Plasma Glucose and Insulin Response to Macronutrients in Nondiabetic and NIDDM Subjects

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Information on the metabolic response in people with non-insulin-dependent diabetes mellitus (NIDDM) to ingested individual macronutrients is limited. Available information is reviewed herein. The major absorbed products of carbohydrate-containing foods are glucose, fructose, and galactose. The quantitative effect of these on the plasma glucose and insulin response is different for each. In addition, available data indicate that the glucose and particularly the insulin response is different from that in nondiabetic people. The quantitative effect of dietary proteins and fats on the circulating glucose and insulin concentrations in nondiabetic and NIDDM subjects also has been reviewed. Neither has a significant effect on the glucose concentration. Protein stimulates insulin secretion, and this is relatively more prominent in people with NIDDM. A strong synergistic interaction with glucose on insulin secretion is present, but this is absent in nondiabetic people. Ingested fat does not independently stimulate insulin secretion. However, when ingested with carbohydrate, it may have a considerable effect on the plasma glucose and/or insulin response to that carbohydrate, and the responses are different in nondiabetic and NIDDM subjects. This is probably not due to altered carbohydrate absorption. Intestinal hormones undoubtedly are playing a large role in the insulin secretory response in all of these studies, but this remains to be completely elucidated. Overall, the data indicate that the metabolic response to various foods determined in people with NIDDM may be different than that in nondiabetic people. In our opinion, much more information is required before dietary recommendations for NIDDM subjects can be made based on solid scientific data. *Diabetes Care* **14:824–38, 1991**

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In nondiabetic people, the insulin secretory rate is primarily determined by the absolute ambient glucose concentration to which the β-cells in the pancreatic islets are exposed. Superimposed on this regulation is a transient and large increase of insulin secretion in response to a rapid rise in glucose concentration referred to as first-phase insulin secretion. This is observed in an isolated pancreas preparation (1) or with a rapid intravenous glucose infusion (2). After ingestion of glucose (or a mixed meal), these two phases become indistinguishable, but the increase in insulin concentration correlates closely with the increase in glucose concentration temporally. However, the return of the insulin concentration to an overnight fasting value is considerably slower than the return of the glucose concentration, i.e., there is a dissociation between the two (3,4). This has never been explained. It may be due to a relatively slow off-rate for glucose-stimulated insulin release, to continued release of gut hormones, or the presence of other metabolites that continue to stimulate insulin secretion or reduce its clearance by the liver. It also may be due to combinations of these. The half-life of insulin is short and unless altered cannot explain the difference.

The amount of insulin secreted after glucose ingestion depends more on the amount of glucose ingested than on the magnitude of the glucose increase (5–7). Also, quantitatively, the increase in insulin concentration greatly exceeds the increase in glucose concentration.

The maximal glucose concentration typically does not exceed 50% of the premeal value, whereas the increase in insulin concentration not uncommonly is 800–900% (8). Overall, the system is designed to maintain the circulating glucose concentration in the nonfed state within narrowly defined limits. It also is designed to allow only a modest rise in glucose after a carbohydrate-containing meal and to rapidly restore the glucose concentration to the nonfed state. There are many reasons why either a chronically elevated glucose concentration or large, relatively sustained elevations in glucose concentration after a meal may be physiologically undesirable. However, one of the most important of these appears to be the chemical reactivity of the aldehydic group on the glucose molecule (9).

In nondiabetic individuals, most insulin secreted during a 24-h period is that secreted during times of the day when ingested food is not being assimilated, the so-called basal insulin secretion (8).

Although the glucose concentration being monitored by the β-cells is the primary determinant of their secretory activity, several other insulin secretogogues have been identified. The importance of these is still incompletely understood but it is becoming increasingly clear that they play an important role in glucose homeostasis and in the regulation of ingested fuel disposition. Commonly, they potentiate the glucose stimulatory effect and by interacting with glucose they determine the insulin secretory response to meals. These nonglucose insulin secretogogues include amino acids, possibly fructose but not galactose, and the incretin hormones secreted by gut mucosal cells. In addition, dietary fats may alter the insulin and/or glucose response to an oral glucose load.

NONGLUCOSE INSULIN SECRETOGOGUES

Amino acids. In humans, intravenously administered arginine, lysine, leucine, and phenylalanine, in descending order, are the most potent amino acid insulin secretagogues. However, a mixture of 10 essential amino acids is more potent than any single amino acid (10). This suggests a synergistic interaction of the amino acids on insulin secretion. The mechanisms by which arginine (and probably other amino acids) and leucine stimulate insulin secretion are different (11,12). Thus, synergistic interactions also are mechanistically possible.

Fructose. It generally is agreed that fructose does not stimulate insulin secretion in an isolated rat or mouse pancreas or islet cell preparation in the absence of glucose (13–15) or in the presence of a subthreshold insulin stimulatory glucose concentration unless an extremely high fructose concentration is present (16). At higher glucose concentrations, fructose has been reported to potentiate glucose-stimulated insulin secretion. However, only large and unphysiological concentrations of fructose were used. In both rats and humans, the circulating fructose concentration rarely exceeds 1 mM, even after a large oral load (17–19). Thus, whether physiological concentrations of fructose potentiate a glucose-stimulated insulin secretory response in an isolated rodent pancreas preparation remains unknown. Presumably, it does not. In the intact rat, oral administration of a large amount of fructose resulted in a modest increase in circulating insulin concentration; however, this could be accounted for by a modest increase in glucose concentration as well (18).

