Stimulation of Insulin Secretion by Fructose Ingested With Protein in People With Untreated Type 2 Diabetes

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OBJECTIVE — Ingested protein provides substrate for gluconeogenesis and strongly stimulates insulin and glucagon secretion, but it has little effect on the glucose concentration in people with type 2 diabetes. Ingested fructose also is a substrate for gluconeogenesis, modestly stimulates insulin and glucagon secretion, and has little effect on the plasma glucose. Therefore, we were interested in determining if ingestion of fructose along with protein would result in an additive, greater than additive, or less than additive effect on circulating insulin, glucagon, and glucose concentrations.

RESEARCH DESIGN AND METHODS — Seven male subjects with untreated type 2 diabetes were fasted overnight and then were given either 25 g fructose, 25 g protein, 25 g fructose plus 25 g protein, or water only at 0800. Subjects also ingested 50 g glucose on two separate occasions. Plasma glucose, insulin, C-peptide, glucagon, α-amino nitrogen, urea nitrogen, nonesterified fatty acids, and triglyceride concentrations were determined over the subsequent 5 h.

RESULTS — The glucose concentration was only modestly increased and the area responses were similar when protein, fructose, or the combination was ingested. Thus, the glucose response to the combination was less than additive. The insulin area response to protein was 2.5-fold greater than to fructose, and the response to the two nutrients was additive and quantitatively similar to the response to 50 g glucose. The glucagon area response was less than additive, i.e., there was an interaction between the protein and fructose that resulted in a smaller than expected response.

CONCLUSIONS — When protein and fructose were ingested together, the insulin response was similar to that following ingestion of 50 g glucose. It also was as expected based on the response to the individual nutrients. In contrast, the glucose and glucagon responses were significantly less than expected. These data may be useful in dietary planning for subjects with type 2 diabetes.

Ingested glucose generally is considered to be the most potent nutrient insulin secretagogue in both normal people and in people with type 2 diabetes. The increased insulin secreted in response to the ingested glucose is due in part to a direct effect of glucose on the β-cell and in part to a glucose-stimulated release of intestinal incretin hormones. The latter bind to receptors on the β-cells and potentiate the effect of the glucose. The net effect is an increase in insulin that is twice the increase stimulated by intravenously administered glucose (1).

We previously reported that ingested protein, which is considerably less potent than glucose in stimulating insulin secretion in normal people, is equally as potent as glucose in stimulating insulin secretion in people with untreated type 2 diabetes (2). In addition, glucose and protein interact synergistically to stimulate insulin secretion in people with type 2 diabetes (2), whereas they are additive in normal people (3).

Ingestion of fructose, even in very large amounts, results in either no rise or only a very modest rise in insulin concentration in normal subjects (4). However, ingested fructose is up to 30% as potent as glucose in stimulating insulin secretion in people with type 2 diabetes (5). This increase in insulin cannot be attributed to a rise in glucose. Ingested fructose is rapidly removed by the liver (6); therefore, it presumably stimulates release of an incretin hormone that has not been identified.

Since both protein and fructose provide gluconeogenic substrates that have only a very modest effect on the circulating glucose concentration but significantly stimulate insulin secretion in people with type 2 diabetes, we were interested in determining whether their effects would be additive, less than additive or synergistic.

In this study, subjects with untreated type 2 diabetes were given fructose or protein or a combination of fructose and protein. The circulating glucose, insulin, and C-peptide responses were determined. Also, the effect on glucagon, nonesterified fatty acids, total amino acids, urea nitrogen, and triglyceride concentrations were monitored.

RESEARCH DESIGN AND METHODS

— Seven men with untreated type 2 diabetes were studied in the clinical research center. All subjects met National Diabetes Data Group criteria for the diagnosis of type 2 diabetes (7). Thyroid, renal, and liver function tests were normal (data not shown). Patient characteristics are listed in Table 1. Written informed consent was obtained from all subjects, and the study was approved by the Department of Veterans Affairs Medical Center and the University of Minnesota committees on human subjects. For 3 days before testing, all subjects had ingested a diet of at least 200 g of carbohydrate per day with adequate food energy. None of the

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Abbreviations: NEFA, nonesterified fatty acid.

