Effect of Added Fat on Plasma Glucose and Insulin Response to Ingested Potato in Individuals With NIDDM

MARY C. GANNON, PHD
NACIDE ERCAN, MD
SYDNEY A. WESTPHAL, MD
FRANK Q. NUTTALL, MD, PHD

OBJECTIVE — In normal subjects, ingestion of butter with potato resulted in considerably lower blood glucose levels but similar or higher insulin concentrations compared with those observed in the same subjects after potato ingestion alone. We determined whether butter ingested with potato would result in a greater stimulation in insulin secretion than ingestion of potato alone in subjects with NIDDM.

RESEARCH DESIGN AND METHODS — Seven male subjects with untreated NIDDM ingested 50 g CHO alone or 50 g CHO with 5, 15, 30, or 50 g fat as a breakfast meal. Fat was ingested in the form of butter, and CHO was given in the form of potato. Subjects received 50 g glucose on two separate occasions for comparative purposes. The subjects also were given only water and were studied over the same time period (water control). Plasma glucose, glucagon, α-amino nitrogen, nonesterified fatty acids, serum insulin, C-peptide, and triglyceride concentrations were determined over 5 h. The integrated area responses were quantified over the 5-h period using the water control as a baseline.

RESULTS — The mean plasma glucose area response after ingestion of potato with or without the various amounts of butter were all similar and were 82% of that observed after ingestion of 50 g glucose. The mean insulin area response to potato alone was 532 pmol · h · L^{-1}. The mean insulin area responses to potato plus 5,15,30, and 50 g of fat meals were 660,774,750, and 756 pmol · h · L^{-1}, respectively. Thus, the mean insulin areas were all greater than for ingestion of potato alone, and a maximal response was observed with addition of 15 g fat (1.4-fold). The C-peptide data did not confirm an increase in insulin secretion. Overall the area responses after ingestion of meals containing fat were not different from the response to potato ingestion alone, although the responses were erratic. The glucagon area response was positive after ingestion of all fat containing meals except for that containing only 5 g fat, and there was a dose-response relationship. The plasma α-amino nitrogen and nonesterified fatty acid area responses were negative after potato ingestion and were not significantly different when fat was added. The serum triglyceride concentration increase was greater after the ingestion of butter with the potato as expected.

CONCLUSIONS — In contrast to the results in normal subjects after ingestion of butter with potato, the glucose response was not smaller in subjects with NIDDM. The insulin response was greater. The insulin area response data indicated the presence of a dose-response relationship. Whether similar responses will be observed with other dietary fat and CHO sources remains to be determined.

FROM THE METABOLIC RESEARCH LABORATORY AND THE SECTION OF ENDOCRINOLOGY, METABOLISM, AND NUTRITION, MINNEAPOLIS VETERANS AFFAIRS MEDICAL CENTER, MINNEAPOLIS; AND THE DEPARTMENTS OF FOOD SCIENCE AND NUTRITION, AND MEDICINE, UNIVERSITY OF MINNESOTA, MINNEAPOLIS, MINNESOTA.

ADDRESS CORRESPONDENCE AND REPRINT REQUEST TO MARY C. GANNON, PHD, DIRECTOR, METABOLIC RESEARCH LABORATORY, 111G, MINNEAPOLIS VA MEDICAL CENTER, ONE VETERANS DRIVE, MINNEAPOLIS, MN 55417.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; RGA, RELATIVE GLUCOSE AREA; CHO, CARBOHYDRATE; AAN, α-AMINO NITROGEN; NEFA, NONESTERIFIED FATTY ACIDS; RIA, RADIOIMMUNOASSAY; CV, COEFFICIENT OF VARIATION; ANOVA, ANALYSIS OF VARIANCE; LSD, LEAST SIGNIFICANT DIFFERENCE; ANCOVA, ANALYSIS OF COVARIANCE; BMI, BODY MASS INDEX.