In humans, a rapid intravenous infusion of fructose stimulated a rise in peripheral insulin concentration, which was not accompanied by a rise in glucose concentration, in both nondiabetic and non-insulin-dependent diabetic (NIDDM) subjects (20). The insulin-area response was twofold greater in the NIDDM subjects. A preceding rapid glucose infusion resulted in a further increase in the insulin response to fructose in both groups. This lead the authors to conclude that fructose does stimulate insulin secretion in humans, and that the vigor of insulin response to fructose is dependent on the ambient glucose concentration. This interpretation of the data depends on whether one considers the fold increase or absolute increase in insulin response. In nondiabetic subjects without prior glucose infusion the maximal insulin increase after fructose infusion was ~5.5-fold. With prior glucose infusion it was ~2.5-fold. However, the absolute increase was ~2.3 times greater after prior glucose infusion. In any regard, a large amount of fructose (30 g) was used in these experiments, and the plasma fructose concentrations that were effective in stimulating insulin secretion greatly exceeded usual physiological concentrations. Also, such dosages are known to result in toxic effects in the liver.

Oral fructose does not increase plasma insulin concentration (17), or results in only a modest increase even at dosages up to 1.75 g/kg (19,21,22). In the latter studies, there was a modest increase in glucose concentration, which could explain the rise in insulin (19,21,22). The insulin rise associated with ingestion of the disaccharide sucrose (glucose + fructose) also has been reported to be accounted for by the serum glucose rise alone (17,23). However, large amounts of fructose (1.75 g/kg) ingested with a large amount of glucose (1 g/kg) or starch may result in additional insulin secretion. This was attributed to a fructose-stimulated increase in gastric inhibitory peptide (GIP) (19).

Overall, these data suggest that dietary fructose ingested in usual amounts does not directly stimulate insulin secretion even in the presence of an elevated glucose concentration in nondiabetic individuals. The data also suggest that fructose does not significantly stimulate insulin secretion indirectly through an incretin hormone mechanism. At best it would appear to be a weak secretagogue. As indicated later, this may not be the case in people with NIDDM.

Incretins. Incretins are hormones released from specific intestinal mucosal cells in response to the presence of

food in the upper intestine. They enter the circulation and are carried to the β-cells in the pancreas where they bind to cell surface receptors. They either directly stimulate insulin secretion, or more commonly, potentiate the effect of an elevated glucose or amino acid concentration on insulin secretion. In effect, they multiply the effectiveness of absorbed food (glucose and amino acids) in stimulating insulin release by the β-cell. Unidentified incretin hormones secreted in response to oral glucose also may reduce the fractional extraction of insulin by the liver and thus facilitate an increase in peripheral insulin concentration (7).

The duodenum is now considered to be a sensor that detects the type and amount of food entering the intestine for digestion and absorption (24). It then sends hormonal signals to the acinar pancreas. Receipt of these signals by the acinar pancreatic cells determines the amount and type of pancreatic secretions to be added to the gut lumen for digestion of various foods. The duodenum also sends hormonal signals to the endocrine cells of the pancreas which, in the presence of an elevated circulating glucose or amino acid concentration resulting from food digestion, stimulate release of pancreatic hormones important in the metabolism of the absorbed food products. Thus, overall, the duodenum and upper jejunum may be considered to be not only sensors but also integrators, which by signaling the pancreas directly and in a complementary fashion with absorbed nutrients, ensure that ingested foods are efficiently digested, absorbed, and stored for later use by the organism. This is a very elegant regulatory system (Fig. 1).