Table 1—*Patient characteristics*

Patient	Age (years)	BMI (kg/m²)	Duration of diabetes	GHb (%)	Concomitant diseases
1	67	30	1 month	9.4	Obesity; hypothyroidism; adjustment disorder with depressive symptoms
2	60	30	2 months	8.4	History of coronary artery disease; peripheral vascular disease; history of anxiety and passive aggressive personality disorder; 50% carotid artery disease; hypertriglyceridemia
3	42	24	10 months	7.3	Depressive symptoms; history of atypical chest pain; hypertriglyceridemia
4	69	30	3 months	6.5	Severe coronary artery disease; status post–coronary artery bypass graft 1984 and 1990; cerebrovascular accident; status post–left iliac occlusion with left embolism; hypertension
5	67	27	new	7.7	Coronary artery disease; peripheral neuropathy; left-sided cardiac valvular disease; history of gout; hypertension
6	75	28	12 years	7.9	Ischemic heart disease; spinal stenosis; hypertension; chronic obstructive pulmonary disease; history of eosinophilic granuloma
7	74	36	3 years	6.5	Treated hyperaldosteronism; obesity.

subjects was treated with either oral hypoglycemic agents or insulin before the study.

After an overnight fast of 10 h, an indwelling catheter was inserted into an antecubital vein. During the sampling period, the catheter was kept patent with intravenous saline. Test meals were randomized and given as a single breakfast meal at 0800. All subjects consumed all test meals. The meals consisted of 25 g fructose, 25 g protein, or 25 g fructose + 25 g protein. Fifty grams glucose (Glutol) was given on two separate occasions as a control. All subjects also ingested only water on a separate occasion, to serve as a baseline. The 25 g of protein was given in the form of cottage cheese, 147 g, grade A, dry, and not more than 0.5% milk fat (Old Home, Minneapolis, MN). Fructose (Sigma, St. Louis, MO) was dissolved in ~250 ml water. The meals were served with 2 cups (~480 ml) decaffeinated coffee and were consumed in <15 min. After each study period, the patient consumed a regular hospital diet ad libitum for the rest of the day.

Blood was obtained before and 0.5, 1, 2, 3, 4, and 5 h after the beginning of the meal. Plasma or serum was assayed for glucose, insulin, C-peptide, urea nitrogen, triglyceride, nonesterified fatty acids (NEFAs), α-amino nitrogen, and glucagon. The plasma glucose concentration was determined by a glucose oxidase method using a Beckman glucose analyzer with an O_2 electrode (Beckman Instruments, Fullerton, CA). Serum immunoreactive