In normal subjects, ingestion of butter with potato resulted in remarkably lower blood glucose levels but similar or higher insulin concentrations compared with those observed in the same subjects after potato ingestion alone (1). These data have been confirmed (2). Although other interpretations are possible, the data could be interpreted to indicate that the butter fat acted synergistically, with the glucose derived from the potato starch, to stimulate insulin secretion.

Previous studies have found that ingested proteins act synergistically with glucose to stimulate insulin secretion in subjects with NIDDM but not in normal subjects (3,4). Therefore, we were interested in determining whether butter, ingested with potato, would result in a greater stimulation in insulin secretion than ingestion of potato alone in subjects with NIDDM. We also were interested in determining if a dose-response relationship existed. Part of these data have been published previously in abstract form (5).

RESEARCH DESIGN AND METHODS

— Seven male subjects were studied in a metabolic unit. All patients met the National Diabetes Data Group criteria for the diagnosis of NIDDM (6). The mean age was 68 ± 1.4 yr with a range of 60–73 yr. The study was approved by the Medical Center Committee on Human Subjects. The mean HbA_1 was 9.2 ± 1.0% (normal = 4.2–6.2%). All subjects were on a weight-maintenance diet, consuming >200 g CHO/day for at least 3 days before the study. None of the subjects were treated with oral hypoglycemic agents or insulin before the study. The clinical characteristics of the patients are listed in Table 1.

After a 8- to 10-h overnight fast, a plastic catheter was placed in a forearm and was kept patent with intravenous saline. Two baseline samples were drawn at 0730 and 0745. The meals were given at 0800, and blood samples were taken at 0800, 0830, 0900, and hourly for 5 h.

Table 1—*Clinical characteristics of NIDDM subjects*

PATIENT	AGE (YR)	BMI (KG/M^2)	HbA_1 (%)*	DURATION OF DIABETES	CONCOMITANT DISEASE
1	68	30	7	6 YR	HISTORY OF RECURRENT URINARY TRACT INFECTIONS, STATUS POST LEFT NEPHRECTOMY; HYPERTENSION; ANGINA; SUPRAVENTRICULAR TACHYCARDIA; HISTORY OF DUODENAL ULCER
2	71	33	14.2	NEW	HISTORY OF LYMPHOCYTIC LEUKEMIA: OF ELEVATED HEMOGLOBIN WITH NORMAL RED CELL MASS; HISTORY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
3	67	34	7.6	2 YR	STATUS POST EXCISION OF LEFT ARM MELANOMA (CLARKE'S) STAGE III, NO METASTASIS
4	60	27	7.1	15 YR	HISTORY OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE; CONGESTIVE HYPOTHYROIDISM; HEART FAILURE, TREATED AND EUTHYROID
5	73	28	13	4 MO	HISTORY OF GALLSTONE PANCREATITIS; HYPERTENSION; CHRONIC BRONCHITIS
6	71	26	9	8 YR	HISTORY OF PEPTIC ULCER DISEASE; PERIPHERAL VASCULAR DISEASE
7	67	27	7.7	1 YR	HISTORY OF PRIMARY HYPOTHYROIDISM, TREATED AND EUTHYROID; HYPERCHOLESTEROLEMIA; PEPTIC ULCER DISEASE
MEAN ± SE	68 ± 1.4	29 ± 1.1	9.2 ± 1.0		

*Normal = 4.2–6.2%.

The subjects ingested a meal of 50 g glucose given as a commercial glucose solution (Glutol, Paddock, Minneapolis, MN) twice during the study. All subjects also received a meal consisting of 50 g CHO as potatoes. The subjects were given potatoes either alone or with melted butter to equal 5,15,30, and 50 g of fat (6.2,18.5,37, and 62 g of butter, respectively). Boiled, peeled red potatoes (240 g raw weight) were cooked in a microwave oven for 2.5–3 min 1 day before being served. They were kept refrigerated overnight and served the following day after being heated in the microwave oven. The meals were given in random order. Water was given as a control meal. The amount of CHO and fat in the meals was calculated from food tables (7).

