Effect of Added Fat on the Plasma Glucose and Insulin Response to Ingested Potato Given in Various Combinations as Two Meals in Normal Individuals

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OBJECTIVE — In normal subjects, ingestion of fat with potato in a morning meal resulted in a decrease in the glucose response. Therefore, we wished to determine whether a fat-induced decrease in blood glucose also would be observed after a second identical meal. In addition, we were interested in determining if fat ingestion with a morning meal would have an effect on the blood glucose and insulin responses to a second meal not containing fat.

RESEARCH DESIGN AND METHODS — Nine healthy male subjects ingested two meals consisting of an amount of potato containing 50 g carbohydrate, either alone or with 50 g fat as butter. The meals were served in four combinations as follows: *1*) potato for the first meal, potato for the second meal; 2) potato for the first meal, potato with fat for the second meal; 3) potato with fat for the first meal, potato for the second meal; and 4) potato with fat for the first meal, potato with fat for the second meal. Meals were ingested at 8:00 A.M. and noon. Plasma glucose and C-peptide, serum insulin, triglyceride, and free fatty acid (FFA) concentrations were determined over an 8-h period. The integrated area responses to the meals were quantified over the subsequent 4-h period using the fasting value or the noon value as baseline for the first and second meals, respectively.

RESULTS — When the first meal contained potato only, the glucose area response to the second meal was significantly less when the second meal contained fat. However, fat ingestion had no effect on the glucose area response to the second meal when fat was present in the first meal. The insulin area responses to the first and second meals were similar after ingestion of potato or potato with fat. However, the insulin response to the second meal always was less than that to the first meal. The C-peptide area responses after ingestion of the second meal also were all higher than those after the first meal. The triglyceride area responses were slightly negative after ingestion of potato alone in the first meal. When fat was ingested, they were positive. When the first meal contained fat but the second meal did not, there was a rise in triglyceride concentration after the second meal as well as after the first meal. That is, a rise occurred without ingestion of fat with the second meal. If fat was present in the second meal the rise was even greater. The FFA area responses were similar to the triglyceride area responses.

CONCLUSIONS — When fat was ingested with carbohydrate in either the first or second meal, the glucose area response was decreased. However, when both meals contained fat, a decrease in the glucose area response did not occur with the second meal. The glucose area responses all were greater after the second meal compared with those after the first meal, i.e., the opposite of a Staub-Traugott effect was observed. The insulin area responses to the first and second meals were similar whether fat was ingested or not.

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Received for publication 16 August 1993 and accepted in revised form 30 June 1994.

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CHO, carbohydrate; FFA, free fatty acid.

In normal people, ingestion of 50 g fat as butter with 50 g carbohydrate (CHO) as potato in a single meal resulted in a significantly lower blood glucose response compared with that after ingestion of potato alone (1). Even though the glucose response was less when butter was ingested with the potato, the insulin response was similar to that in the absence of butter. In a subsequent study, we confirmed these results (2). The reason for the smaller glucose but not smaller insulin response when butter was ingested with the potato is unclear. It is known that fat delays gastric emptying (3–5). However, a delay in either the peak glucose or insulin concentration was not present.

In normal subjects ingesting three identical high-fat (75%) mixed meals 4 h apart, the magnitude and the time of the glucose rise was as expected after the first meal, considering the amount of carbohydrate present (6). However, after the second and third meals there was a progressive decrease in amplitude and a delay in the rise of both glucose and insulin concentrations. Therefore, we were interested in determining if the fat-induced decrease in the glucose response after a morning potato-fat meal also would be seen with a second identical meal ingested 4 h later. We also wished to determine whether fat ingested with the first meal would influence the glucose and insulin response to a second meal not containing fat, i.e., whether fat would have a delayed effect on glucose metabolism or starch digestion. In this study, plasma glucose and insulin responses to 50 g CHO as potato, ingested with or without 50 g fat as butter, given in various combinations as two meals 4 h apart were determined. In addition, the C-peptide, triglyceride, and free fatty acid (FFA) concentrations were monitored. The glucose, insulin, and C-peptide data obtained with the first meal containing potato or potato with butter have been reported previously (2).

