 mg/dl.

B) Enzyme activity (Table 1)

Lactase activity was 9.2 ± 0.7 IU, sucrase activity 89.5 ± 4.2 IU and maltase activity 295.2 ± 18.0 IU in alloxan-diabetic group. Lactase activity was 10.9 ± 0.9 IU, sucrase activity 54.1 ± 2.6 IU and maltase activity 161.1 ± 10.1 IU in the control group. In alloxan-diabetic group sucrase and maltase activity was significantly higher than in the control group, but lactase activity was not different between the two groups.

Table 1. Disaccharidase activities in small intestinal mucosa of alloxan-diabetic mice (mean ± S.E.)

	No. of mice	Blood sugar mg/dl	Lactase activity	Sucrase activity	Maltase activity
Alloxan-diabetes	21	308.0 ± 53.7	9.2 ± 0.7	89.5 ± 4.2	295.2 ± 18.0
Control	10	84.1 ± 6.1	10.9 ± 0.9	54.1 ± 2.6	161.1 ± 10.1

C) Relationship between disaccharidase activity and blood sugar level

Activity of the enzyme was plotted against blood sugar level in each mouse of the combined group of 10 controls and 26 alloxan-diabetics to see a relationship between them. There was a positive correlation between sucrase activity and blood sugar level as shown in Fig. 1 ($Y = 42.82 + 0.15\,X$, $r = 0.7349$, $P < 0.001$). As shown in Fig. 2, there was also a positive correlation between maltase activity and blood sugar level ($Y = 121.00 + 0.56X$, $r = 0.6932$, $P < 0.001$). There was no correlation between lactase activity and blood sugar level (Fig. 3).

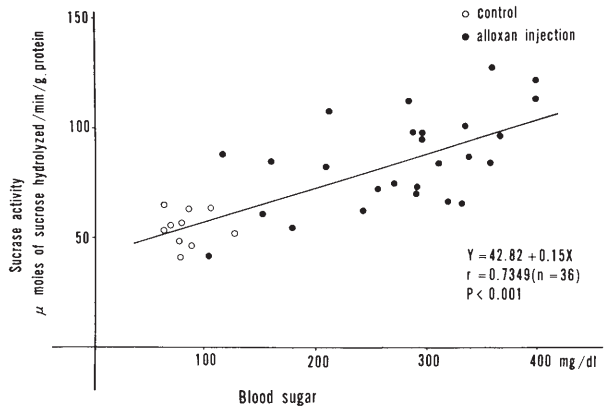

Fig. 1. Relationship between sucrase activity of small intestinal mucosa and blood sugar level.

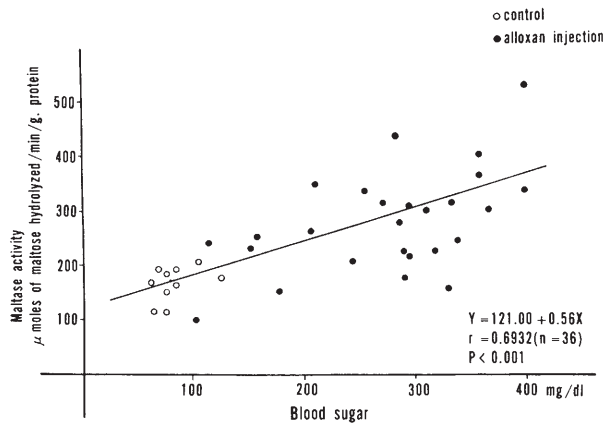

Fig. 2. Relationship between maltase activity of small intestinal mucosa and blood sugar level.

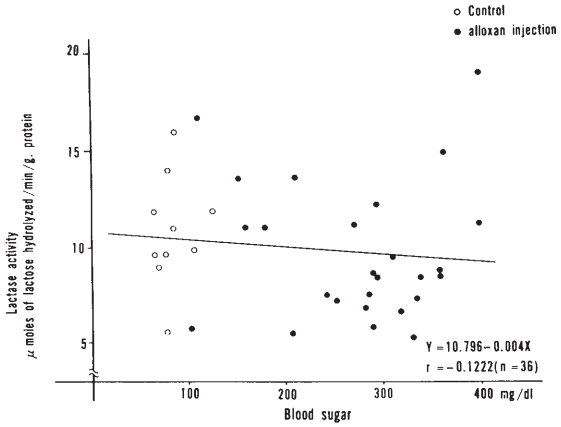

Fig. 3. Relationship between lactase activity of small intestinal mucosa and blood sugar level.

