Response to Single Dose of Aspartame or Saccharin by NIDDM Patients

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Twelve normal subjects and 10 subjects with non-insulin-dependent diabetes mellitus were given, in random order at intervals of ≥1 wk, three drinks of the same beverage: one unsweetened, one sweetened with 400 mg aspartame, and one sweetened with 135 mg saccharin. The amount of sweetener approximated that in 1 L of sugar-free soft drink. Plasma glucose, insulin, and glucagon were measured for 3 h after ingestion of the test beverage. Plasma glucose declined slightly throughout the test period, probably due to fasting, with no differences between the three treatments. Neither sweetener affected peak insulin levels in subjects with or without diabetes. Analysis of area under the curve showed that mean insulin levels were statistically significantly higher after aspartame than after saccharin or unsweetened beverage in normal subjects only, but the magnitude of the difference was small and unlikely to be of physiological importance in the absence of differences in glucose levels. Furthermore, the differences could largely be accounted for by a decrease in insulin values after both unsweetened beverage and saccharin, with no change from baseline after aspartame. Glucagon levels showed time-to-time variation but no overall differences. We conclude that ingestion of aspartame- or saccharin-sweetened beverages by fasting subjects, with or without diabetes, did not affect blood glucose homeostasis. *Diabetes Care* 11:230–34, 1988

Aspartame (*N*-L-α-aspartyl-L-phenylalanine 1-methyl ester, or NutraSweet) is commonly used as a noncarbohydrate sweetener by people with diabetes. We have previously shown that chronic administration of aspartame, in a dose of 0.9 g with each meal (2.7-g total daily dose) for 18 wk, causes no alteration of glycemic control or other adverse reactions (1). However, it is also important to determine whether aspartame may affect blood glucose levels when it is consumed in the absence of food, because people frequently consume items such as unsweetened soft drinks at times other than normal meal times.

In large amounts, e.g., 0.5 g/kg body wt, many amino acids are known to stimulate insulin secretion (2). Protein meals are also a stimulus to glucagon secretion, especially in a carbohydrate-deprived state (3). This is probably not a direct effect of absorbed amino acids but is mediated by signals arising from the gastrointestinal tract. Aspartame is hydrolized to phenylalanine and aspartic acid after ingestion. It is not known whether amounts of these amino acids that might be typically consumed alone as aspartame can cause physiologically significant insulin and/or glucagon secretion. Also, it may be asked whether sweetness itself stimulates insulin secretion.

Although aspartame is unlikely to directly alter blood glucose levels, it may do so indirectly via effects on insulin or glucagon secretion. Unpublished anecdotal reports of hypoglycemic-type symptoms after aspartame ingestion by both diabetic and nondiabetic individuals suggest this possibility, although such symptoms have never been objectively documented. This study was designed to determine whether aspartame alters blood levels of glucose, insulin, or glucagon.

MATERIALS AND METHODS

Study population. All subjects were ≥18 and ≤65 yr old. Normal subjects had no history of diabetes, weighed

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between 55 and 75 kg, and were <120% of ideal body weight (IBW) as determined by Metropolitan Life Insurance tables. The 12 normal subjects were women. Diabetic subjects all had non-insulin-dependent diabetes mellitus (NIDDM), diagnosed by a history of fasting plasma glucose >140 mg/dl or plasma glucose concentration >200 mg/dl 2 h after ingestion of 75 g glucose. None of the diabetic subjects were taking insulin or had a history of ketoacidosis. All had stable diabetic control for at least 1 mo before entry into the study and, if on an oral hypoglycemic agent, the dose was stable for 30 days before entry into the study. The NIDDM subjects included 5 men and 5 women. Men and women showed similar results, and their values are combined in all analyses.

The normal subjects had a mean ± SD age of 28 ± 8 yr, weight of 62.1 ± 6.9 kg, and height of 166 ± 7.5 cm. The diabetic subjects had a mean ± SD age of 57 ± 8 yr, weight of 94.1 ± 15.7 kg, and height of 167.2 ± 9.9 cm. No subject's weight was >150% IBW. Excluded from the study were pregnant women, people with phenylketonuria, people with concomitant illnesses that might affect diabetic control, and people taking, acutely or in changing doses, medications that might affect plasma glucose levels or interact with oral hypoglycemic agents. The study was approved by the University of Illinois Institutional Review Board.