RESEARCH DESIGN AND METHODS

— Ten healthy male subjects were studied in a metabolic unit. One patient dropped out for personal reasons. The mean age was 29 ± 1.8 years (range 22–38). The mean body mass index was 24 ± 0.8 kg/m^2. The study was approved by the Medical Center Committee on Human Subjects. All subjects were on a weight maintenance diet and consuming >200 g carbohydrate for at least 3 days before the study.

After a 8- to 10-h overnight fast, a plastic catheter was placed in a forearm vein. It was kept patent with intravenous saline. Two baseline samples were drawn at 7:30 and 7:45 A.M. The first meal of the day was given at 8:00 A.M., and the second meal was given at noon. Blood samples were taken at 30 min, 1, 2, 3, and 4 h after each meal. All subjects received two meals on each study day consisting of 50 g CHO as potatoes, either alone or with 50 g fat as butter. The meals were served in four combinations as follows: *1*) potato for the first meal, potato for the second meal; 2) potato for the first meal, potato and fat for the second meal; 3) potato and fat for the first meal, potato for the second meal; and 4) potato and fat for the first meal, potato and fat for the second meal.

Peeled potatoes were cut into eight pieces and cooked in a microwave oven for ~3 min until tender. They were then mashed with or without butter (62 g) and refrigerated. The next day they were reheated for 30 s in a microwave oven, blended, reheated for another 20 s, and then served. The meals were given in random order. The amount of CHO and fat in the meals was calculated from food tables (7). All subjects were allowed to ingest water ad libitum throughout the study. Studies were performed 1 week apart.

Plasma glucose was determined by a glucose oxidase method using a Beckman glucose analyzer with an O_2 electrode (Beckman, Fullerton, CA). Serum immunoreactive insulin and plasma C-peptide were measured using a double-antibody radioimmunoassay method with kits produced by Incstar (Stillwater, MN). The cross-reactivity of the C-peptide antibody to proinsulin was 4%. Triglycerides were determined using an EktaChem Analyzer (Eastman Kodak, Rochester, NY). Serum free fatty acid concentration was determined enzymically using a kit purchased from Wako (Dallas, TX).

The 4-h area responses were calculated using the trapezoid rule (8) and presented as the mean ± SE. The initial fasting concentrations were used as the baseline from which the areas after the first meal were calculated. The coefficients of variation in baseline concentrations for glucose, insulin, C-peptide, and triglyceride were 3, 4, 2, and 6%, respectively. The concentrations of the parameters measured 4 h after the first meal, i.e., at noon, were taken as the initial values from which the areas after the second meal were calculated.

Statistics were done by two-way analysis of variance, for the randomized complete block design, using the MacAnova (by G.W. Oehlert, Version 2.4) program for the Macintosh computer. Where appropriate, multiple comparisons were done by the Bonferroni method. The results of the first meal (potato vs. potato + fat) also were analyzed by Student's *t* tests. The peak concentrations were compared by Student's *t* tests. A *P* value <0.05 was the criterion for significance. Data are presented as means ± SE. The power of the study for a sample size of $n = 9$ was 0.89.

RESULTS

— The mean fasting glucose concentration in the four studies was 5.2 ± 0.1 mmol/l. After the first meal, the peak glucose concentration occurred at 30 min regardless of the composition of the meals (Fig. 1*A*). After ingestion of the second meal, the peak glucose rise occurred at 1 h rather than 30 min except when the subjects ingested just potato for both meals. In the latter case, the peak concentration again occurred at 30 min just as with the first meal. When the subjects ingested fat in the first meal but not in the second meal, the initial rate of glucose rise after the second meal was similar to that observed when the subjects ingested only potato in both meals, although the absolute peak occurred at 60 min.

When the subjects ingested fat in both the first and second meals, the glucose rise was not attenuated after the second meal as it had been for the first meal.