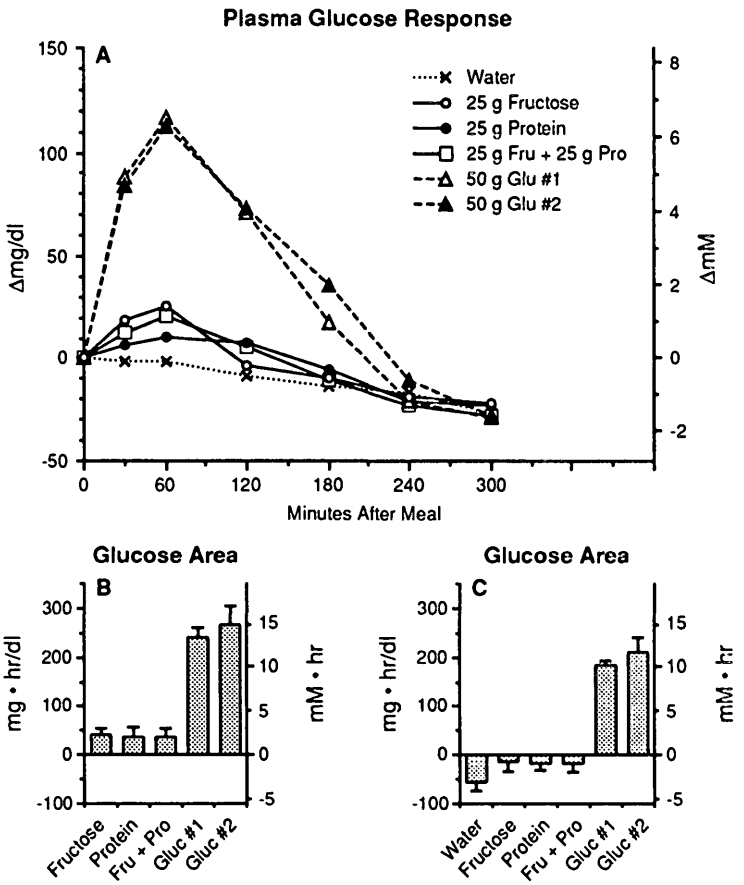

Figure 1—*Plasma glucose response in seven men with untreated type 2 diabetes. Fru, fructose; glu or gluc, glucose; pro, protein. A: the mean plasma glucose concentration change following ingestion of the test substances. The mean fasting glucose concentration was 134 ± 4 mg/dl (7.4 ± 0.2 mmol/l). Fifty grams of glucose was given on two separate occasions. B: the glucose area response integrated over 5 h using the response to water only as a baseline. C: the glucose area response integrated over 5 h using the overnight fasting concentration as a baseline.*

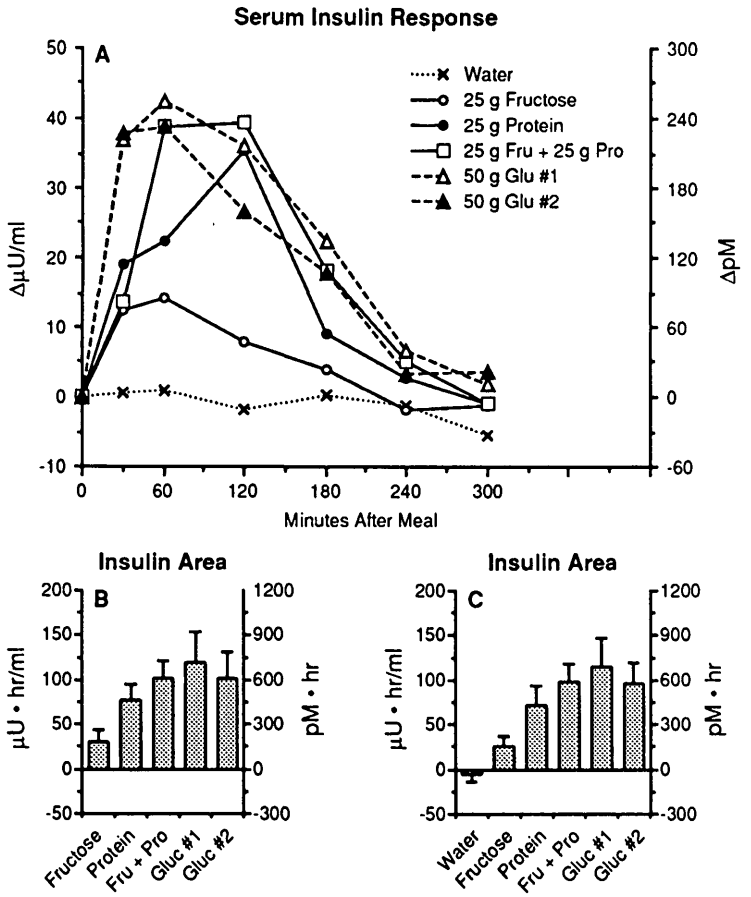

Figure 2—*Serum insulin response in seven male subjects with untreated type 2 diabetes. Fru, fructose; glu or gluc, glucose; pro, protein. A: the mean serum insulin concentration change following ingestion of the test substances. The mean fasting insulin concentration was 22 ± 1.7 μU/ml (131 ± 10.2 pmol/l). Fifty grams of glucose was given on two separate occasions. B: the insulin area response integrated over 5 h using the response to water only as a baseline. C: the insulin area response integrated over 5 h using the overnight fasting concentration as a baseline.*

insulin was measured by a standard double-antibody radioimmunoassay method using kits produced by Endotech (Louisville, KY). C-peptide was measured using a double-antibody radioimmunoassay method with kits produced by Incstar (Stillwater, MN); the antibody to C-peptide has only a 4% reactivity with proinsulin. Glycohemoglobin was determined using boronate agarose affinity columns (Isolab, Akron, OH). Glucagon was determined by radioimmunoassay using 30K antiserum purchased from Health Science Center (Dallas, TX). Serum NEFA was determined using a NEFA C kit (Wako Chemicals, Dallas, TX). α-Amino acid nitrogen was determined by the method of Goodwin (8). Triglycerides and urea nitrogen were determined using an EktaChem analyzer (Eastman Kodak, Rochester, NY).