Plasma glucose was determined by a glucose oxidase method with a Beckman glucose analyzer with an O_2 electrode (Beckman Instruments, Fullerton, CA). Serum immunoreactive insulin was measured using a double-antibody RIA method with kits produced by Incstar (Stillwater, MN). The interassay CV of the insulin assay was 8.9% at an insulin concentration of 15 μU/ml. Glucagon was determined by RIA using 30K antiserum purchased from Health Science Center (Dallas, TX). The interassay CV of the glucagon assay was 22.9% at a glucagon concentration of 140 pmol/ml. C-peptide was measured using a double-antibody RIA method with kits produced by Incstar. The cross-reactivity of the C-peptide antibody to proinsulin was 4%. The interassay CV of the C-peptide assay was 7.9% at a C-peptide concentration of 1.36 pmol/ml. AAN was determined by the method of Goodwin (8). Serum NEFA were determined enzymatically, using a kit purchased from Wako Chemicals (Dallas, TX). Triglycerides and urea nitrogen were determined using an EktaChem Analyzer (Eastman Kodak, Rochester, NY).

The 5-h area responses were calculated using the trapezoid rule (9) and presented as means ± SE. Data obtained after ingestion of water alone were used as the baseline from which to calculate area responses (10). Statistics were done by two-way ANOVA, for the randomized complete block design, using the MacAnova (by G.W. Oehlert, Vers. 2.4) program for the Macintosh computer. Where appropriate, multiple comparisons were done by the Bonferroni and LSD methods. ANCOVA was used to improve the precision between treatment means. The observed responses were adjusted for the effect of the covariate. The amount of fat ingested (g) was taken as the covariate variable in this study. Linear regression analysis was performed using the least-squares method. $P < 0.05$ was considered significant. Data are presented as means ± SE.

RESULTS — The mean fasting glucose concentration was 7.5 ± 0.6 mM. After water ingestion alone fasting glucose

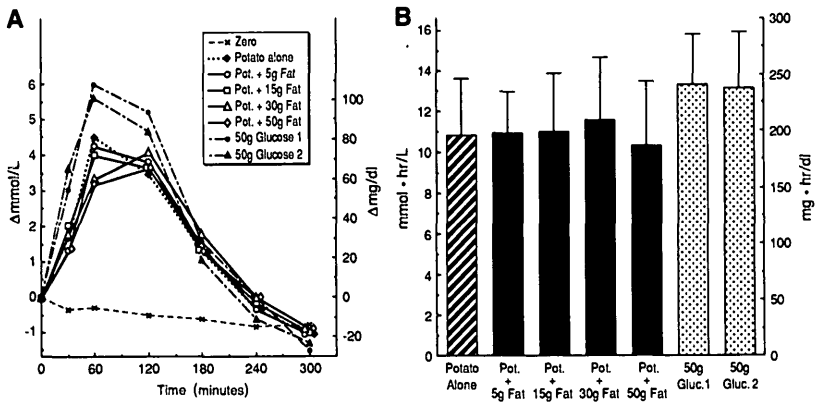

Figure 1—*A: Effect of fat ingestion on plasma glucose response. Lower dashed line represents glucose concentration when only water was ingested. Incremental changes in plasma glucose were determined for 5 h after ingestion of meals. Seven subjects with NIDDM were studied. Each subject ingested every test meal. Mean initial fasting glucose concentration was 7.5 ± 0.6 mM. B: Effect of fat ingestion of plasma glucose area response. Areas above fasting glucose concentration were determined with trapezoid rule using water control as baseline. Bars indicate means ± SE.*

concentration decreased gradually and was 0.8 mM lower at 300 min. After the ingestion of 50 g glucose, the mean maximal increase was 5.9 ± 0.6 mM at 60 min. Fasting glucose concentration then decreased and was 1.4 mM below the initial value by 300 min. After the ingestion of potato alone, the plasma glucose increase was 4.5 mM at 60 min. Plasma glucose then decreased and was 1.1 mM below the initial value by 300 min. After ingestion of potato plus 5, 15, 30, and 50 g of fat meals, the maximal plasma glucose responses were similar. However, for the meals containing 30 and 50 g fat, the peak response was delayed to 120 min (Fig. 1*A*).