II. Influence of Adrenalectomy, Administration of Glucocorticoid and Administration of Glucocorticoid after Adrenalectomy on Disaccharidase Activity

As indicated in Table 2, lactase activity was 10.3 ± 1.1 IU, sucrase activity 40.0 ± 1.1 IU and maltase activity 186.6 ± 5.4 IU in the adrenalectomized group. In the sham-operated group lactase activity was 9.0 ± 0.5 IU, sucrase activity 42.5 ± 0.9 IU and maltase activity 173.4 ± 6.3 IU. There was no significant difference in lactase, sucrase and maltase activity between the adrenalectomized and the sham-operated in nondiabetic mice.

As indicated in Table 3, lactase activity was 10.9 ± 1.1 IU, sucrase activity 66.9 ± 2.3 IU and maltase activity 316.1 ± 11.6 IU in the glucocorticoid-administered group, while lactase activity was 10.5 ± 1.2 IU, sucrase activity 41.6 ± 4.3 IU and maltase activity 239.3 ± 23.6 IU in the control group. The glucocorticoid-treated group showed a significant increase in sucrase and maltase activity as compared with the control group. There was no difference in lactase activity between the two groups.

As indicated in Table 4, lactase activity was 10.8 ± 2.0 IU, sucrase activity 58.7 ± 2.1 IU

Table 2. Disaccharidase activities in small intestinal mucosa of adrenalectomized mice (mean ± S.E.)

	No. of mice	Lactase activity	Sucrase activity	Maltase activity
Adrenalectomy	5	10.3 ± 1.1	40.0 ± 1.1	186.6 ± 5.4
Sham operation	5	9.0 ± 0.5	42.5 ± 0.9	173.4 ± 6.3

Table 3. Disaccharidase activities in small intestinal mucosa of glucocorticoid administered mice (mean ± S.E.)

	No. of mice	Lactase activity	Sucrase activity	Maltase activity
Administration of glucocorticoid	5	10.9 ± 1.1	66.9 ± 2.3	316.1 ± 11.6
Control*	5	10.5 ± 1.2	41.6 ± 4.3 $P < 0.001$	239.3 ± 23.6 $P < 0.02$

* Physiological saline 0.1 ml/day was administered by subcutaneous injection for 3 successive days.

Table 4. Influence of administration of glucocorticoid after adrenalectomy on disaccharidase activity (mean ± S.E.)

	No. of mice	Lactase activity	Sucrase activity	Maltase activity
Adrenalectomy, Administration of glucocorticoid	5	10.8 ± 2.0	58.7 ± 2.1	292.9 ± 9.0
Adrenalectomy	5	10.3 ± 1.1	40.0 ± 1.1 $P < 0.001$	186.6 ± 5.4 $P < 0.001$

and maltase activity 292.9 ± 9.0 IU in glucocorticoid-treated adrenalectomized mice. In the untreated group, lactase activity was 10.3 ± 1.1 IU, sucrase activity 40.0 ± 1.1 IU and maltase activity 186.6 ± 5.4 IU. The administration of glucocorticoid significantly raised activities of sucrase and maltase but not lactase in adrenalectomized mice.

III. Influence of Adrenalectomy and Administration of Glucocorticoid after Adrenalectomy on Disaccharidase Activity in Alloxan-diabetic Mice

A) Blood sugar level

Adrenalectomy or sham-operation was performed 5 days after alloxan injection into mice, in which urine sugar was found positive. The adrenalectomized group was divided into two groups. In one group glucocorticoid was injected once daily for three consecutive days and physiological saline was injected into the other. Three days after the operation the animals were sacrificed after urine sugar was tested.

Urine sugar was converted to negative in two out of 15 adrenalectomized mice, but 13 remained positive. Blood sugar levels were 412.8 ± 55.0 mg/dl for the sham-operated, and 188.0 ± 27.6 mg/dl for the adrenalectomized. Administration of glucocorticoid raised the level lowered by adrenalectomy to 441.6 ± 20.3 mg/dl. The adrenalectomized group in alloxan-diabetic mice showed a lower blood sugar level than the other two groups. The fall in blood sugar level was probably caused by glucocorticoid deficiency induced by adrenalectomy.