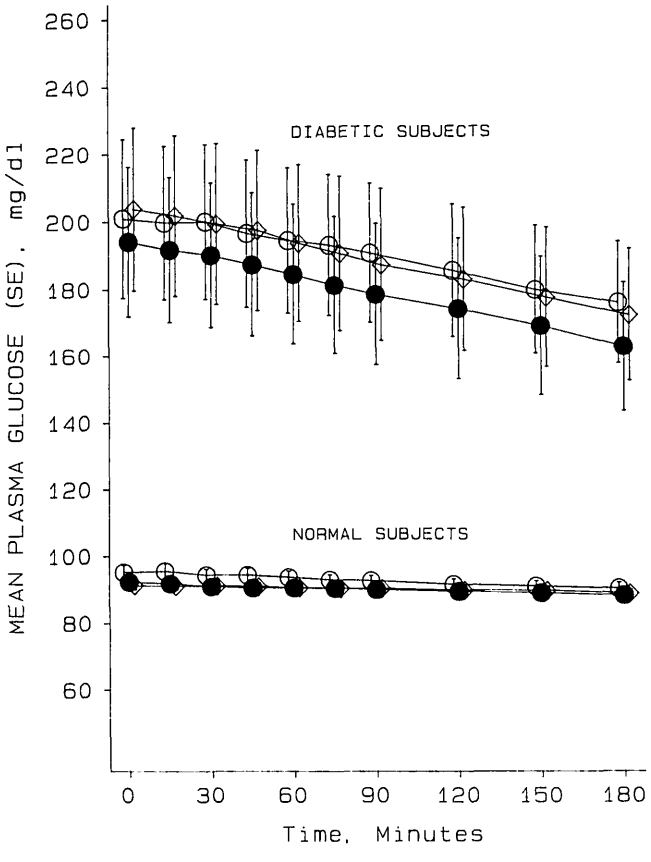

FIG. 1. Plasma glucose concentrations (mean ± SE for each time point) after ingestion of unsweetened beverage (◇) or beverage sweetened with 400 mg aspartame (○) or 135 mg saccharin (●).

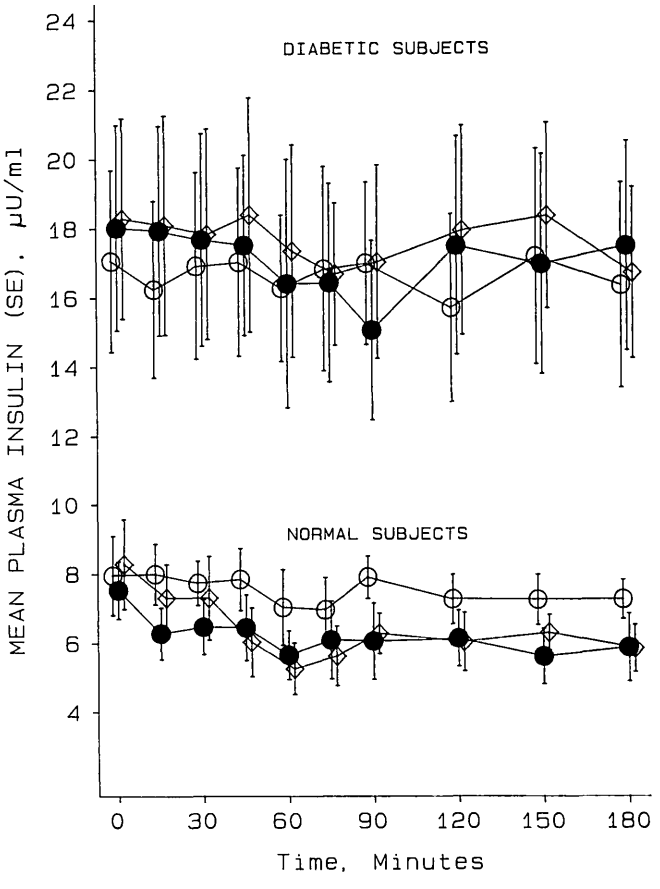

FIG. 2. Plasma insulin concentrations (mean ± SE for each time point) after ingestion of unsweetened beverage (◇) or beverage sweetened with 400 mg aspartame (○) or 135 mg saccharin (●).