After the glucose meals, the mean glucose area response was 13.5 ± 2.7 mmol · h · L^{-1}. After potato alone and potato plus 5, 15, 30, and 50 g of fat meals, the glucose area responses were 11.0 ± 2.8, 11.1 ± 2.1, 11.1 ± 2.9, 11.7 ± 3.1, and 10.5 ± 3.2 mmol · h · L^{-1}, respectively. The differences were not significant statistically ($P > 0.05$) (Fig. 1*B*).

The mean fasting insulin level was 158 ± 13 pM. After water ingestion the serum insulin concentration decreased gradually and was 19 pM below the initial value at 300 min. After the ingestion of glucose, the mean serum insulin increased by 258 ± 50 pM at 60 min. Mean serum insulin then decreased to near the initial value but was still elevated at 300 min. After ingestion of potato alone, serum insulin increased by 212 pM at 60 min. Serum insulin also decreased to near the initial value by 300 min. After ingestion of potato plus 5 and 15 g fat, the serum insulin increased by 260 and 322 pM, respectively, at 60 min. After ingestion of potato plus 30 and 50 g fat, the peak serum insulin increased by 251 and 274 pM, respectively, and the peak responses were delayed to 120 min. The insulin concentrations were all near initial values by 300 min (Fig. 2*A*).

The mean insulin area response after ingestion of the glucose meals was 690 ± 168 pmol · h · L^{-1}. The insulin area response after ingestion of potato alone was 532 ± 144 pmol · h · L^{-1}. After potato plus 5, 15, 30, and 50 g of fat meals, the mean insulin area responses were 660 ± 144, 774 ± 96, 750 ± 180, and 756 ± 168 pmol · h · L^{-1}, respectively. The differences between potato alone and potato and all of the fat-containing meals, except for the meal containing 5 g fat, were statistically significant ($P < 0.05$). The mean maximal insulin area response after ingestion of the 15, 30, and 50 g of fat-containing meals (as a group) was ~140% of that after ingestion of potato alone (Fig. 2*B*).

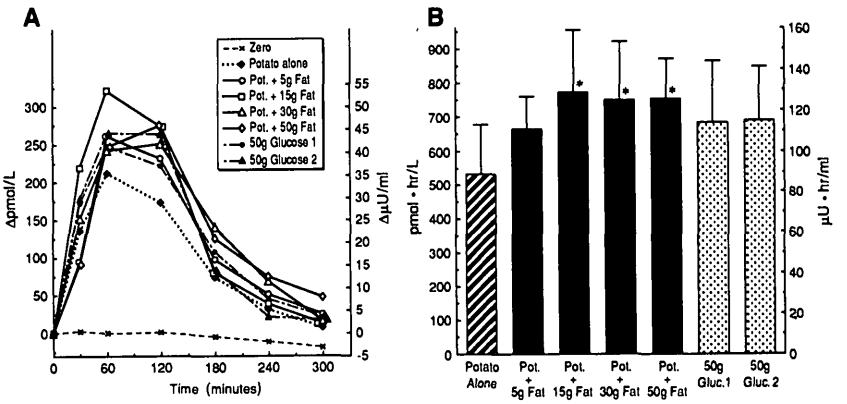

Figure 2—*A: Effect of fat ingestion on serum insulin response. Lower dashed line represents insulin concentration when only water was ingested. Incremental changes in plasma insulin were determined for 5 h after ingestion of meals. Seven subjects with NIDDM were studied. Each subject ingested every test meal. Mean initial fasting insulin concentration was 158 ± 13 pM. B: Effect of fat ingestion on serum insulin area response. Areas above fasting insulin concentration were determined with trapezoid rule using water control as baseline. Bars indicate means ± SE. *Statistical significance, $P < 0.05$.*