The areas under the curves were calculated using the trapezoidal rule (9). The areas were calculated using either the initial fasting value or the concentration of the respective hormone or metabolite, measured over the 5-h period after the ingestion of water only. Statistics were determined using Student's *t* test for paired variates with the Statview 512+ program (Brain Power, Calabasas, CA) for the Macintosh computer (Apple Computer, Cupertino, CA). A *P* value of <0.05 was the criterion for significance. Data are presented as means ± SE.

RESULTS — The mean plasma glucose responses to 25 g fructose, 25 g cottage cheese protein, and 25 g fructose ingested with 25 g protein are shown in Fig. 1*A*. The response to water only and to 50 g glucose given on two separate occasions also is shown for comparison. The plasma glucose area responses integrated over 300 min (5 h) using the response to water as a baseline are shown in Fig. 1*B*. The area responses using the overnight fasting concentration as baseline are shown in Fig. 1*C*. The absolute differences in Figs. 1*B* and 1*C* show the importance of including a fasting control when determining area responses. If the area response to glucose is considered to be 100%, the area responses to fructose, protein, and fructose ingested with protein were 16, 15, and 14%, respectively; i.e., they were similar (Fig. 1*B*). Thus, the glucose area response to the ingestion of protein with fructose was only 47% of the sum of the responses when the protein and fructose were ingested individually.

The mean serum insulin responses are shown in Fig. 2*A*. The rise was greatest after glucose ingestion, intermediate after protein, and the least after fructose. When protein was ingested with fructose, the increase approached that after glucose ingestion. The integrated insulin area responses, when compared with glucose were 27, 68, and 90% for fructose, protein, and protein ingested with fructose, respectively (Fig. 2*B* and *C*). Thus, the response to protein ingested with fructose was similar to the sum of the responses to protein and to fructose ingested individually. Considering that 25 g protein ingested with 25 g fructose resulted in an insulin increase that approached the increase with 50 g glucose, the combination of fructose with protein was essentially equivalent to glucose stimulation when integrated over 5 h and when considered on a mass basis. This was due to an early increase, stimulated by fructose, and a later increase stimulated by ingested protein in these subjects.

The ordering of C-peptide responses was similar to that of the insulin responses (data not shown). However, because by 5 h the C-peptide values had not returned to the water control, it is not possible to accurately quantify these data. The C-peptide area response to fructose ingested with protein was smaller compared with the area response to glucose. It also was relatively smaller than the insulin response (56 vs. 90%). If the C-peptide concentrations had been determined over a longer time period, the discrepancy likely would have been greater. The data also suggest that ingested protein and fructose may affect the removal rate of insulin from the circulation.

As expected, ingested glucose resulted in a decrease, whereas protein resulted in an

increase in plasma glucagon concentration (Fig. 3*A*). Also as we reported previously, fructose ingestion resulted in a modest rise in glucagon (5). Interestingly, when fructose was ingested with protein, the rise was not greater than with protein, but less. The glucagon area response also was significantly less ($P < 0.04$; Fig. 3*B* and *C*); i.e., fructose had modified the protein-stimulated glucagon response, or at least there was an interaction between the ingested fructose and protein that resulted in a smaller than expected glucagon response.

The mean α-amino nitrogen concentration decreased after glucose and fructose and increased after protein ingestion (data not shown). However, the area response resulting from the ingestion of fructose with protein was less than expected from the individual responses. This did not reach statistical significance ($P = 0.3$).