Test substances. For each test, subjects were asked to drink 300 ml of unsweetened cherry-flavored Kool-Aid (General Foods, White Plains, NY). The beverage was given without added sweetener or sweetened with 135 mg saccharin or 400 mg aspartame. These amounts of saccharin and aspartame were chosen to give comparable degrees of sweetness and are comparable to those found in ~1 L of sugar-free soft drink.

Experimental design. An open, randomized crossover design was used to compare the three test beverages. Subjects were assigned, in the order they were accepted into the study, to receive one of the six possible sequences of the three beverages according to a random assignment schedule. Five minutes before and again immediately before ingesting each test beverage, baseline levels of glucose, insulin, and glucagon were determined. Samples were also collected at 15, 30, 45, 60, 75, 90, 120, 150, and 180 min after consuming the test beverage. Subjects fasted at least 8 h before each test and remained fasting except for water during the test. Tests were separated by at least 1 wk.

Analytical methods. Plasma glucose was measured with a YSI model 23A glucose analyzer (YSI, Yellow Springs,

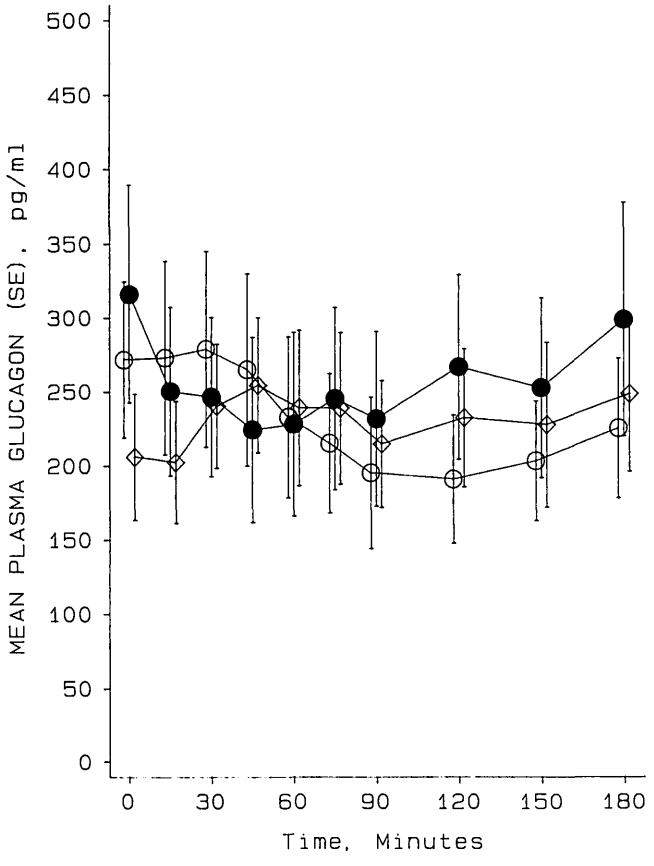

FIG. 3. Plasma glucagon concentrations in normal subjects (mean ± SE for each time point) after ingestion of unsweetened beverage (◇) or beverage sweetened with 400 mg aspartame (○) or 135 mg saccharin (●).

OH). Insulin and glucagon were measured by immunoassay with commercial kits (Cambridge Med. Diagnostics, Billerica, MA). Samples for glucagon measurement were collected in tubes containing 14 mg sodium EDTA and 500 μl Trasylol (5000 KIU) and immediately chilled to 4°C.

Statistical methods. Statistical analyses, done separately for normal and NIDDM subjects, included the appropriate analysis of variance and tests of the three differences between treatment means. Significance was set at the 5% two-sided level with no adjustment for the many statistical tests conducted. Variables subjected to analysis included changes in concentration, areas under the curve (AUC) to 180 min, peak concentration (C_{max}), and time to peak concentration (t_{max}).