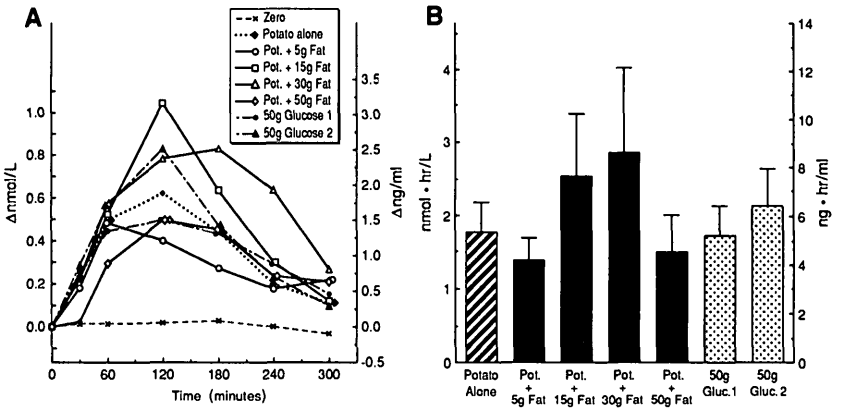

Figure 3—*A: Effect of fat ingestion on plasma C-peptide response. Lower dashed line represents C-peptide concentration when only water was ingested. Incremental changes in plasma C-peptide were determined for 5 h after ingestion of meals. Seven subjects with NIDDM were studied. Each subject ingested every test meal. Mean initial fasting C-peptide concentration was 0.79 ± 0.05 nM. B: Effect of fat ingestion on plasma C-peptide area response. Areas above fasting C-peptide concentration were determined with trapezoid rule using water control as baseline. Bars indicate means ± SE.*

The mean fasting C-peptide concentration was 0.79 ± 0.05 nM. After water ingestion, the C-peptide concentration decreased slightly and was 0.03 nM below the initial value at 300 min. The maximal C-peptide increase after glucose ingestion was 0.66 nM at 120 min. The mean C-peptide increase after ingestion of potato alone or with fat was highly variable both in regard to the maximal rise as well as the time at which it reached a maximum. All serum C-peptide concentrations decreased toward the end of the experiment but were still elevated compared with the water control (Fig. 3*A*).

The mean C-peptide area response after glucose ingestion was 1.92 ± 0.50 nmol · h · L^{-1}. After ingestion of potato alone, C-peptide was 1.79 ± 0.40 nmol · h · L^{-1}. The mean C-peptide area responses after ingestion of potato with various amounts of fat again were highly variable, and none of the differences were significant statistically. However, overall, the mean maximal C-peptide area increase, i.e., the average of the C-peptide area response after ingestion of potato with 15, 30, or 50 g fat was 1.3 times higher than that after ingestion of potato alone (Fig. 3*B*).

The variation in the C-peptide data was caused by results from 1 patient who showed an unusually high C-peptide increase after ingestion of potato alone and potato plus 15 and 30 g of fat meals. If the data are analyzed with the results from this individual excluded, then the mean C-peptide area response after ingestion of potato plus 15, 30, and 50 g fat is only 1.06 times of that after ingestion of potato alone. The serum insulin response of this patient to the various amounts of fat ingested with potato was not unusual and very similar to that of other subjects.

The mean fasting glucagon concentration was 371 ± 73 ng/L. After water ingestion alone, fasting glucagon concentration decreased below the initial value by 30 min. The maximal decrease was 30 ng/L at 120 min. After the ingestion of 50 g glucose, plasma glucagon concentrations decreased further. The maximal decrease was 95 ng/L at 180 min. After glucose ingestion, a small increase in glucagon concentration frequently is observed at 30 min followed by a decrease. After ingestion of potato or potato plus fat, this biphasic response was exaggerated (Fig. 4*A*).