The urea nitrogen concentration decreased modestly after fructose ingestion compared with water-only ingestion (Fig. 4*A*), and the decrease was similar to that after ingestion of glucose. These decreases were not statistically significant compared with the water control. The urea nitrogen concentration increased after ingestion of protein without or with fructose. However, as with the α-amino nitrogen concentration, fructose reduced the response to protein. The mean calculated urea nitrogen area response to ingested protein with fructose also was significantly less than the response to protein ingested independently ($P < 0.04$; Fig. 4*B* and *C*).

The NEFA concentration decreased after ingestion of all of the fuels (data not shown), and this largely correlated with the stimulated rise in insulin concentration. However, the mean decrease was modestly greater after fructose and modestly less after protein ingestion than might be expected. The reason for this is unclear. As noted previously (5,10), there was a 30-min delay before the ingested fuel resulted in a decrease in NEFA; and, not uncommonly, the NEFA increased during this period, in spite of a prompt increase in insulin concentration.

The triglyceride data are presented for only five subjects (Fig. 5*A*). Two subjects had grossly elevated fasting triglycerides (500 mg/dl or greater) and were eliminated from the analysis. In the remaining subjects, ingested glucose had little effect on the overall triglyceride concentration. There was an increase after fructose ($P < 0.02$) and/or protein ($P = 0.3$) ingestion. The response

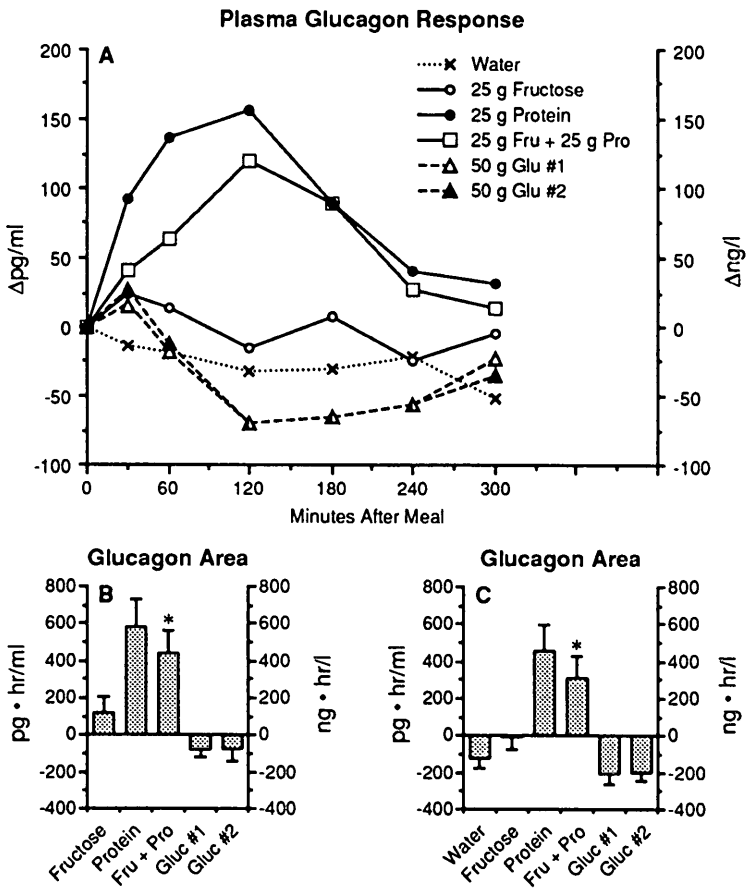

Figure 3—*Plasma glucagon response in seven men with untreated type 2 diabetes. Fru, fructose; glu or gluc, glucose; pro, protein. A: the mean plasma glucagon concentration change following ingestion of the test substances. The mean fasting glucagon concentration was 222 ± 12 pg/ml (222 ± 12 ng/l). Fifty grams of glucose was given on two separate occasions. B: the glucagon area response integrated over 5 h using the response to water only as a baseline. C: the glucagon area response integrated over 5 h using the overnight fasting concentration as a baseline. *Statistically different from protein alone (P < 0.04).*

was greatest after fructose. However, the responses to fructose and protein were not additive. The area response was only ~60% of the sum of the individual responses ($P = 0.19$; Fig. 5*B* and *C*).

Thus, overall, the area responses to fructose and protein when ingested together were additive for insulin, C-peptide, α-amino nitrogen, and NEFAs but were less than additive for glucose, glucagon, urea nitrogen, and triglyceride.