RESULTS

Twelve normal subjects and 10 subjects with NIDDM completed the study. There were 3 subjects (2 normal, 1 NIDDM) who were randomized but dropped from the study before administration of test article because of unwillingness to have repeated blood collection, inability to collect adequate blood samples, or occurrence

TABLE 1
Glucose levels in normal and NIDDM subjects after 400 mg aspartame, 135 mg saccharin, or unsweetened beverage

	AUC (mg · dl^{-1} · min^{-1})	C_{max} (mg/dl)	t_{max} (min)
Normal			
Unsweetened	16,213 ± 174	92 ± 1	19 ± 6
Aspartame	16,664 ± 314	96 ± 2	19 ± 10
Saccharin	16,179 ± 191	92 ± 1	8 ± 6
NIDDM			
Unsweetened	33,860 ± 4010	205 ± 24	15 ± 12
Aspartame	34,135 ± 3720	205 ± 23	28 ± 10
Saccharin	32,208 ± 3767	195 ± 22	9 ± 5

There were no statistically significant differences between treatments. Results are means ± SE. AUC, area under the curve to 180 min; C_{max}, peak concentration; t_{max}, time to peak concentration.

of nausea and vomiting after insertion of a needle. Plasma glucose, insulin, and glucagon concentrations are shown in Figs. 1–4. There was no significant effect of sweetener on plasma glucose levels at any time point in either the normal or diabetic group. For insulin values, there were no treatment effects at any time with the exception of

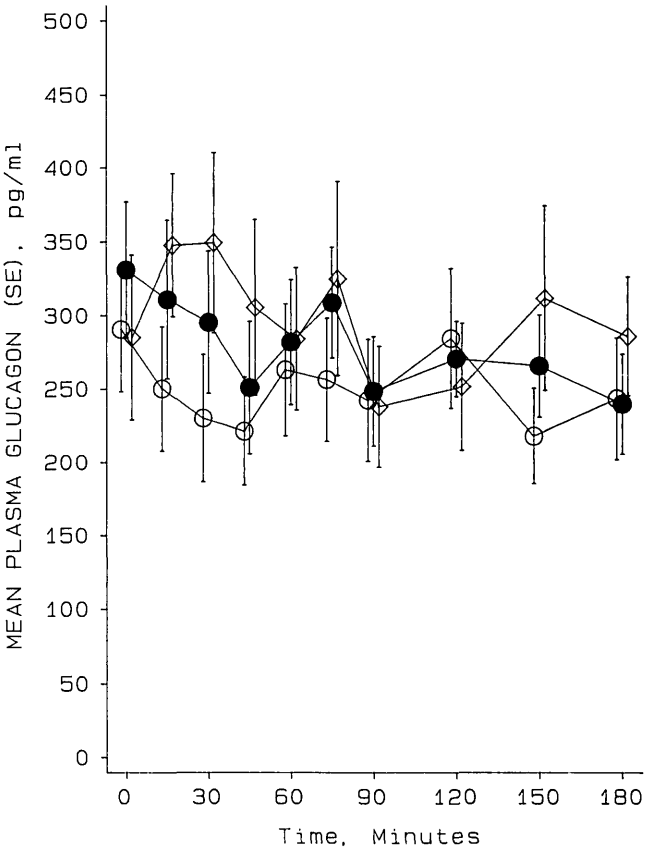

FIG. 4. Plasma glucagon concentrations in diabetic subjects (mean ± SE for each time point) after ingestion of unsweetened beverage (◇) or beverage sweetened with 400 mg aspartame (○) or 135 mg saccharin (●).

the 15-min value in normal subjects, at which analysis of variance showed a statistically significant difference between aspartame and saccharin ($P < .05$). Although glucagon values showed statistically significant differences at several time points, the differences were minor and can be largely accounted for by the statistically significant differences at baseline.

AUC, C_{max}, and t_{max} of glucose, insulin, and glucagon concentrations are given in Tables 1–3. Analysis of variance for AUC showed no differences for diabetic subjects. For normal subjects, only insulin AUC showed statistically significant differences between unsweetened and aspartame ($P < .05$) and aspartame and saccharin ($P < .01$). No treatment effects were seen in C_{max} or t_{max} in either group of subjects. No subject experienced an adverse reaction after ingesting any of the test beverages.