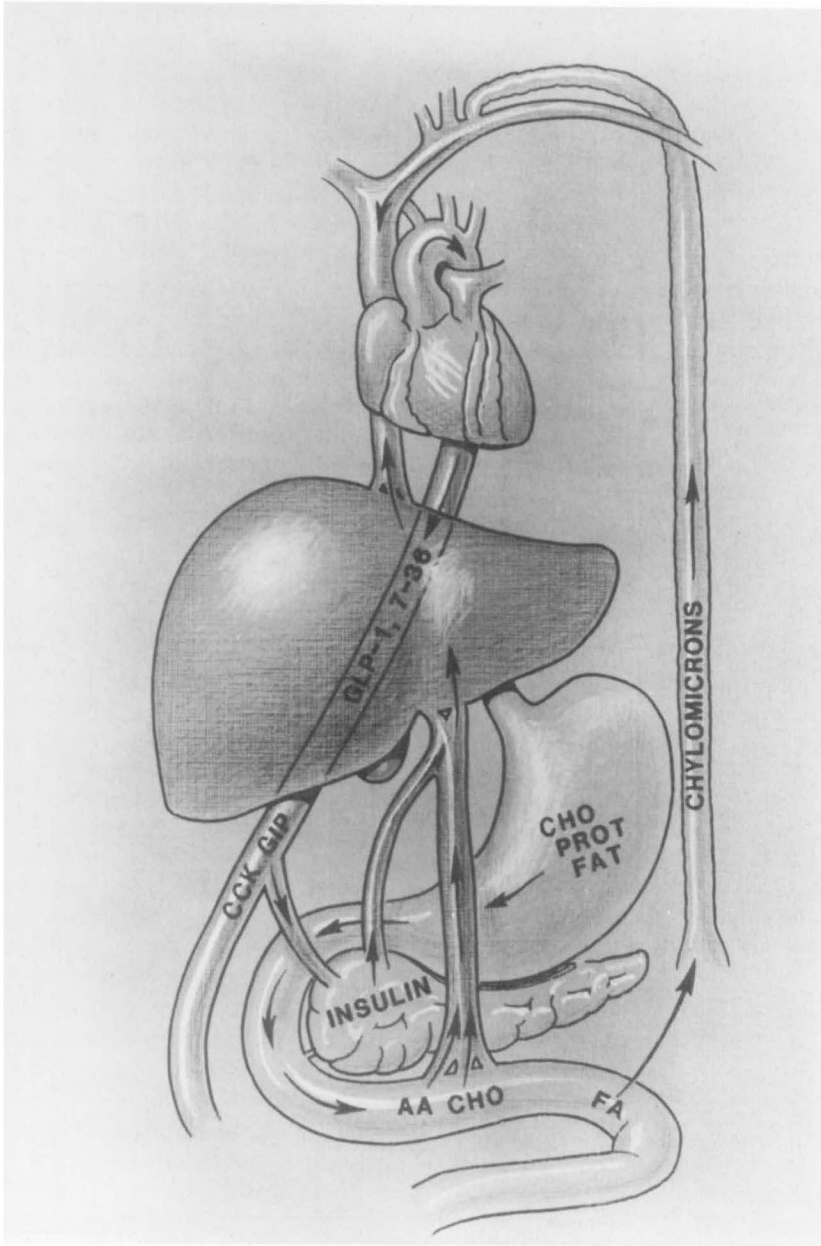

FIG. 1. Interaction of absorbed nutrients and incretin hormones on insulin secretion. Incretins are released from specific intestinal mucosal cells in response to presence of food in upper intestine. CHO, carbohydrate; PROT, protein; CCK, cholecystokinin family; GIP, gastric inhibitory polypeptide; GLP-1, 7–36, glucagonlike peptide I-7–36 amide; AA, amino acids; FA, fatty acids.

The number of incretin hormones secreted in response to a meal is not known. However, four major candidate incretin peptides have been identified. They include GIP, secretin, the cholecystokinin family (CCK), and glucagonlike peptide I-7–36-amide (GLP-I-[7–36]-amide) (25–28). After glucose ingestion, GIP and GLP-I-(7–36)-amide are clearly elevated; CCK is not. Ingested galactose but not fructose also stimulates a rise in the circulating GIP concentration (24). The integrated GIP response to progressively larger amounts of orally administered glucose is approximately linear (7). A dose-response relationship between ingested galactose and GIP response has not been reported to our knowledge. Also, to our knowledge, the effect on GLP-I-(7–36)-amide secretion of nutrients other than glucose has not been studied.

In addition to stimulating insulin secretion, GLP-I-(7–36)-amide inhibits glucagon release (29). This is of considerable interest, because both glucagon and GLP-I-(7–36)-amide are derived from the same proglucagon precursor protein by differential posttranslational processing in the pancreatic α-cells and intestinal enteroglucagon cells, respectively (30).

After the ingestion of a protein meal, CCK increases in the circulation (28,31). Evidence for a CCK-facilitated stimulation of insulin secretion in the presence of a raised amino acid concentration has been obtained by several investigators (27,32,33), and it is likely to play a significant role in a protein-stimulated rise in insulin concentration. In humans, CCK does not stimulate insulin secretion in the presence of an increased glucose concentration as it does in the presence of an elevated amino acid concentration (27).

Dietary fat has been reported to stimulate a rise in CCK and GIP (25,28). Stimulation of GIP release requires the digestion of triglyceride, the absorption of the resulting digestive products, and incorporation of these into chylomicrons (34). Triglycerides composed of medium chain fatty acids do not stimulate GIP secretion (34), and fish oils are relatively weak in this regard (35). How ingested fats stimulate CCK secretion is poorly understood.

Secretin stimulates insulin secretion in vitro, and the effect is potentiated by glucose (36). Secretin also rises after a glucose or protein meal (31). However, the rise generally is considered to be insufficient for it to function independently as an insulin incretin (25,36). It is likely that synergistic or inhibitory interactions between gut mucosal hormones also occur. Thus, secretin could still affect insulin secretion through such a mechanism.

INCRETINS AND INSULIN SECRETION

The importance of incretin hormones in facilitating insulin secretion after the ingestion of glucose or of glucose-containing foods has been shown by several investigators (7,37–41). It can be estimated that ≥40% of the peripheral insulin response after glucose ingestion is due to incretin hormones; it may be as much as 90% (Table 1). These data clearly indicate the importance of incretin hormones in stimulating insulin secretion and possibly reducing first-pass hepatic removal of insulin after the ingestion of glucose-yielding foods (7).