CONCLUSIONS — In people with untreated type 2 diabetes, we previously reported that on a weight basis, ingested beef protein is just as potent in stimulating an increase in insulin concentration as is ingested glucose (2). Cottage cheese protein also was just as potent or even more potent (10,11), which was confirmed in the present study. Ingestion of 25 g cottage cheese protein resulted in an insulin area response that was 68% of the response stimulated by ingestion of 50 g glucose, although the response was somewhat delayed. Thus, proteins are highly significant insulin secretagogues in people with type 2 diabetes even when the fasting glucose concentration is only modestly elevated or not elevated at all.

When protein is ingested with glucose, there is a synergistic effect on insulin secretion. This was particularly impressive when 25 g cottage cheese was ingested with 50 g glucose (10). The integrated insulin area response was 360% of that stimulated by ingestion of 50 g glucose alone.

Ingested fructose also rather strongly stimulates insulin secretion in people with type 2 diabetes. In addition, it stimulates glucagon secretion and, like protein, provides a gluconeogenic substrate. It has only

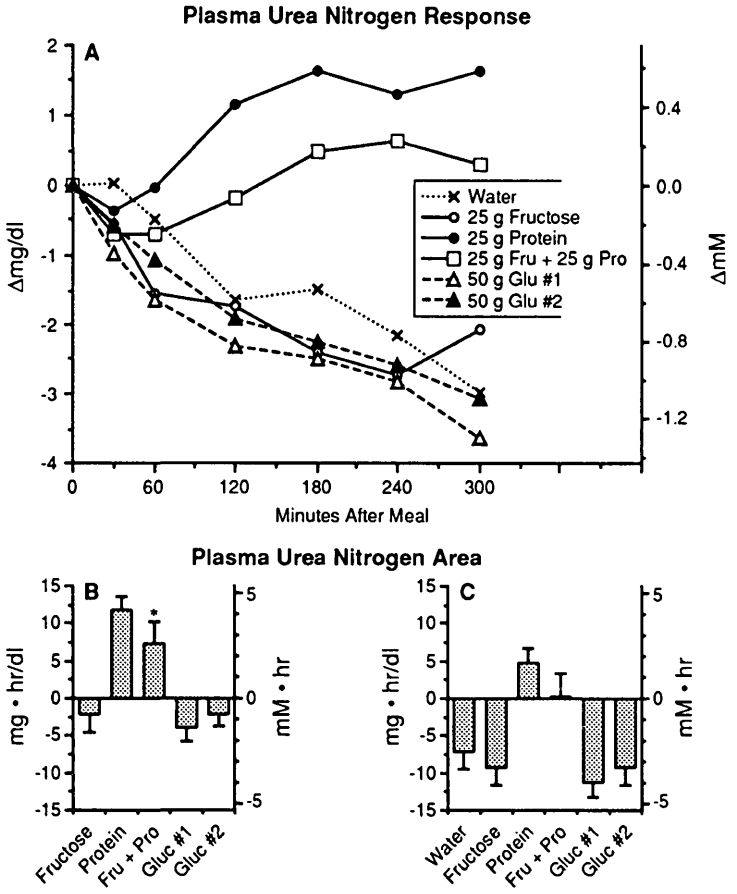

Figure 4—*Plasma urea nitrogen response in seven men with untreated type 2 diabetes. Fru, fructose; glu or gluc, glucose; pro, protein.* A: *the mean plasma urea nitrogen response change following ingestion of the test substances. The mean fasting urea nitrogen concentration was 18 ± 0.9 mg/dl (6.4 ± 0.32 mmol/l). Fifty grams of glucose was given on two separate occasions.* B: *the plasma urea nitrogen area response integrated over 5 h using the response to water only as a baseline.* C: *the plasma urea nitrogen area response integrated over 5 h using the overnight fasting concentration as a baseline.* **Statistically different from protein alone* ($P < 0.04$).

a modest effect on the peripheral glucose concentration. Therefore, we were interested in whether a synergistic effect on insulin secretion might be present. We had previously demonstrated that the insulin area response to fructose ingested with glucose was additive or less than additive, not synergistic, and was similar to the response stimulated by sucrose ingestion (12).

