Effects of Aspartame on Diabetic Rats and Diabetic Patients

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Summary The effects of aspartame (L-aspartyl-L-phenylalanine methyl ester) on plasma glucose and insulin levels were investigated in diabetic rats and patients with non-insulin-dependent diabetes mellitus. The oral administration of 0.45 mg aspartame per 100 g body weight, which is equivalent to 150 mg of glucose in sweetness, to streptozotocin-induced diabetic rats had no effect on the plasma glucose or insulin levels. Also, 225 mg oral aspartame loading, which is equivalent to 75 g of glucose in sweetness, to patients with non-insulin-dependent diabetes mellitus did not increase plasma glucose or insulin levels, although 75 g of oral glucose loading increased plasma glucose and insulin levels in diabetic patients as expected. Aspartame ingestion for three days at a dose of 24-48 mg per day and the intake of snacks flavored with 240 mg of aspartame also did not increase fasting plasma glucose levels. These results suggest that acute administration of aspartame has no influence on plasma glucose or insulin levels in diabetic rats and patients with non-insulin-dependent diabetes mellitus.

Key Words aspartame, diabetic rats, non-insulin-dependent diabetes mellitus, plasma glucose, insulin

Aspartame, a sweetening agent, has been investigated for its safety as a food additive for two decades in the United States (1). It has been used widely in Japan since 1983. Aspartame (L-aspartyl-L-phenylalanine methyl ester) is approximately 200 times as sweet as sucrose although its caloric value is 4 kcal per g. As aspartame

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makes it possible to reduce energy intake without alteration in taste (2), this agent may be useful for diabetic patients as well as for obese people. However, to date very few reports have been made on the effects of aspartame in the diabetic state. Therefore, the present study was performed to clarify whether aspartame is useful for diabetics as a substitute for sucrose with regards to sweetness.

EXPERIMENT

1) Animal experiment. Ten female Sprague-Dawley rats were purchased from Charles River Japan Inc. (Osaka, Japan). The animals each weighed about 200 g (mature females) and were housed in a temperature-controlled room (22 ± 2°C) under artificial lighting from 0600 h to 1800 h each day. Commercial powdered chow (Charles River Japan Inc., Osaka, Japan) and tap water were available ad libitum for 7 days. Five rats were then injected intravenously with streptozotocin (STZ) (The Upjohn Co., Kalamazoo, Michigan) at a dose of 45 mg per kg, and the remaining five rats were injected with citrate buffer. STZ, buffered to pH 4.5 with a citrate buffer, was freshly prepared just prior to injection in each rat. The animals were subsequently isolated in individual cages in the colony maintained at our university with ad libitum food and water for a period of ten days. Ten and fifteen

Table 1. Clinical characteristics of patients (Experiment 2a).

| No | Initials | Age | Sex | Obesity index* | Duration of diabetes (yrs) | Diabetic complications | Treatment       |
|----|----------|-----|-----|----------------|--------------------------|-----------------------|------------------|
| 1  | E.S.     | 65  | M   | 1.0           | 10                       | (—)                   | Diet             |
| 2  | S.U.     | 66  | F   | 1.3           | 1                        | (—)                   | Diet             |
| 3  | T.S.     | 60  | M   | 1.1           | 2                        | Retino, Renal         | Diet             |
| 4  | M.T.     | 64  | M   | 1.1           | 1                        | Renal                 | Diet             |
| 5  | M.R.     | 53  | M   | 1.0           | 7                        | (—)                   | Diet             |
| 6  | M.S.     | 48  | F   | 1.1           | 1                        | (—)                   | Diet             |
| 7  | K.Y.     | 33  | M   | 1.3           | 4                        | Renal                 | Sulfonylurea     |
| 8  | S.O.     | 83  | F   | 1.4           | 2                        | (—)                   | Sulfonylurea     |
| 9  | Y.O.     | 79  | M   | 1.1           | 29                       | Retino, Renal Neuro   | Sulfonylurea     |
| 10 | U.U.     | 63  | F   | 1.0           | 10                       | Retino                | Sulfonylurea     |
| 11 | T.I.     | 68  | M   | 1.0           | 9                        | Renal                 | Sulfonylurea     |
| 12 | T.Y.     | 67  | M   | 0.8           | 29                       | Retino, Neuro         | Sulfonylurea     |
| 13 | K.S.     | 53  | M   | 1.0           | 1                        | Retino                | Sulfonylurea     |
| 14 | S.I.     | 78  | F   | 1.1           | 22                       | Retino, Neuro         | Insulin          |
| 15 | M.I.     | 64  | M   | 0.8           | 20                       | Retino, Renal Neuro   | Insulin          |