The quantitative importance of incretins in protein-stimulated insulin secretion has been less certain. Raptis et al. (42) reported a greater rise in insulin concentration when 10 essential amino acids were given intraduodenally (30 g) rather than intravenously, although the total plasma amino acid concentration was greater when they were given intravenously. When given intravenously, this mixture and amount of amino acids had been reported previously to produce a maximum insulin response (10). Thomas et al. (43), with a similar protocol, obtained similar data. However, they also reported an increase in serum GIP when the amino acids were given intraduodenally. The additional increase in insulin, when the amino acids were given intraduodenally, was attributed, at least in part, to the release of GIP into the circulation. As mentioned previously, GIP does not increase after ingestion of a protein meal as it apparently does after intraduodenal amino acid administration. Therefore, the data implicating an important incretin role in insulin secretion obtained with mixtures of amino acids given intraduodenally and intravenously may not directly relate to results obtained with protein ingestion. Intraduodenal administration of amino acids or a protein hydrolysate as well as protein does stimulate CCK release from the intestine (44,45).

Other information suggests that an incretin response to ingested protein is of major importance in insulin

TABLE 1
Insulin response to oral compared with intravenous glucose

Ref./glucose dose	Insulin-area response ($\mu U \cdot h^{-1} \cdot ml^{-1}$)	Percent due to incretins
Perley and Kipnis (37)		
Oral, 100 g	126	72
Intravenous, 32 g	35	
Rehfeld and Stadil (38)		
Oral, 50 g	43	92
Intravenous, 17 g	3.5	
Hampton et al. (39)		
Oral, 100 g	70	70
Intravenous, 67 g	21	
Nauck et al. (7)		
Oral, 25–100 g	26–91	81–88
Intravenous, 19–21 g	5–11	
Morgan et al. (40)		
Oral, 100 g	110	60
Intravenous, 63 g	44	
Shuster et al. (41)		
Oral, 1 g/kg	59	42
Intravenous, 0.68 g/kg	34	70

Mean for all studies was 70.

secretion, although the data are indirect. Evidence in support of this concept is as follows. First, after protein ingestion, a rise in plasma insulin concentration before a rise in amino nitrogen concentration can be demonstrated (46). Second, when three identical meals high in protein were given to nondiabetic subjects, there was a rapid increase in insulin concentration after each meal, although there was little change in α-amino nitrogen concentration and little change in glucose concentration after the second and third meal of the day (8,47). Third, ingestion of protein as egg white, a rather poorly digestible protein, resulted in a significant increase in serum α-amino nitrogen (total amino acids) concentration but it did not stimulate insulin and C-peptide secretion (M.C.G., F.Q.N., J.T. Lane, L.A. Burmeister, unpublished observations). Fourth, gelatin, an atypical dietary protein containing only modest amounts of amino acids known to be the most potent insulin secretagogues, nevertheless, was very potent in raising the serum insulin concentration in NIDDM subjects when ingested with glucose (49). Lastly, as mentioned previously, amino acid mixtures given orally have been shown to be far more potent than intravenously administered amino acids in raising serum insulin (10,42,43).

Direct quantitation of the incretin effect in both nondiabetic and NIDDM subjects awaits data obtained after ingestion of a known quantity of a specific protein, the determination of the integrated increase in specific amino acids reaching the periphery, and the integrated insulin rise over a defined period of time. This may then be compared with the integrated insulin response to intravenous administration of such a mixture of amino acids in amounts required to simulate the peripheral concentrations observed after protein ingestion.

NIDDM

In people with NIDDM, several abnormalities in insulin and glucose metabolism have been identified. Characteristically, people with mild to moderately severe NIDDM are moderately obese. They have a normal or an elevated overnight fasting serum insulin, nevertheless, this is inappropriately low considering the elevated glucose concentration. They also have an impaired serum insulin response to ingestion of a standardized amount of glucose. In addition, insulin insensitivity is present (50). The rate of glucose disposal is reduced, and impaired hepatic glucose output suppression to a given concentration of insulin has been demonstrated with a glucose-clamp technique (51–53).

The plasma glucose concentration is variably elevated depending on the severity of insulin insensitivity and of β-cell unresponsiveness to a raised circulating glucose concentration. A reduced insulin response to intravenous mixed amino acids (54) and to arginine (55,56) has been reported. An abnormality in the usual pulsatile pattern of insulin secretion also is present (53,57), as well as an increase in the proportion of proinsulin to insulin in the circulation (52,58,59). Thus, several abnormalities have been identified.

It is becoming increasingly clear that a high circulating insulin concentration, a moderately increased fasting glucose concentration, and a modestly impaired glucose tolerance may be present many years before the occurrence of diabetes, as currently defined (60,61). However, the occurrence of diabetes is always associated with an impairment in insulin secretory response to a rise in glucose concentration (53).

The pathogenesis of NIDDM remains unknown. The β-cell mass is either normal or only modestly reduced (53,62), and the ability to synthesize insulin is intact. However, the maximal capacity to secrete insulin may be impaired (53). One hypothesis is that there is an abnormality in glucose sensing by the β-cells (53,63) and/or in coupling to the insulin secretory response element. If this is the case, then the abnormality in sensing must extend to the pharmacological administration of a mixture of amino acids and arginine as indicated above. Alternatively, it may be indicative of an impairment of glucose potentiation of these insulin secretogogues (53,63).