The present data indicate that the insulin area response to the ingestion of fructose with protein also was only additive when considered on a weight basis and with the amount and type of protein ingested. Thus, of the orally provided nutrients studied to date, only proteins result in a synergistic insulin response with ingested glucose.

The present data also indicate that ingested fructose and protein stimulate insulin secretion by independent mechanisms. Fructose has been reported not to directly stimulate insulin secretion in an islet preparation but may potentiate the effect of glucose. Whether this occurs at physiological concentrations of fructose remains uncertain (4). To our knowledge, stimulation of incretin hormones by ingested fructose has not been studied.

At least some amino acids derived from the ingested protein may directly stimulate insulin secretion (13). Ingested protein also stimulates an incretin response. However, the specific incretin or incretins involved remains unknown (1). Whether fructose and proteins stimulate independent incretin hormones also remains to be determined, but it appears likely.

Although an interaction between ingested fructose and proteins affecting insulin secretion was not present, there clearly was an interaction affecting the glucagon response. As expected, the increase in glucagon concentration was considerably less after fructose than after protein ingestion (~20% of the protein response). However, when they were ingested together, the glucagon area response was less than additive; indeed, it was slightly less than the response to protein alone. This observation is difficult to explain. It is unlikely that the 25 g protein ingested resulted in a maximal glucagon response and thus stimulation by addition of fructose was ineffectual. It also cannot be due to a greater rise in glucose concentration, because the glucose area response was similar to that after protein ingestion alone. It may have been due to the greater increase in insulin concentration, which could have occurred through two potential mechanisms. A higher insulin concentration in the islets may have inhibited glucagon release directly (14), or the higher insulin concentration may have lowered the circulating concentration of those amino acids that stimulate glucagon secretion (15). In the present study, the rise in total amino acid concentration was less than additive when fructose and protein were ingested together, but individual amino acid concentrations were not determined. However, if the higher insulin concentration is important, it would require the presence of an exponential or threshold effect of insulin on glucagon secretion because the insulin increase when both fructose and protein were ingested was merely additive compared with the response to the individual nutrients. Lastly, it is possible that fructose stimulated release of a gut hormone that, while stimulating glucagon secretion, also inhibited the effect of the ingested protein products on glucagon secretion. Alternatively, fructose may stimulate release of two or more gut hormones, one of which stimulates glucagon secretion whereas the others inhibit the response to protein. Our data do not allow us to chose between these possibilities.

In any case, an increased insulin response without an increased glucagon response was associated with a glucose increase that was not greater than when protein was ingested alone (Fig. 1*B*). Also, whereas the glucagon response to protein alone was 5-fold greater than to fructose alone, the insulin response was only 2.5-fold greater than to the same amount of fructose.

The effect of protein ingestion on glucose production by the liver is unclear at

present. Wahren et al. (16) reported that splanchnic glucose output was not increased after ingestion of 3 g lean beef protein/kg body wt by normal subjects despite an increase in both glucagon and insulin concentrations. We reported that the rate of glucose appearance after a meal of 50 g protein, given as cottage cheese, was modestly increased in normal young men (17). Both the glucagon and insulin concentrations were markedly increased. However, based on the gluconeogenic potential of cottage cheese, only 23% of the ingested protein could be accounted for as glucose entering the circulation. The peripheral circulating glucose concentration did not change. In preliminary studies in people with type 2 diabetes, 50 g protein given as lean beef had little effect on the rate of glucose appearance, in spite of an increase in glucagon concentration (unpublished observations). In dogs given 0.7 g/kg of an amino acid mixture, the plasma glucose concentration decreased despite an increase in hepatic glucose output, a transient increase in portal insulin concentration, and a sustained increase in glucagon concentration (18).

These data suggest that although ingestion of protein or amino acids results in an increase in glucagon concentration, there is little or no increase in hepatic glucose output or in the circulating glucose concentration. This is likely due to the simultaneous increase in insulin concentration and the resultant peripheral uptake of glucose.