*a Obesity index calculated as body weight/(height−100)×0.9. Abbreviations: Retino, diabetic retinopathy; Renal, diabetic nephropathy; Neuro, diabetic neuropathy.
Table 2. Clinical characteristics of patients (Experiment 2b).

| No | Initials | Age | Sex | Obesity indexa | Duration of diabetes (yrs) | Diabetic complications | Treatment |
|----|----------|-----|-----|---------------|---------------------------|-----------------------|-----------|
| 1  | M.K.     | 48  | M   | 1.3           | 6                         | (—)                   | Diet      |
| 2  | T.F.     | 68  | M   | 1.3           | 1                         | (—)                   | Diet      |
| 3  | T.O.     | 70  | M   | 1.1           | 25                        | Retino, Neuro Renal   | Diet      |
| 4  | S.H.     | 39  | F   | 1.1           | 1                         | (—)                   | Diet      |
| 5  | Y.K.     | 40  | F   | 1.0           | 1                         | (—)                   | Diet      |
| 6  | S.K.     | 39  | F   | 1.1           | 1                         | (—)                   | Diet      |
| 7  | M.S.     | 48  | F   | 1.2           | 1                         | (—)                   | Diet      |
| 8  | K.S.     | 53  | M   | 1.0           | 1                         | Retino                | Sulfonylea |
| 9  | S.S.     | 54  | M   | 1.1           | 1                         | Retino                | Sulfonylea |
| 10 | Y.M.     | 65  | F   | 1.3           | 1                         | (—)                   | Sulfonylea |
| 11 | S.M.     | 67  | F   | 1.4           | 1                         | (—)                   | Sulfonylea |
| 12 | B.A.     | 84  | M   | 1.0           | 2                         | Renal                 | Sulfonylea |
| 13 | S.A.     | 82  | M   | 1.1           | 3                         | Renal                 | Sulfonylea |
| 14 | M.I.     | 64  | M   | 0.8           | 20                        | Retino, Neuro Renal   | Insulin   |
| 15 | M.S.     | 70  | F   | 1.4           | 3                         | Neuro                 | Insulin   |
| 16 | I.O.     | 31  | F   | 1.0           | 13                        | Retino, Neuro Renal   | Insulin   |
| 17 | S.O.     | 32  | F   | 0.9           | 10                        | Retino, Neuro Renal   | Insulin   |
| 18 | H.O.     | 15  | F   | 1.0           | 1                         | (—)                   | Insulin   |
| 19 | K.M.     | 76  | M   | 1.0           | 30                        | Neuro, Renal          | Insulin   |
| 20 | S.O.     | 16  | F   | 0.8           | 2                         | (—)                   | Insulin   |

*aObesity index calculated as body weight/(height - 100) × 0.9. Abbreviations: Retino, diabetic retinopathy; Renal, diabetic nephropathy; Neuro, diabetic neuropathy.

days after the administration of STZ, glucose and aspartame loading tests were performed, respectively. Following 18 h of fasting, glucose (150 mg per 100 g body weight) or aspartame (0.45 mg per 100 g body weight, which is equivalent to 150 mg per 100 g body weight of glucose in sweetness) were dissolved in 2 ml of saline and administered through a stomach tube to these STZ diabetic and control rats, respectively. Blood samples were obtained through a polyethylene catheter inserted into the femoral vein for the measurement of plasma glucose and insulin levels at appropriate intervals.