We are not aware of studies comparing the insulin responsiveness to incretin hormones in nondiabetic and NIDDM subjects at defined glucose concentrations. There are only limited studies in which the insulin response to orally administered nonglucose-yielding foods has been determined in subjects with NIDDM (22,64–66). There also are few studies of the interaction of nonglucose food constituents on the insulin response to oral glucose in these subjects (66). Our data would suggest the presence of several differences in insulin response when compared with nondiabetic young subjects. In people with NIDDM, incretin hormone response to absorbed nutrients other than glucose may be playing an even more important role than in nondiabetic subjects.

Our major interest has been the determination of the insulin and glucose response to dietary constituents in mild untreated subjects with NIDDM. We became interested in determining the insulin response to various macronutrients in these subjects for four reasons. First of all, because amino acids and perhaps fructose stimulate insulin secretion directly (10,13) without increasing the glucose concentration significantly (22,67), dietary sources of these may prove useful in the management of NIDDM patients. Second, because fats, proteins, and possibly nonglucose carbohydrates stimulate a rise in incretin hormones, we were interested in determining whether the addition of these foods to a glucose meal could facilitate insulin secretion in subjects with NIDDM and thus reduce the circulating glucose response to glucose-yielding foods. The pattern of incretins released are different for different foods; therefore, this appeared to be a likely possibility. Third, in nondiabetic subjects, the plasma glucose concentration is elevated above an overnight fasting value for only 1–3 h after a mixed meal (3,8). However, in people with

mild to moderately severe NIDDM, this time is extended to ≥4 h, and the excursions above the fasting glucose concentration are much larger (68,69). Thus, any mechanism for reducing the postprandial glucose rise is likely to be important in preventing or delaying the long-term complications of diabetes that have been associated with a high-glucose concentration. Lastly, if hyperinsulinemia is playing a role in the long-term cardiovascular complications of diabetes, as suggested from population studies (70), it is important to understand the plasma insulin response to various foods in order to advise these patients appropriately. Ultimately, we would like to be able to predict both the integrated plasma glucose and insulin response to mixed meals based on their constituent foods.

After digestion, the major macronutrients absorbed are glucose, fructose, galactose, amino acids, and fatty acids reconstituted into triglycerides in chylomicrons. In a usual American diet consisting of 45% carbohydrate, 40% fat, and 15% protein, it can be calculated that glucose is quantitatively the most important sugar absorbed. Of the absorbed sugars, ~75% is glucose, ~22% is fructose, and 3% is galactose. In the diet recommended by the American Diabetes Association that contains 55% carbohydrate, 30% fat, and 15% protein and with the composition suggested, available glucose is increased to 82% and fructose is reduced to 13% (71). In this review, we focus on the effects of these individual nutrients on glucose and insulin concentrations in nondiabetic and NIDDM subjects and not on the food forms in which they are usually ingested.

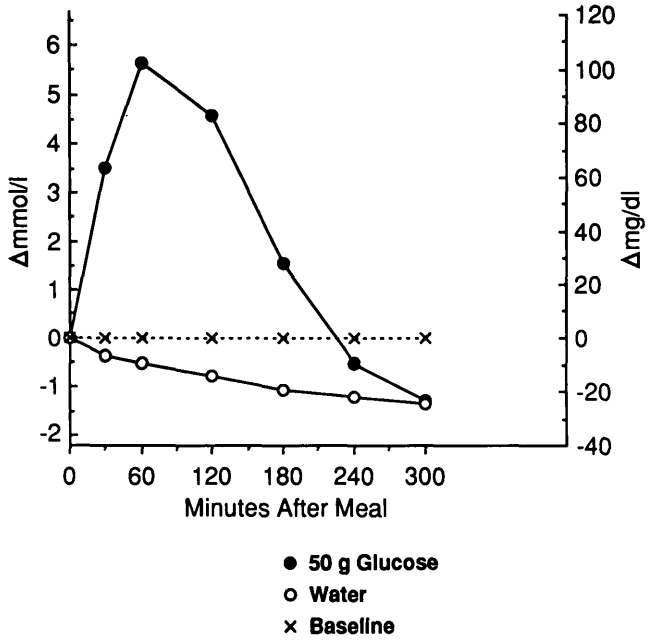

FIG. 2. Glucose response to 50 g glucose or water in non-insulin-dependent diabetic subjects (mean fasting glucose 8.1 mM). After ingestion of only water, glucose concentration decreases progressively during 5 h of study. Use of 0 time point for determining area response (*dashed line*) would result in underestimation of response (n = 23).

To quantitate the glucose, insulin, and C-peptide response, we determined the integrated incremental area response of these in response to various foods over a defined period of time. The results are compared to the same values obtained when the subjects fast over this time period. The insulin, C-peptide, and particularly the glucose concentration are not stable over the 5-h duration of these studies in fasting subjects with NIDDM. Thus, it is not appropriate to use the 0 time point for determining the area response as we as well as others have used in the past (72–76). Typical glucose results are shown in Fig. 2. Other confounding variables that may influence the interpretation of glucose or insulin-area responses have been reviewed elsewhere (77).

GLUCOSE AND INSULIN RESPONSE TO ORAL GLUCOSE

Nondiabetic subjects. In nondiabetic subjects, most studies have indicated little difference in the maximal glucose concentration reached but rather a prolongation in the time duration over which the glucose remained elevated when progressively larger amounts of glucose are ingested. The dosages used have varied from 30 to 300 g (78). This has been attributed to a regulated metering of glucose from the stomach (79). In the few studies where the response was quantitated, it was found to be linearly related to the dosage or there was a modest decrease in proportionality at the higher doses.