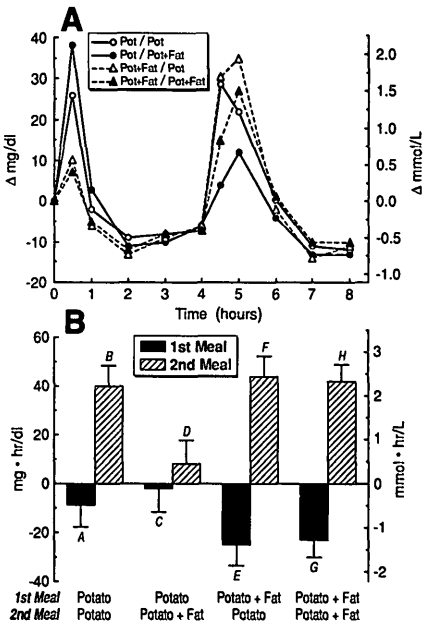

Figure 1—A: *effects of ingestion of potato with fat in various combinations as two meals on the plasma glucose response. Nine healthy male subjects were studied. Each subject ingested every test meal. The mean initial fasting glucose concentration was 5.2 ± 0.1 mmol/l.* B: *effects of ingestion of potato with fat in various combinations as two meals on plasma glucose area response. The 4-h area responses above the fasting glucose concentration were determined with the trapezoid rule. The plasma glucose concentration 4 h after the first meal was taken as the initial value from which the area after the second meal was calculated. The glucose area responses after ingestion of potato with fat in the first meal* (E, G) *were significantly less than those after ingestion of potato alone with the first meal* (A, C) *(P < 0.05). The area response after ingestion of potato with fat in the second meal* (D) *was significantly less than the other area responses in the second meal* (B, F, H) *(P < 0.05).*

When fat was present in the second meal but not in the first meal, an attenuated glucose response occurred after the second meal ($P < 0.05$).

When potato only was ingested in the first and second meals, the area response was considerably greater after the second meal (Fig. 1*B*, $B > A$ [$P < 0.05$]). When potato only was ingested in the first meal but potato with fat was ingested in the second meal, the area response to the second meal was again less than that to the first meal ($P < 0.05$) ($D > A$, C). However, the second meal response was considerably less when fat was present ($D < B$) ($P < 0.05$). It also was less than that for all other second meals ($D < B$, F, H). When the first meals contained fat, the area response to the second meal was positive and essentially the same whether fat was present in the second meal or not (F vs. H). It also was similar to the second meal response when neither the first nor the second meals contained fat (B vs. F, H). Thus, fat had no effect on the glucose area response to the second meal when fat was present in the first meal.

The mean fasting insulin concentration was 84 ± 7 pmol/l. The mean peak insulin concentration was lower after ingestion of potato with fat for the first meal ($P < 0.05$) (Fig. 2*A*). The peak insulin concentrations after the second meal were similar regardless of whether fat was present or not.

Serum insulin concentrations were higher at 4 h when fat was present in the meals ($P < 0.05$). The incremental rise in insulin concentration after the second meal was modestly but statistically significantly greater when both the first and second meals did not contain fat when compared with the other second meals ($P < 0.05$). When fat was present in the second meal, the peak insulin concentration was delayed irrespective of whether fat was present in the first meal.

The insulin area response to the first meal was similar after ingestion of potato or potato with fat (A, $C \simeq E$, G) (Fig. 2*B*). This also was true for the second meal (B, $D \simeq F$, H). However, overall, the insulin response to the second meal was greater than that to the first meal (B, D, F, H vs. A, C, E, G) ($P < 0.05$).