2) Experiments with diabetic patients.

a) Aspartame loading test in diabetic patients. The subjects were selected at random from patients with non-insulin-dependent diabetes mellitus (NIDDM) who were admitted to our hospital for diabetic control. Fifteen subjects (Table 1) were given a 75-g oral glucose tolerance test (OGTT) and five days after the test, a 225-mg
oral aspartame loading test, which is equivalent to 75 g of glucose in sweetness. Plasma glucose and insulin levels were measured at 0, 30, 60, 90, 120, and 180 min.

b) Effects of a three-day diet sweetened with aspartame on fasting plasma glucose levels. The other twenty subjects with NIDDM (Table 2) and six non-diabetic subjects (2 men and 4 women, 50.2 ± 5.6 yrs.) were selected from patients who were admitted to our hospital. They consumed diets sweetened with 24–48 mg of aspartame, which is equivalent to the estimated daily sucrose intake (4.8–9.6 g) on a sweetness basis, for three consecutive days. Fasting plasma glucose was measured before and one and three days after the initiation of diets sweetened with aspartame.

c) Effects of snacks sweetened with aspartame on fasting plasma glucose levels. Twenty subjects with NIDDM (same as Experiment 2b) consumed jellies sweetened with 240 mg of aspartame, which is equivalent to 96 g of sucrose in sweetness, at 3:00 pm in addition to the prescribed diet. The fasting plasma glucose was measured in the morning before and after aspartame loading.

Plasma glucose was analyzed by the glucose oxidase method using a Beckman Glucose Analyzer 2 (Beckman Instruments, Inc., Fullerton, California) and plasma insulin was determined with commercial insulin kits (Insulin Riabead®, Dainabot Co., Tokyo, Japan). All data are shown as the mean ± SEM. Student’s t-test was used for statistical analysis. The purpose and methods of the proposed studies were fully explained to each subject. The procedures followed were in accordance with the Helsinki Declaration as updated in Tokyo, Japan in 1975.

RESULTS

1) Animal experiment

Figures 1 and 2 show the results of the oral administration of glucose, aspartame, and physiological saline in normal and diabetic rats.

In normal rats, the administration of glucose (150 mg per 100 g body weight) led to a significant increase (p<0.05–0.001) of plasma glucose, compared to its basal value and its level after physiological saline infusion. The elevation of plasma glucose was accompanied by concomitant increases in plasma insulin levels from 22.4 ± 2.9 μU/ml to 38.9 ± 3.7 μU/ml at 60 min. On the other hand, the administration of aspartame (0.45 mg per 100 g body weight) had no effect on plasma glucose and insulin levels (Fig. 1).

In diabetic rats, the oral administration of glucose increased the plasma glucose levels as expected, but aspartame administration had no effect on the plasma glucose level, as with physiological saline infusion. On the other hand, plasma insulin levels remained unchanged from the basal values after the administration of glucose or aspartame (Fig. 2).

2) Experiments with diabetic patients

a) Aspartame loading test in diabetic patients. Figure 3 shows the results of 75-g OGTT and aspartame loading tests in patients with NIDDM. After the
administration of 75 g glucose, plasma glucose levels increased from $145 \pm 12.5$ mg/100 ml at the basal value to $342.1 \pm 16.6$ mg/100 ml at 120 min. The elevation of plasma glucose was accompanied by concomitant increases of plasma insulin levels from the basal value of $11.8 \pm 1.5 \mu$U/ml to $29.7 \pm 3.5 \mu$U/ml at 120 min. However, the administration of 187.5 mg of aspartame had no effect on plasma glucose and insulin levels.

b) Effects of three-day diets sweetened with aspartame on fasting levels of plasma glucose. Table 3 shows the fasting levels of plasma glucose in normal controls and in diabetics fed diets sweetened with aspartame (24–48 mg per day), respectively. Plasma glucose levels did not change significantly in either the normal or diabetic patients during the ingestion of aspartame.

c) Effects of snacks sweetened with aspartame on fasting plasma glucose levels. The fasting plasma glucose levels were also unaffected by the ingestion of snacks sweetened with aspartame (135.0 $\pm$ 8.2 mg/100 ml before, 138.6 $\pm$ 8.1 mg/100 ml after).
Fig. 2. Effects of oral administration of aspartame (0.45 mg/100 g body weight), glucose (150 mg/100 g body weight), and physiological saline on plasma glucose and insulin levels in streptozotocin-induced diabetic rats. The data are shown as the mean ± SEM.