TABLE 3
Glucagon levels in normal and NIDDM subjects after 400 mg aspartame, 135 mg saccharin, or unsweetened beverage

	AUC (pg · ml^{-1} · min^{-1})	C_{max} (pg/ml)	t_{max} (min)
Normal			
Unsweetened	41,465 ± 8151	327 ± 49	68 ± 13
Aspartame	40,549 ± 8687	376 ± 67	45 ± 17
Saccharin	45,498 ± 10,893	359 ± 75	95 ± 24
NIDDM			
Unsweetened	52,757 ± 8060	423 ± 60	54 ± 18
Aspartame	44,599 ± 6576	350 ± 49	63 ± 17
Saccharin	49,388 ± 5898	394 ± 40	69 ± 19

There were no statistically significant differences between treatments. Results are means ± SE. AUC, area under the curve to 180 min; C_{max}, peak concentration; t_{max}, time to peak concentration.

DISCUSSION

In this study, aspartame had no effect on plasma glucose levels. In normal and, to a greater degree, NIDDM subjects, glucose declined slightly at a constant rate throughout the 3-h study period. The declines were similar when unsweetened, aspartame-sweetened, and saccharin-sweetened beverages were tested. Thus, the glucose decline is probably due to fasting and not to the test substances.

Although there was no effect on peak insulin levels in either group of subjects, calculation of AUC showed higher insulin levels after aspartame than after saccharin or unsweetened beverage in normal subjects. This difference can be largely accounted for by a decrease in insulin values after both the unsweetened and saccharin-sweetened beverages, with no change from baseline after aspartame. Correlation analysis showed no consistent relationship between changes in glucose concentration and changes in insulin levels. The small apparent differences in insulin levels are thus unlikely to be physiologically important. None of the test substances was associated with hypoglycemia. The absence of any meaningful changes in insulin levels after saccharin ingestion suggests that, in the time intervals measured in this study, sweetness itself does not stimulate insulin secretion. Although there were differences in mean glucagon concentrations at different times, no consistent pattern emerged, and the AUC values showed no differences.

TABLE 2
Insulin levels in normal and NIDDM subjects after 400 mg aspartame, 135 mg saccharin, or unsweetened beverage

	AUC (μU · ml^{-1} · min^{-1})	C_{max} (μU/ml)	t_{max} (min)
Normal			
Unsweetened	1135 ± 119	9.7 ± 1.2	42 ± 12
Aspartame	1345 ± 107*	11.1 ± 0.8	76 ± 18
Saccharin	1098 ± 133	9.6 ± 0.8	58 ± 15
NIDDM			
Unsweetened	3184 ± 503	20.9 ± 3.1	71 ± 16
Aspartame	2990 ± 477	19.7 ± 2.9	93 ± 16
Saccharin	3058 ± 509	21.5 ± 3.4	75 ± 18

Results are means ± SE. AUC, area under the curve to 180 min; C_{max}, peak concentration; t_{max}, time to peak concentration.
*Significantly different from unsweetened ($P \leq .05$) and saccharin ($P \leq .01$) means.

There are few studies in the literature examining the acute effects of aspartame on glucose, insulin, or glucagon levels. Okuno et al. (4) showed that a single dose of 500 mg aspartame induced no change in glucose in control subjects or untreated diabetic subjects. As in our study, they found a gradual decrease in blood glucose levels, with the greatest decrease occurring in subjects with the highest initial blood glucose. They found no significant changes in insulin or glucagon concentrations. Shigeta et al. (5) gave an acute dose of 225 mg aspartame to patients with NIDDM and also found no changes in glucose or insulin levels. In both of these studies, postaspartame values were compared to baseline rather than control values. Our data, as shown in Fig. 2, agree with these studies in that insulin levels in NIDDM were unchanged after aspartame ingestion. However, in nondiabetic subjects, insulin levels declined after saccharin or unsweetened beverage, resulting in significant differences in the AUC.

In conclusion, ingestion of 400 mg aspartame (approximate amount of aspartame in 1 L sugar-free soft drink) in the absence of food appears to cause no adverse changes in blood glucose concentration in normal subjects or subjects with NIDDM. These data provide additional assurance on the safety of aspartame-sweetened beverages in the meal plans of people with diabetes and suggest that there is no physiologic basis for aspartame to cause hypoglycemia in diabetic or nondiabetic individuals.

ACKNOWLEDGMENTS

This study was supported in part by a grant from The NutraSweet Company.

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