The insulin incremental area response to increasing dosages of glucose reported in the literature has varied widely. It has been reported to be linear, exponential, or sigmodial (7,78). The proportion of secreted insulin attributable to incretin hormones increased progressively with the doses of glucose (7).

NIDDM subjects. We are unaware of quantitative glucose and insulin-area data in untreated NIDDM subjects other than our own (78). With the use of the 0 time point glucose concentration to determine the 5-h glucose area response, an exponential relationship to the dosage was observed. However, if the area was calculated with the fasting glucose concentration over the same time period in the same subjects as a baseline, the glucose area response was modestly sigmoidal, and a major error would not be present if it were considered to be linear. These data indicate the importance of the method used in determining area response data.

The insulin-area response was highly sigmoidal with either method. Ingestion of 15 g glucose resulted in only a modest insulin response. Maximal sensitivity of the insulin response occurred between the 15- and 35-g dosages. A maximal response occurred with a 35-g dose. A 50-g dose did not result in a further increase (Fig. 3). The C-peptide data were similar (78).

These data suggest the meals yielding between 15 and 35 g of glucose after digestion are most likely to have

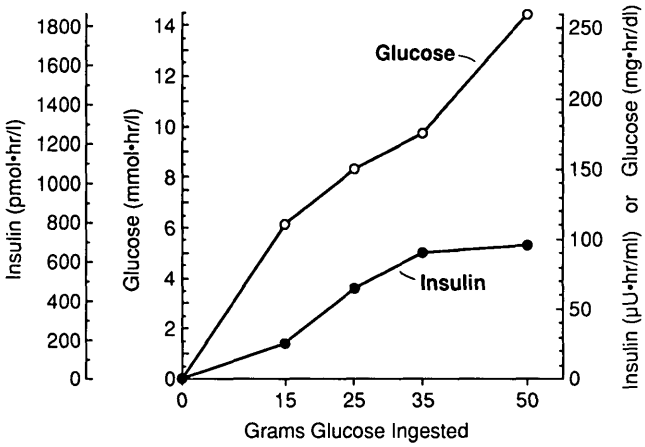

FIG. 3. Glucose and insulin-area response to various amounts of glucose in non-insulin-dependent diabetic subjects (mean fasting glucose 7.1 mM, mean fasting insulin 187 pM). Data demonstrate nonlinear dose-response relationships (n = 10). From Gannon et al. (78). © by the American Diabetes Association.

the smallest glucose response relative to the insulin response. They also suggest that meals yielding amounts of glucose >35–50 g are likely to have a rather large effect on the postmeal glucose rise, because little additional insulin is likely to be secreted. If these data are confirmed, they may prove useful in meal planning for people with NIDDM. A near-maximal suppression of glucagon, nonesterified fatty acids, and amino acid concentrations as well as a maximal rise in lactate also occurred at these dosages, suggesting a near-maximal effect on glucose oxidation as well.

GLUCOSE AND INSULIN RESPONSE TO ORAL FRUCTOSE

Nondiabetic subjects. As mentioned previously, fructose ingestion by nondiabetic people results in little or no change in insulin concentration and little increase in glucose concentration (17,21,22). In nondiabetic subjects, fructose also is not a significant insulin secretagogue (22) even when absorbed simultaneously with glucose (17).

NIDDM subjects. In people with severe NIDDM (mean fasting glucose 13.9 mM) 50 g fructose did not stimulate an increase in insulin concentration, but the insulin response to glucose administration was strikingly impaired (22). This suggests that these subjects had an impaired ability to secrete insulin in general. In subjects with less severe NIDDM (fasting glucose <11.1 mM), ingestion of 50 g fructose alone clearly was associated with a rise in insulin concentration (20,80). However, the glucose concentration increased, and quantitatively the area increases were approximately proportional. Thus, whether there was an independent effect of fructose itself could not be distinguished.

In a subsequent dose-response study, the glucose area increase was curvilinear and compatible with an exponential relationship when compared with the fasting glucose concentration over the same time frame (Fig. 4). However, the area response was relatively small. At a dose of 35 g, the area response was <10% of that produced by 50 g glucose. At a dose of 15 g, the smallest dose studied, the area response was actually slightly negative. If compared with the 0 time point all of the areas would have been negative except for the 50-g dose and could have been interpreted as resulting in a decrease in glucose concentration (F.Q.N., M.C.G., L.A.