In the present study, fructose ingestion alone resulted in a rise in triglycerides. Protein, when ingested independently, also resulted in a small rise (Fig. 5*A*, *B*, and *C*). Both fructose and protein stimulated a rise in insulin. Insulin activates adipose tissue triglyceride lipase, which facilitates triglyceride removal from the circulation (19). It also inhibits release from the liver of VLDLs, which are triglyceride rich (20). Thus, insulin secreted in response to fructose and to protein should have lowered the triglyceride concentration. Presumably, the amount of insulin secreted when fructose and protein were ingested individually was not sufficient to overcome an independent inhibitory effect of these nutrients on triglyceride removal and/or a stimulation of VLDL release. However, the high concentration of insulin when they were ingested together presumably was able to do so. Ingested fructose (21,22) and sucrose (23) have been reported to delay the clearance of triglycerides (24) and to stimulate VLDL synthesis and release (25). To our knowledge, ingested protein has not been reported to affect triglyceride clearance, production, or release. Nevertheless, the current data, as well as data we have obtained previously, suggest that protein ingestion stimulates a late rise in triglyceride concentration in people with or without type 2 diabetes (11,26).

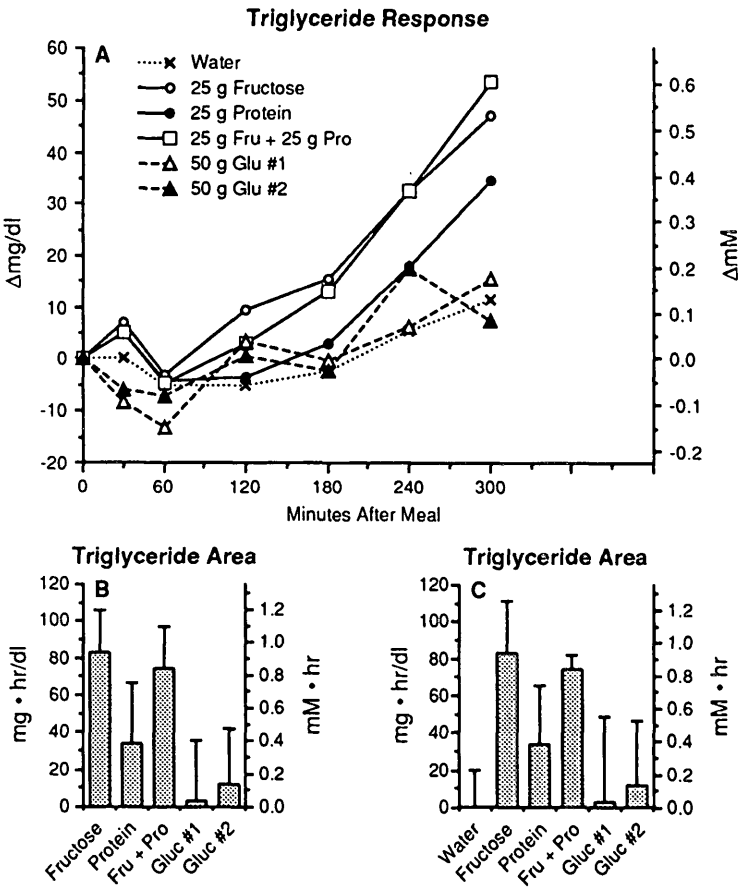

Figure 5—*Serum triglyceride response in five men with untreated type 2 diabetes. Fru, fructose; glu or gluc, glucose; pro, protein. A: the mean triglyceride response change following ingestion of the test substances. The mean fasting triglyceride concentration was 178 ± 9 mg/dl (2.0 ± 0.01 mmol/l). Fifty grams of glucose was given on two separate occasions. B: the triglyceride area response integrated over 5 h using the response to water only as a baseline. C: the triglyceride area response integrated over 5 h using the overnight fasting concentration as a baseline.*

In conclusion, co-ingestion of 25 g fructose and 25 g protein resulted in an insulin area response that was similar to that following ingestion of 50 g glucose and was similar to the sum of the responses to fructose alone and protein alone. In contrast, both the glucagon area response and the glucose area response to fructose plus protein were less than the sum of the responses to the individual nutrients. These data indicate the complexity of nutrient interactions. The data also emphasize the importance of the protein component of the meal in affecting the postprandial plasma glucose concentration.

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