After the ingestion of glucose, the glucagon area response was negative as expected (−308 ng · h · L^{-1}). After ingestion of potato alone and potato plus 5 g of fat meals, the glucagon areas were

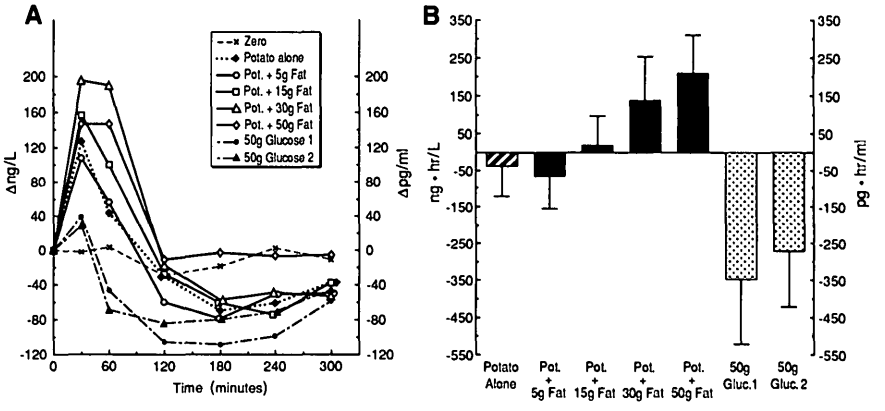

Figure 4—*A: Effect of fat ingestion on plasma glucagon response. Lower dashed line represents glucagon concentration when only water was ingested. Incremental changes in plasma glucagon were determined for 5 h after ingestion of meals. Seven subjects with NIDDM were studied. Each subject ingested every test meal. Mean initial fasting glucagon concentration was 371 ± 73 ng/L. B: Effect of fat ingestion of plasma glucagon area response. Areas above fasting glucagon concentration were determined with trapezoid rule using water control as baseline. Bars indicate means ± SE.*

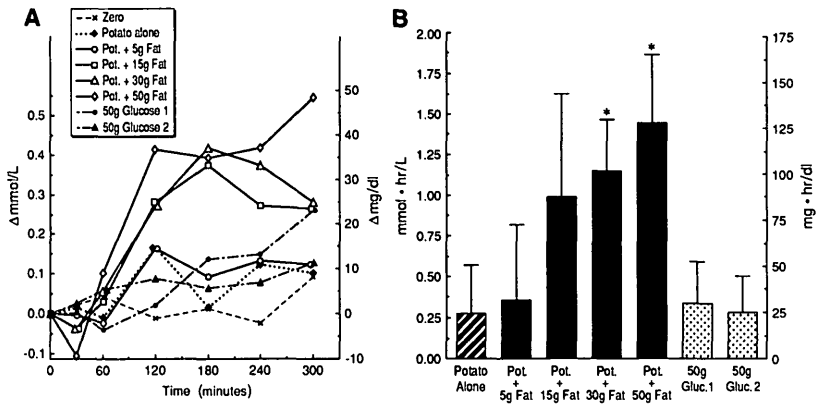

Figure 5—*A: Effect of fat ingestion on serum triglyceride response. Lower dashed line represents triglyceride concentration when only water was ingested. Incremental changes in serum triglyceride were determined for 5 h after ingestion of meals. Seven subjects with NIDDM were studied. Each subject ingested every test meal. Mean initial fasting triglyceride concentration was 2.08 ± 0.31 mM. B: Effect of fat ingestion on serum triglyceride area response. Areas above fasting triglyceride concentration were determined with trapezoid rule using water control as baseline. Bars indicate means ± SE. *Statistical significance, $P < 0.05$.*

only modestly negative. After ingestion of potato plus 15 g fat, little change occurred compared with the water control. After ingestion of the potato plus 30 and 50 g fat of meals, the glucagon area responses were positive and progressively larger (Fig. 4*B*). Differences in the glucagon area responses after ingestion of potato alone or potato with increasing amounts of fat were significant when ANOVA was done with the covariate (g fat ingested) ($P < 0.05$). The estimated regression line is $y = 5.6 + 60x$; where x is the grams of fat ingested and y is the glucagon response, $R^2 = 97.4$. The slope was significantly different from zero (model utility test, $P = 0.01$).

The mean fasting triglyceride concentration was 2.08 ± 0.31 mM. After water ingestion alone, triglyceride levels remained near the initial value throughout the study. After ingestion of glucose or potato alone, a modest increase occurred, and with increasing amounts of butter, the increases were progressively larger (Fig. 5*A*).