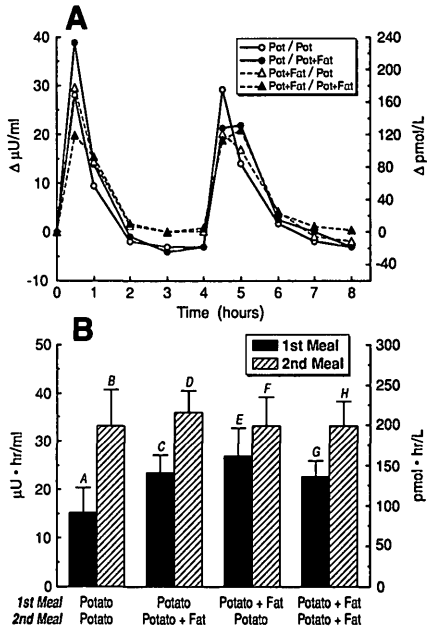

Figure 2—A: *effects of ingestion of potato with fat in various combinations as two meals on the serum insulin response. The mean initial fasting insulin concentration was 84 ± 7 pmol/l.* B: *effects of ingestion of potato with fat in various combinations as two meals on serum insulin area response. The following were significantly different from each other:* B, D, F, H > A, C, E, G ($P < 0.05$).

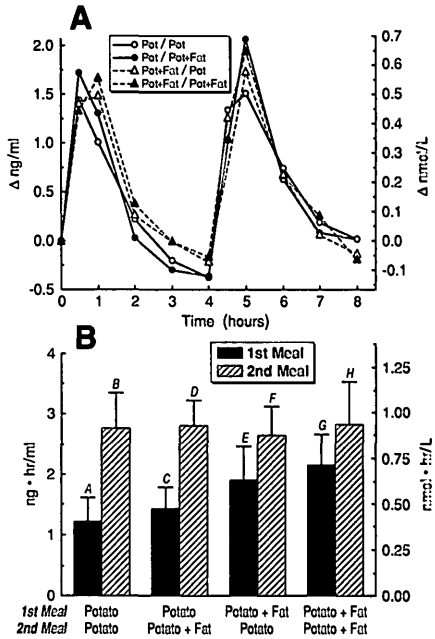

Figure 3—A: *effects of ingestion of potato with fat in various combinations as two meals on the plasma C-peptide response. The mean initial fasting C-peptide concentration was 0.43 ± 0.05 nmol/l.* B: *effects of ingestion of potato with fat in various combinations as two meals on plasma C-peptide area response. The following were significantly different from each other:* B, D, F, H > A, C, E, G; E, G > A, C ($P < 0.05$).

The mean fasting C-peptide concentration was 0.43 ± 0.05 nmol/l. The maximal increases in C-peptide concentrations were similar after the first and the second meals regardless of the combination of meals ingested (Fig. 3*A*). However, the peak was delayed after the first meal when fat was present in that meal. This occurred even though the insulin rise was not delayed. When fat was present in the meals, serum C-peptide concentrations at 4 h were higher than those after ingestion of potato alone ($P < 0.05$). Generally, all the peaks were delayed after the second meal.

The C-peptide area responses after ingestion of the second meal were all considerably higher than those after the first meal (B, D, F, $H > A$, C, E, G) and were similar whether or not fat was ingested (Fig. 3*B*).

The mean fasting triglyceride concentration was 0.97 ± 0.14 nmol/l. After ingestion of potato alone in the first meal, the triglyceride concentrations decreased modestly (Fig. 4*A*). After ingestion of fat in the first meal, the serum triglyceride concentrations increased modestly by 1 h and then remained essentially unchanged until the second meal. After the second meal, the triglyceride concentrations increased irrespective of whether the second meal contained fat. However, the peak triglyceride concentration was greater when fat was present in the second meal ($P < 0.05$). When the subjects ingested potato alone in the morning followed by a potato + fat second meal, the triglyceride concentration increased after the second meal. The concentration was