B) Enzyme activity (Table 5)

Lactase activity was 10.3 ± 0.9 IU, sucrase activity 50.3 ± 4.8 IU and maltase activity 226.4 ± 18.6 IU in the adrenalectomized group of alloxan-diabetic mice. In sham-operated group of alloxan-diabetics, lactase activity was 9.9 ± 1.1 IU, sucrase activity 73.8 ± 6.8 IU and maltase activity 371.8 ± 22.6 IU. In alloxan-diabetic mice injected with glucocorticoid following adrenalectomy, lactase activity was 8.8 ± 1.2 IU, sucrase activity

Table 5. Influence of adrenalectomy, administration of glucocorticoid and administration of glucocorticoid after adrenalectomy on disaccharidase activity in alloxan-diabetic mice (mean± S.E.)

	No. of mice	Blood sugar mg/dl	Lactase activity	Sucrase activity	Maltase activity
Alloxan diabetes, Sham operation	5	412.8 ± 55.0	9.9 ± 1.1	73.8 ± 6.8	371.8 ± 22.6
Alloxan diabetes, Adrenalectomy	5	188.0 ± 27.6*	10.3 ± 0.9	50.3 ± 4.8*	226.4 ± 18.6*
Alloxan diabetes, Adrenalectomy, Administration of glucocorticoid	5	441.6 ± 20.3	8.8 ± 1.2	83.1 ± 7.6	352.3 ± 29.1

* $P < 0.01$: Significant difference between adrenalectomy group and other groups.

83.1 ± 7.6 IU and maltase activity 352.3 ± 29.1 IU. The adrenalectomized alloxan-diabetic mice group showed a significant fall in sucrase and maltase activity as compared with the other groups.

There was no difference in sucrase and maltase activity between the latter two groups. There was no difference in lactase activity among three gorups.

C) Relationship between disaccharidase activity and blood sugar level

As indicated in Fig. 4, there was a positive correlation between blood sugar level and

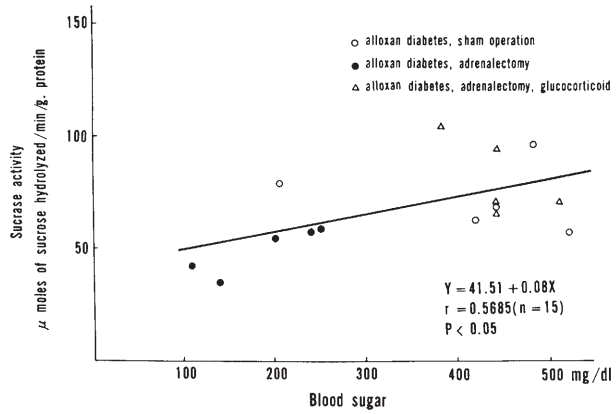

Fig. 4. Relationship between sucrase activity of small intestinal mucosa and blood sugar level.

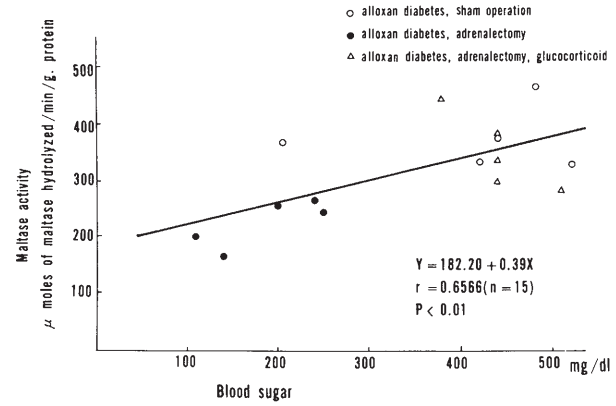

Fig. 5. Relationship between maltase activity of small intestinal mucosa and blood sugar level.

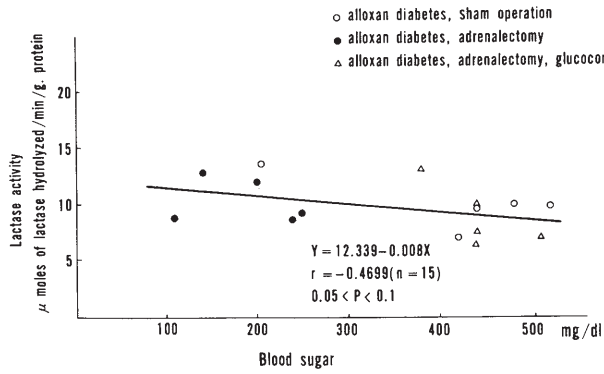

Fig. 6. Relationship between lactase activity of small intestinal mucosa and blood sugar level.

sucrase activity in the combined group of the three ($Y = 41.51 + 0.08\,X$, $r = 0.5685$, $P < 0.05$). As shown in Fig. 5, there also was a positive correlation between maltase activity and blood sugar level ($Y = 182.20 + 0.39\,X$, $r = 0.6566$, $P < 0.01$). No correlation was observed between lactase activity and blood sugar level (Fig. 6).