The mean triglyceride area response after the glucose meals was 0.309 ± 0.24 mmol · h · L^{-1}. Overall, the mean triglyceride area response increased with increasing fat content of the meals when compared with the potato alone and the glucose meals. The difference between potato alone and potato with 30 and 50 g of fat meals was significant statistically ($P < 0.05$) (Fig. 5*B*).

The mean fasting AAN concentration was 2.90 ± 0.14 mM. After ingestion of water alone, the AAN concentration decreased below the initial value by 30 min. AAN reached a nadir by 120 min. The AAN concentration decreased further after all meals. This occurred without delay for the two glucose meals and after 30–60 min for the other meals (Fig. 6*A*).

The mean 5-h integrated AAN area response after the glucose meals was −0.92 ± 0.34 mmol · h · L^{-1}. After potato alone or potato plus fat ingestion the areas were all negative. The differences were not statistically significant ($P > 0.05$) (Fig. 6*B*).

The serum mean NEFA areas were all negative compared with the water control and were similar (Table 2).

Urine glucose excretion during the 5-h study is shown in Table 3. The amounts of glucose excreted were small.

CONCLUSIONS— In this study, the maximal plasma glucose concentrations after the ingestion of potato with or without butter were similar. The glucose area responses after ingestion of the various amounts of fat with potato also were similar to those after potato alone. Overall, the glucose area response for the potato-

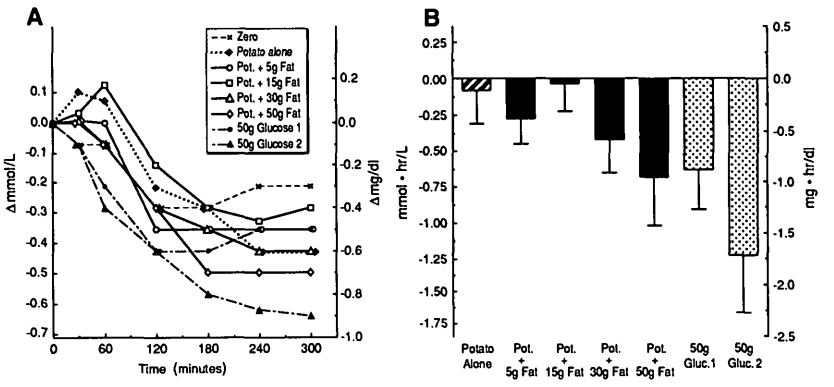

Figure 6—*A: Effect of fat ingestion on plasma AAN response. Lower dashed line represents AAN concentration when only water was ingested. Incremental changes in plasma AAN were determined for 5 h after ingestion of meals. Seven subjects with NIDDM were studied. Each subject ingested every test meal. Mean initial fasting AAN concentration was 2.90 ± 0.14 mM. B: Effect of fat ingestion on plasma AAN area response. Areas above fasting AAN concentration were determined with trapezoid rule using water control as baseline. Bars indicate means ± SE.*

Table 2—*Mean serum NEFA area changes below water control integrated over 5 h*

	CHANGE ($G \cdot H \cdot L^{-1}$)
50 G GLUCOSE NO. 1	−0.33 ± 0.11
50 G GLUCOSE NO. 2	−0.16 ± 0.14
POTATO	−0.28 ± 0.11
PLUS 5 G FAT	−0.26 ± 0.08
PLUS 15 G FAT	−0.28 ± 0.11
PLUS 30 G FAT	−0.24 ± 0.08
PLUS 50 G FAT	−0.19 ± 0.10

Data are means ± SE.

containing meals was 82% of that after ingestion of 50 g glucose.

These data, obtained in subjects with NIDDM, are different from those reported previously in normal subjects (1,2). In the latter studies, a strikingly smaller rise occurred in blood glucose concentration after the meals containing fat.