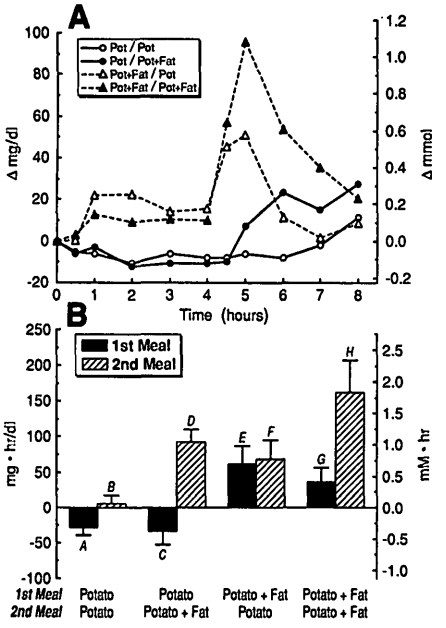

Figure 4—A: *effects of ingestion of potato with fat in various combinations as two meals on the serum triglyceride response. The mean initial fasting triglyceride concentration was 0.97 ± 0.14 nmol/l.* B: *effects of ingestion of potato with fat in various combinations as two meals on serum triglyceride area response. The following were significantly different from each other:* E, G > A, C; H > F, D, B ($P < 0.05$).

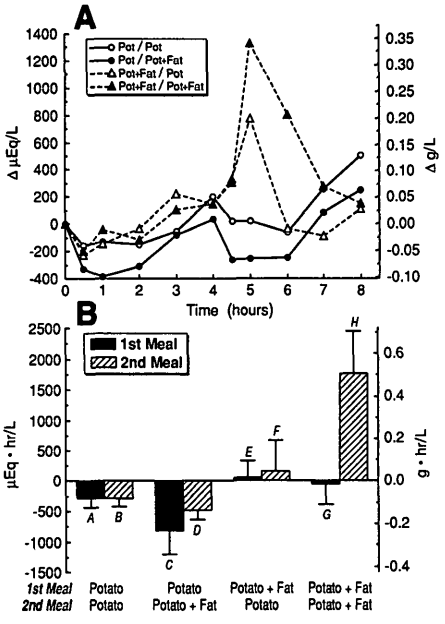

Figure 5—A: *effects of ingestion of potato with fat in various combinations as two meals on the serum FFA response. The mean initial fasting FFA concentration was 0.16 ± 0.03 g/l.* B: *Effects of ingestion of potato with fat in various combinations as two meals on the serum FFA area response. The following were significantly different from each other:* F > B, D; H > B, D, F ($P < 0.05$).

similar to that measured when the first meal contained fat.

The triglyceride area responses were slightly negative when potato alone was ingested as the first meal (*A*, *C*), whereas they were positive, as expected, when fat was present in the first meal (*E*, *G*) (Fig. 4*B*). When both meals were only potato, the triglyceride area response also was slightly positive after the second meal (*B*). The area response after ingestion of potato alone in the second meal when the preceding meal was potato with fat was the same as the area response to the first meal which contained fat ($F \simeq E, G$). It also was similar to the triglyceride response when the second meal contained potato with fat but the first meal did not (*F* vs. *D*). However, all were less than the response to the second meal when both the first and second meal contained fat ($H > D, F$) ($P < 0.05$).

The mean fasting FFA concentration was 0.16 ± 0.02 g/l. After ingestion of potato alone in the first meal, the serum FFA concentration decreased, as expected (Fig. 5*A*). When fat was present in the first meal, the decrease was very transient. Subsequently, it increased gradually after all meals and was near the initial values by 4 h. After ingestion of potato as the first meal, an initial decrease in the serum FFA concentration was observed after the second meal whether fat was ingested in the second meal or not. However, when the first meal contained fat, the serum FFA concentration promptly increased after the second meal irrespective of whether fat was present in the second meal. It reached a peak at 1 h after ingestion of the second meal and subsequently decreased. The incremental increase was considerably greater when both meals had contained fat ($P < 0.05$).