DISCUSSION

During the process of carbohydrate digestion, starch is first hydrolyzed into oligosaccharides in the intestinal lumen by amylase secreted by the salivary gland and pancreas. These oligosaccharides and disaccharides, *i.e.*, sucrose, lactose etc, are ultimately hydrolyzed into monosaccharides by disaccharidases on the brush border of enterocytes in the small intestinal mucosa. Monosaccharides produced are readily absorbed into the enterocytes via the active transport system.[13),14)]

Since it was found in experimental diabetes mellitus that absorption of hexose in the small intestine is enhanced and that the active monosaccharide transport system and disaccharidase are closely related to each other,[15~17)] studies of carbohydrate absorption in diabetes mellitus have been made on disaccharidases, enzymes in the small intestinal mucosa.

Disaccharidases such as lactase, sucrase and maltase are present mainly in the brush border of the enterocytes in the small intestinal mucosa and function in the final step of carbohydrate digestion.[18)] Therefore, the present study was designed to clarify the mechanism of change of these enzymes in experimental diabetes mellitus.

Experimental diabetes mellitus used in the present study was alloxan induced diabetes. Alloxan, a classical diabetogenic chemical substance, produces insulin-deficient diabetes mellitus by destroying β-cells of the islets of Langerhans of the pancreas, as does streptozotocin. There have been a lot of studies on alloxan diabetes.[19),20)] In alloxan diabetes, it was reported that there is a definite difference between short-term experiment of five to eight days and long-term experiment of one month or longer after administration of alloxan in food consumption and length and weight of the intestine.

In short-term experiment, food consumption of the diabetic animal does not differ from that of the controls. However, there is loss of body weight resulting from excretion of glucose in urine, while wet weight of the intestinal mucosa is increased. In long-term experiment body weight decreases, although food consumption, length of the intestine and both wet and dry weight of the mucosa are increased as compared with controls.[21),22)]

Therefore, enhanced hexose absorption in the small intestine may be attributable to an increase in the maximal transport capacity of hexose per wet weight of intestinal mucosa in short-term alloxan diabetes and to an increase in the total intestinal transport capacity in long-term alloxan diabetes.[8)]

In the present study, alloxan diabetes is of a short-term experiment carried out five days after administration of alloxan, where an increase in sucrase activity and maltase activity was observed in the small intestinal mucosa.

Hyperglycemia in diabetes is maintained by insulin deficiency, increased absorption of glucose from the small intestine and increased gluconeogenesis in the liver due to adrenal hyperfunction. In the present study there was a significant positive correlation between the blood sugar level and both sucrase and maltase activity in the combined group of controls and diabetics. There has been found a positive correlation between blood sugar level and glucose absorption from the small intestine.[23)] These facts suggest that the

digestive function of sucrase and maltase as well as absorption of glucose of the small intestinal mucosa increases in proportion to severity of diabetes.

Hypertrophy of the adrenal gland has been found in alloxan diabetes.[24~27] In short-term experiment, the adrenal becomes hypertrophied. The increase in weight begins on the 2nd day after administration of alloxan. The hypertrophy is histochemically confirmed as being attributed to hyperplasia of zona fasciculata of the adrenal cortex and there is an increase in serum level of corticosterone.[25~28]

The author studied the influence of the adrenal function on disaccharidase in the small intestinal mucosa of alloxan-diabetic mice. After adrenalectomy, administration of glucocorticoid or administration of glucocorticoid following adrenalectomy to normal or diabetic mice, activities of the enzymes were measured.

Adrenalectomy performed on normal mice had no effect on lactase, sucrase and maltase activity in the small intestinal mucosa. In contrast, a 3-days' successive subcutaneous injection of glucocorticoid into normal mice resulted in an increase in sucrase and maltase activity in the small intestinal mucosa.

Furthermore, treatment with glucocorticoid of nondiabetic adrenalectomized mice induced an increase in sucrase and maltase activity in the small intestinal mucosa compared with the untreated adrenalectomized group. However, no significant change was observed in lactase activity. These results show that sucrase and maltase activities in the small intestinal mucosa of normal mice are raised by glucocorticoid.