The attenuated glucose response in the normal subjects when fat was added was attributed by others to a fat-induced delay in gastric emptying that resulted in delayed glucose absorption (1). The possibility of an accelerated removal of the absorbed glucose from the circulation was considered less likely (1). We repeated that study using the same protocol with very similar results (2). However, we considered a delayed glucose absorption to be mechanistically less important, because the peak glucose concentration occurred at the same time regardless of whether fat was present.

A fat-induced delay in gastric emptying has been well documented (11–14). However, a delay in gastric emptying does not necessarily result in a reduction or delay in glucose response. In studies in which dietary fiber was added to meals, a significant delay occurred in gastric emptying, but the delay did not correlate with changes in glucose rise (15–17). Indeed, a delay in gastric emptying commonly was observed without a significant effect on the glucose curve.

In this study of subjects with NIDDM, the rise in plasma glucose concentration was delayed only when the two largest amounts of butter were ingested; even with these meals, the return of the glucose concentrations to a fasting level was not delayed, and fat did not affect the overall area response. Presumably the ingested fat resulted in delayed gastric emptying in both the normal subjects and the subjects with NIDDM. If this is the case then it is difficult to implicate this phenomenon as an explanation for the much smaller glucose area response in the normal subjects. The smaller glucose area also should have occurred in the subjects with NIDDM.

A possible explanation for the smaller glucose rise in normal subjects would be an accelerated plasma glucose removal rate stimulated by some unknown factor. Alternatively, the smaller glucose rise may be the result of a relatively larger insulin response when fat was ingested. That the glucose area response was not smaller in the subjects with NIDDM when the insulin response was greater may be caused by the absence of this factor, or it may be caused by a fat-induced insulin resistance or a rise in glucagon concentration or both.

In the subjects with NIDDM, the data on the insulin area response after ingestion of butter and potato indicated the presence of a rather sensitive dose-response relationship. Compared with potato alone, the increase in insulin area response was evident after ingestion of only 5 g fat. The insulin area response reached a plateau after ingestion of 15 g fat.

The average maximal C-peptide area response after ingestion of potato plus 15, 30, and 50 g fat was 1.3 times of that after ingestion of potato alone and was similar to the percentage increase in insulin concentration. However, if the data are analyzed without the results of the one individual who had an extraordinarily large response to some meals, a difference between the C-peptide area response to meals with or without fat disappeared. Thus, whether the increase in insulin area response to fat ingestion is the result of an increased secretion of insulin cannot be determined from these data. The increase in insulin response may be the result of a decrease in hepatic extraction of insulin rather than an increase in insulin secretion.

Glucose ingestion depresses, and

Table 3—*5-h urine glucose excretion**

	EXCRETION (G/G CREATININE EXCRETED)
WATER ALONE	0.095 ± 0.029
50 G GLUCOSE NO. 1	3.565 ± 1.968
50 G GLUCOSE NO. 2	2.179 ± 1.319
POTATO	1.654 ± 0.903
PLUS 5 G FAT	1.323 ± 0.926
PLUS 15 G FAT	1.346 ± 0.911
PLUS 30 G FAT	1.893 ± 1.153
PLUS 50 G FAT	0.937 ± 0.639

Data are means ± SE.
*Mean creatinine excretion = 0.34 g/5 h.

protein and fructose stimulate a rise in circulating glucagon concentration (4,18–20). This study also indicates an increase in the glucagon area response after ingestion of butter with potato. A strong dose-response relationship occurred with the amount of butter ingested. A fat-induced increase in glucagon concentration also has been reported in dogs using intraduodenal administration of peanut oil (21). However, in normal subjects (22) and in subjects with NIDDM (23), fat ingestion has been reported to not result in a rise in glucagon concentration. Of particular interest is the observation of a similar simultaneous rise in insulin and glucagon concentrations after protein ingestion (4,20). In this study, whether the fat in the meal synergized with the small amount of protein present (or CHO) in stimulating glucagon secretion remains to be determined. Also, whether similar glucagon, insulin, and glucose results will be obtained with other sources of dietary CHO and fat, or in individuals with more severe NIDDM, remains to be determined.

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