The FFA area responses after ingestion of the first meal were negative when the first meal did not contain fat (*A*, *C*) (Fig. 5*B*). When the first meal contained fat (*E*, *G*), the average FFA area responses were essentially neutral. When the first meal contained potato alone, the FFA area responses to the second meal were negative whether the second meal contained fat or not (*B*, *D*). However, when the first meal contained fat, the FFA area responses to the second meal were positive whether fat was ingested with the second meal or not (*F*, *H*). The area response was considerably greater when both meals contained fat (*F* vs. *H*) ($P < 0.05$).

DISCUSSION— When fat was present in the first meal, the glucose area response and the peak glucose concentration were considerably less than when it was absent (Fig. 1: *A*, *C* vs. *E*, *G*), as indicated previously (1,2).

These data indicate that when a second meal contained butter with potato but the first meal consisted of only potato, a smaller glucose rise occurred with the second meal. That is, the presence of butter resulted in an attenuated glucose area response just as when it was present in the first meal. However, if both meals contained fat, the glucose area was not decreased with the second meal. The reason for this is unknown. It cannot be attributed to a smaller insulin rise. The insulin concentration was modestly higher after the second meal. Thus, an insulin resistance appears to have developed, although incomplete digestion of the first meal at the time of the second meal cannot be ruled out. It is not likely to be due to a counterregulatory hormone (9) response to the modest decrease in glucose late in the course after the meal was ingested, because the decrease in glucose concentration was similar after all meals.

With the first meal of the day, the blood glucose response was not delayed when fat was ingested with CHO. This has been a uniform finding in the literature (1,2,4,6,10). However, when fat was

present in the second meal, a delay in the rise in glucose concentration was present. Why it occurs with the second meal but not the first is not readily understood. Ingestion of fat at different times of the day must affect starch digestion and/or glucose metabolism differently.

The delay in the peak glucose rise with the second meal is similar to that observed previously when high-fat, mixed meals were ingested (6). Thus, a fat-induced delay in glucose rise appears to have a circadian component, at least in men and under the conditions of these experiments. In the mixed-meal study, there also was a smaller glucose rise after the second and third meals. However, the amount of fat ingested relative to the CHO content was higher in that study (6). It is of particular interest that in the mixed-meal study, the delayed and attenuated glucose rise after the second and third meals did not occur in female subjects. In this study, all of the subjects were men.

Collier et al. (10) have studied the effects of a first meal containing 50 g CHO as white bread and 23 g protein as cottage cheese with or without 26 g fat as butter on the glucose and insulin response to that meal and to a different standardized mixed meal given 4 h later. The glucose response to the first meal was not attenuated when fat was present, in contrast to our observations (2) and those reported previously by Collier and O'Dea (1). The difference in the results may be due to the relatively large amount of protein present. It also could be due to white bread rather than potato being the source of starch. These are issues that must be studied further using different sources of starch and fat with and without various amounts of protein.

The glucose response to the standardized second meal was interpreted by Collier et al. (10) as being greater when the first meal contained fat compared with the meal that did not contain fat. However, from the data presented, it appears that the difference was primarily in the baseline glucose concentration before the second meal. If the data are adjusted for the difference in the baseline values, the glucose responses after the second meal appear similar. Thus, when the first meal contained fat, there was little influence on the blood glucose response to a second meal. These results are similar to the results in this study.

In our study, we were somewhat surprised that the glucose area response to the second meal was greater than that to the first meal in general. This was observed irrespective of the fat content of each meal and was the opposite to that expected from the Staub-Traugott effect (11,12). It also did not correlate with the magnitude of the FFA increase after each of the second meals.

The availability of FFAs has been shown to affect the glucose oxidation rate (13,14). However, because there were major differences in FFA concentrations after the second meals but little difference in glucose area response, this does not appear to be an adequate explanation unless there is a threshold effect. Abraira and Lawrence (15) also reported a dissociation between the presence of the Staub-Traugott effect and suppression of FFAs. In addition, it appears unlikely that growth hormone and/or glucagon play an important role in the Staub-Traugott effect (15–17).