Most reports on the influence of glucocorticoid on disaccharidases in the small intestinal mucosa dealt with the precocity of the small intestine: by the administration of glucocorticoid weaning develops earlier and a rapid increase in sucrase and maltase activity and decrease in lactase activity normally observed after birth take place earlier.

In adult animals, Deren *et al.*[29] reported that sucrase and maltase activities in the small intestinal mucosa are not affected by either adrenalectomy or oral administration of glucocorticoid (cortisone acetate). Levin *et al.*[30] reported that adrenalectomy lowered maltase activity and that administration of 1 per cent saline solution resulted in restoration of maltase activity, suggesting that imbalance of electrolytes has some influence on the small intestinal mucosa. Hossain[5] reported that maltase activity was not affected by adrenalectomy and that administration of corticosterone to adrenalectomized rats resulted in an increase in maltase activity.

Results obtained in the present study differ from those of Deren *et al.* The discrepancy may possibly be accounted for by the difference in chemical structure, dose or route of administration of glucocorticoid, for prednisolone hemisuccinate was administered by subcutaneous injection in the former, while cortisone acetate was given by mouth in the latter.

After adrenalectomy, activities of sucrase and maltase of alloxan-diabetic mice were significantly decreased as compared with the sham-operated diabetic mice. Negative conversion of glucosuria and a significant fall in blood sugar level were noted in two of adrenalectomized mice. Furthermore, the group to which glucocorticoid was administered after adrenalectomy showed an increase in sucrase and maltase activity and also a rise in the blood sugar level compared with the untreated adrenalectomized.

However, there was no difference in either activities of sucrase and maltase in the small intestinal mucosa or blood sugar level between the sham-operated and the glucocorticoid-treated adrenalectomized.

This fact is considered to indicate that the influence of adrenalectomy in alloxan-diabetic

mice, either increase or decrease in lactase activity was not found in the present study. This is partially inconsistent with the report of Younoszai *et al.*, in which activities of the three enzymes were raised in alloxan-diabetic rats. Younoszai *et al.* observed the increase in lactase activity only in the proximal one third of small intestinal mucosa including the duodenum and no increase in the remaining two thirds. In this study enzymes were assayed on the proximal two thirds of the small intestinal mucosa excluding the duodenum and no increase in lactase activity was found.

It is unknown why variations in lactase activity in the small intestinal mucosa were not observed in the present study. Lactase activity by nature is high during the suckling period and rapidly declines in the weaning period. As it is not subject to substrate induction after weaning,[32),33)] it may hardly be subject to hormonal control.

Studies on disaccharidase activities in the small intestinal mucosa of diabetic patients have been made on biopsy specimens since an increase in disaccharidase activities was reported in experimental diabetes mellitus. However, no increase in disaccharidase activities in the small intestinal mucosa has been observed in either maturity-onset[34)] or juvenile-onset[35),36)] diabetes mellitus.

Alloxan diabetes, an insulin-deficient variety is considered to be a similar condition to the so-called insulin-requiring juvenile-onset type in man. However, the study on patients with juvenile-onset diabetes mellitus is different in condition from alloxan-diabetic mice, for insulin has been used till the day before collection of the small intestinal mucosa in the former.

There has been no report on disaccharidases in the small intestinal mucosa in the insulin-requiring diabetic patients who had not been treated with insulin.

SUMMARY

Determination was made of activities of lactase, sucrase and maltase located in the brush border of the enterocytes of the small intestinal mucosa of alloxan-diabetic adult mice. Furthermore, studies were made on the influence of adrenalectomy and/or administration of glucocorticoid on activities of the enzymes in normal and alloxan-diabetic mice.
The following results were obtained.

1) Alloxan-diabetic mice showed an increase in sucrase activity and maltase activity compared with the control group.
2) Adrenalectomy did not affect the activities of sucrase and maltase in normal mice, while glucocorticoid administration raised the activities in both normal and adrenalectomized mice compared with their respective controls.
3) When adrenalectomy was performed on alloxan-diabetic mice, sucrase activity and maltase activity were decreased compared with the unoperated group. When glucocorticoid was administered after adrenalectomy, sucrase activity and maltase activity were increased compared with the nonadministered adrenalectomized group.
4) There was a positive correlation between sucrase activity, maltase activity and blood sugar level.

From the above data it was suggested that adrenal hyperfunction plays an important role in the increase in sucrase and maltase activity of the small intestinal mucosa of short-term alloxan-diabetic mice.

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