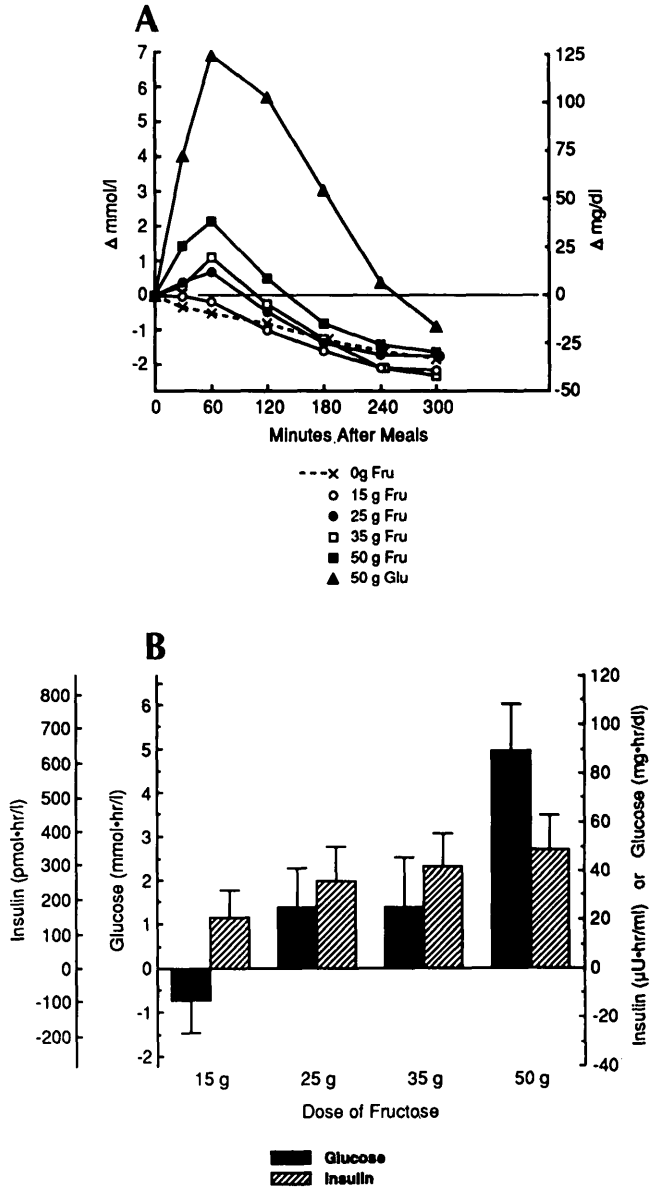

FIG. 4. *A*: effect of ingestion of various amounts of fructose on plasma glucose concentration in non-insulin-dependent diabetic subjects (mean fasting glucose 8.5 mM). *B*: effect of ingestion of various amounts of fructose on glucose and insulin-area response in non-insulin-dependent diabetic subjects (mean fasting insulin 237 pM). From Nuttall et al. (81). © by the American Diabetes Association.

Burmeister, J.T. Lang, K.L. Pyzdrowski, unpublished observations).

The insulin-area response also was curvilinear but hyperbolic and thus opposite to that of the plasma glucose response to various dosages of fructose (Fig. 4). Also, even the smallest dose of fructose resulted in a relatively large increase in insulin-area response. Just as with glucose administration, a nearly maximal response was present with a 35-g dose. The area response to 50 g fructose, the highest dosage studied, was ~39% of that for a 50-g glucose dose. Again the C-peptide dose-response curves were similar to the insulin curves (F.Q.N., M.C.G., L.A. Burmeister, J.T. Lang, K.L. Pyzdrowski, unpublished observations). Mechanistically, these data suggest a sensitive but easily saturable response system. Because the plasma glucose concentration was not increased with the smallest fructose dose used, it also strongly suggests that fructose-stimulated incretins are playing an important mechanistic role. The nature of these remains to be determined. GIP secretion is not stimulated by fructose ingestion, as indicated previously (25).

Because the increase in glucose concentration is modest but the insulin rise is relatively dramatic, the data suggest that meals containing ≤35 g of fructose may be useful in the dietary management of people with NIDDM. However, the insulin stimulatory effect of fructose may be blunted when ingested with glucose. In previous studies, the insulin response to an equimolar ratio of glucose and fructose, or to sucrose or fruit juices, could be largely accounted for by the glucose component alone (80). Thus, the possibility that a glucose-stimulated insulin secretion negates a fructose stimulation of insulin needs to be investigated more carefully.

In contrast to the negative glucagon area response induced by glucose ingestion the glucagon area response to fructose was positive and little changed by increasing dosages of fructose. Thus, just as with proteins (82), ingested fructose stimulates an increase in both insulin and glucagon concentrations (F.Q.N., M.C.G., L.A. Burmeister, J.T. Lang, K.L. Pyzdrowski, unpublished observations). In nondiabetic subjects, oral fructose apparently does not stimulate glucagon secretion (83) but this needs to be confirmed.

GLUCOSE AND INSULIN RESPONSE TO GALACTOSE

Nondiabetic subjects. In nondiabetic people ingestion of galactose results in only a modest increase in peripheral serum glucose concentration (84–86). At a dose of 0.5 g/kg this was only ~0.8 mM (84). A rise in insulin concentration is stimulated, but this has been attributed to the rise in glucose concentration (85) and to stimulation of release of GIP and probably other hormones from gut mucosal cells. Intravenously administered galactose does not affect the blood glucose concentration (87). It also does not stimulate insulin secretion directly in nondiabetic people (88). Galactose either does not stimulate insulin secretion in an isolated rat pancreas preparation (85) or is only a relatively weak secretagogue (89).