DISCUSSION

It is clinically important to know how aspartame affects glucose metabolism. We found that aspartame had no effect on the plasma glucose or insulin level in STZ diabetic rats or normal control rats. The findings in normal rats agree with those in non-diabetic primates by Reynolds and Bauman (1983), reported in the review of Horwitz (3). As aspartame did not influence the plasma glucose or insulin level in diabetic rats, we examined its effect on diabetic patients. To minimize the influence of the variation of food intake, we selected volunteers from among patients who were admitted to our hospital. Our results with diabetic patients showed that, although plasma glucose and insulin levels increased reasonably after the oral

* p<0.05
** p<0.01
*** p<0.005
vs basal

# p<0.05
## p<0.005
### p<0.001
vs saline control
Fig. 3. Effects of oral administration of aspartame (225mg) and glucose (75g) on plasma glucose and insulin levels in patients with non-insulin-dependent diabetes mellitus. The data are shown as the mean±SEM.

Table 3. Effects of three-day diet sweetened with aspartame (24–48mg/day) on fasting plasma glucose levels in normal controls and diabetics.

| Blood glucose (mg/100 ml) | Before | 1 day after | 3 days after |
|---------------------------|--------|-------------|--------------|
| Normal (n=6)              | 76.0 ± 1.3 | 73.7 ± 1.4  | 76.3 ± 1.7   |
| Diabetic (n=20)           | 139.4 ± 11.7 | 144.4 ± 11.3 | 138.6 ± 12.8 |

The data are shown as the mean±SEM.
administration of glucose (75 g), these parameters did not increase significantly after the administration of aspartame, which was equivalent to 75 g of glucose in sweetness. However, although the amount of aspartame administered was equivalent to that of glucose in sweetness, the caloric or metabolic effect might differ from that of glucose. Furthermore, the sucrose-aspartame ratio between rats and human subjects may be different. This point requires further examination.

Other results of studies in diabetics showed that aspartame ingestion (24–48 mg per day as seasoning, snacks flavored with 240 mg aspartame) did not have any effect on the fasting plasma glucose level. Therefore, we confirmed that administration of aspartame as a substitute for sucrose with regards to sweetness would not have any effect on the plasma glucose or insulin level in patients with NIDDM.

We concluded that aspartame had no influence on the plasma glucose or insulin level, nor on fasting plasma glucose over a short time of ingestion in diabetics. On the other hand, the effects of chronic ingestion of aspartame in diabetics should be further studied. Stern et al. (4) have already reported that in 43 NIDDM patients daily administration of 1.8 g of aspartame in capsules for 90 days did not affect the fasting plasma glucose level and had no prominent side effects, although they did not check the insulin level. Therefore, our present observations combined with the report of Stern et al. (4), suggest that NIDDM patients can use aspartame as a food additive without affecting their blood glucose level.

We did not examine the effect of aspartame in patients with insulin-dependent diabetes mellitus who have little ability to secrete intrinsic insulin. This problem remains to be clarified.

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REFERENCES

1) Mazur, R. H. (1984): Discovery of aspartame, in Aspartame Physiology and Biochemistry, ed. by Stegink, L. D., and Filer, L. J., Jr., Marcel Dekker, Inc., New York and Basel, pp. 3–9.
2) Porikos, K. P., Booth, G., and Van Itallie, T. B. (1977): Effect of convert nutritive dilution on the spontaneous food intake of obese individuals: A pilot study. Am. J. Clin. Nutr., 30, 1638–1644.
3) Horwitz, D. L. (1984): Aspartame use by persons with diabetes, in Aspartame Physiology and Biochemistry, ed. by Stegink, L. D., and Filer, L. J., Jr., Marcel Dekker, Inc., New York and Basel, pp. 633–639.
4) Stern, S. B., Bleicher, S. J., and Flores, A. (1976): Administration of aspartame in non-insulin-dependent diabetics. J. Toxicol. Environ. Health, 2, 429–439.