Collier et al. (10) have reported that the amount of CHO in the first meal influenced the glycemic response to a subsequent meal. In their study, improved glucose tolerance after the second meal, i.e., the Staub-Traugott effect, was seen only after ingestion of a large amount of CHO in the first meal (100 g). Ingestion of a smaller amount of CHO in the first meal (50 g), as in this study, resulted in the glucose area after the second meal being increased. Thus, the Straub-Traugott effect appears to be dependent on the amount of CHO ingested in a meal.

The generally impaired glucose disposal rate after the second meal irrespective of the content of the first meal also may represent a circadian variation in glucose tolerance. An impairment in glucose tolerance later in the day has been reported several times (18–22) and was generally associated with an increased and delayed insulin response (19–21). The impairment in tolerance may be due to the early-morning increase in cortisol secretion (23). Previous studies have indicated that the maximum rise in the blood glucose concentration occurs 5–6 h after a rise in serum cortisol concentration (24,25). Glucocorticoids also affect FFA metabolism (26).

In all cases, the increase in second-meal glucose area responses were not associated with a concomitant change in the insulin area response. The C-peptide data largely confirmed the insulin data.

The serum FFA data in this study are intriguing. The concentration decreased after ingestion of the first meal irrespective of whether fat was present. It then returned to the initial values by 4 h. We were surprised to find that when fat was ingested with the first meal, the serum FFA concentration increased after the second meal even if fat was not present in the second meal. If fat was present in the second meal, the increase was even greater. On the other hand, if fat was present only in the second meal, an increase in FFA did not occur. This suggests that ingestion of fat results in an increase in FFA concentration even in the presence of a high insulin concentration, although the effect is delayed. That is, there appears to be an uncoupling of the expected effect of insulin on lipolysis. In this regard, Griffiths et al. (27) recently reported that the smaller decrease in FFA concentration after a mixed meal containing a high fat content compared with one with a low fat content was probably caused by the release of FFAs into the circulation as a consequence of hydrolysis of chylomicrons. Hydrolysis of chylomicrons also could potentially explain the increase in FFAs observed in this study.

The triglyceride responses also were of interest. When potato with fat was ingested at 8:00 A.M. or noon, the subsequent 4-h triglyceride area responses

were similar (*E*, *D*) (Fig. 4*B*). When potato alone was ingested in the morning (*A*, *C*), there was a negative triglyceride area response. In contrast, when only potato was ingested in the second meal and the first meal contained potato with fat, the triglyceride area response to the second meal was positive (*F*) and was the same as if potato with fat had been ingested as the second meal (*D*). Thus, when fat was present in the first meal, the ingestion of just potato in the second meal resulted in a considerable rise in the triglyceride concentration. This correlated with the increase in FFAs (*F* vs. *B*). When fat was ingested in both meals, the increase in triglyceride also was greater than expected after the second meal (*H*). The mechanism by which this increase occurs is unknown. It may be due to a secondary rise in triglycerides resulting from the fat in the first meal. It recently was reported that in ~77% of individuals, there are two or three triglyceride peaks during an 8-h period after a single fat-rich meal (28). In any regard, it is an intriguing observation.

It should be kept in mind that potato is not pure starch. It contains protein, which may confound the interpretation of the results (29). For every 50 g CHO in potato, there are ~7 g protein. This should have only a modest effect on insulin secretion and on the glucose concentration but could significantly stimulate glucagon secretion (30). Nevertheless, the data indicate that the metabolic response to ingested CHOs and fats is complex and varies depending on the meal order. It also probably has a circadian component.

Acknowledgments— This research was supported by funds from the National Dairy Promotion and Research Board administered in cooperation with the National Dairy Council, Merit Review research funds from the Department of Veterans Affairs, and Grant DK-43018–01A1 from the National Institutes of Health.

The authors thank the subjects for their participation in this study; the staffs of the Metabolic Research Laboratory, the Special Diagnostic and Treatment Units, and the Clinical Chemistry Laboratory; Marie Matlack, Joanna Aretz, and Mary Adams for expert technical assistance; and Claudia Durand for excellent clerical help.

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