NIDDM subjects. In a subject with NIDDM an intravenous infusion of galactose (0.5 g · kg^{-1} · h^{-1}) over an 8-h period did not raise the blood glucose concentration. In a subject with IDDM it raised the blood glucose concentration considerably (~11.1 mM increase; 87). All but 10% of the galactose was retained, suggesting its metabolism to other substances, most likely glycogen. There is an apparent lack of information in the literature regarding the circulating glucose and insulin response to oral galactose ingestion by people with NIDDM. Many years ago Roe and Schwartzman (90) reported that fermentable sugar in the blood (glucose) did not rise in nondiabetic subjects after galactose ingestion; it did increase in diabetic subjects but the increase was modest. We are unaware of comparative data having been published since.

Galactose and glucose interactions. Galactose rarely is ingested as the monosaccharide itself but rather is ingested in the form of the disaccharide, lactose (milk sugar), which is composed of equimolar amounts of galactose and glucose. In nondiabetic subjects, the serum galactose, glucose, and insulin response to lactose is the same as that to an equimolar mixture of glucose and galactose (85).

When glucose is ingested with galactose, the expected serum galactose concentration is considerably less than would be expected from the ingestion of that amount of galactose ingested independently (84,91). This effect clearly is mediated by a facilitated utilization of the galactose and not by an effect on its rate of absorption. Ingested lactose results in the same phenomenon. The mechanism of this is uncertain, but it may be due to a facilitated utilization of galactose for glycogen synthesis in the liver. Glucose and galactose are equipotent in activating liver glycogen synthase, at least in the rat (93,94; C.B. Niewoehner, B. Neil, unpublished observations). The combination of a rise in galactose and glucose concentrations in the liver should result in a greater activation of this rate-limiting enzyme if both are present at less than saturating concentrations. Because galactose (95) but not glucose (94–96) is primarily metabolized in the liver and because galactose enters the glycogen synthetic pathway directly, the impact of synthase activation is likely to be greater on the circulating galactose concentration than on the glucose concentration. Galactose also is actively taken up by the liver (94). This as well as the activation of synthase may be a mechanism for preventing galactose toxicity. Insulin has little effect on galactose metabolism (85).

The glucose and insulin response to lactose ingestion by people with NIDDM does not appear to have been studied extensively. We reported the glucose and insulin-area responses to 50 g lactose to be the same or moderately less than would be expected from the amount of available glucose in the lactose ingested (80).

Both were less than expected if a significant fraction of galactose was converted to glucose. It is another area in need of further research.

GLUCOSE AND INSULIN RESPONSE TO INGESTED PROTEIN

Nondiabetic subjects. It has been known since 1913 (97) that ingested protein does not raise the plasma glucose concentration in nondiabetic people even when ingested in large amounts (67–97). It also does not raise the glucose concentration in people with NIDDM when compared with the initial fasting glucose concentration (67). This lack of change in glucose concentration occurs, although 50–70% of the ingested protein can be accounted for by deamination and urea synthesis in the liver (67,98). Presumably, most deaminated amino acids are converted to glucose.

Although the glucose concentration is little changed, ingestion of a large protein meal results in a rise in insulin concentration (99,100). In nondiabetic subjects, the rise is variable and considerably less than that resulting from glucose ingestion (100). In the only study in which the potencies were compared directly, the integrated area response was only ~28% of that stimulated by the same mass of glucose (46). As indicated previously, ingested protein probably stimulates insulin secretion by a direct effect of the ingested amino acids on the β-cells and indirectly through an incretin mechanism. In nondiabetic subjects, ingested glucose and protein have additive effects on insulin secretion when ingested in equal amounts (46). When less protein is ingested with the glucose, the response to the protein is less than additive (4).

In normal rats, oral protein (101) or a protein hydrolysate (102) did not stimulate insulin secretion, whereas in fish, amino acids rather than glucose appear to be the major stimuli for insulin secretion (103).

NIDDM subjects. In people with NIDDM the insulin response to ingested protein is considerably different. In these subjects, ingested protein is a relatively stronger stimulus for insulin secretion than in nondiabetic subjects, although the integrated insulin response to 50 g glucose was similar in the two groups (64,104). Indeed, protein on a mass basis is just as potent as glucose in stimulating a rise in serum insulin concentration. In these subjects, the integrated insulin-area response to 50 g protein was 3.5-fold greater than in nondiabetic subjects (46). However, the group with diabetes were older and moderately obese compared with nondiabetic subjects. Whether the difference is due to age and/or obesity and not diabetes remains to be determined. Also, whether the observed difference is the result of a relative difference in β-cell sensing of a rise in glucose and amino acid concentrations or is due to a difference in incretin hormone secretion or β-cell sensitivity to gut hormones remains unknown.

Of greater interest was an identified synergistic interaction on insulin secretion when protein was ingested with glucose. This resulted in a smaller rise in a glucose concentration, and the rise was even less with a second identical meal when the meals were ingested 4 h apart (104; Fig. 5). In single meals, when various amounts of beef protein were added to 50 g glucose, there was a linear relationship between the amount of protein ingested and the integrated insulin response. The increase was 2.8 $\mu U \cdot ml^{-1} \cdot h \cdot g\ protein^{-1}$.

In a subsequent study, seven different proteins added in 25-g amounts to 50 g glucose were studied in subjects with NIDDM (49). A synergistic interaction on insulin response was observed for all. In these subjects, if the area response in each individual to 50 g glucose alone

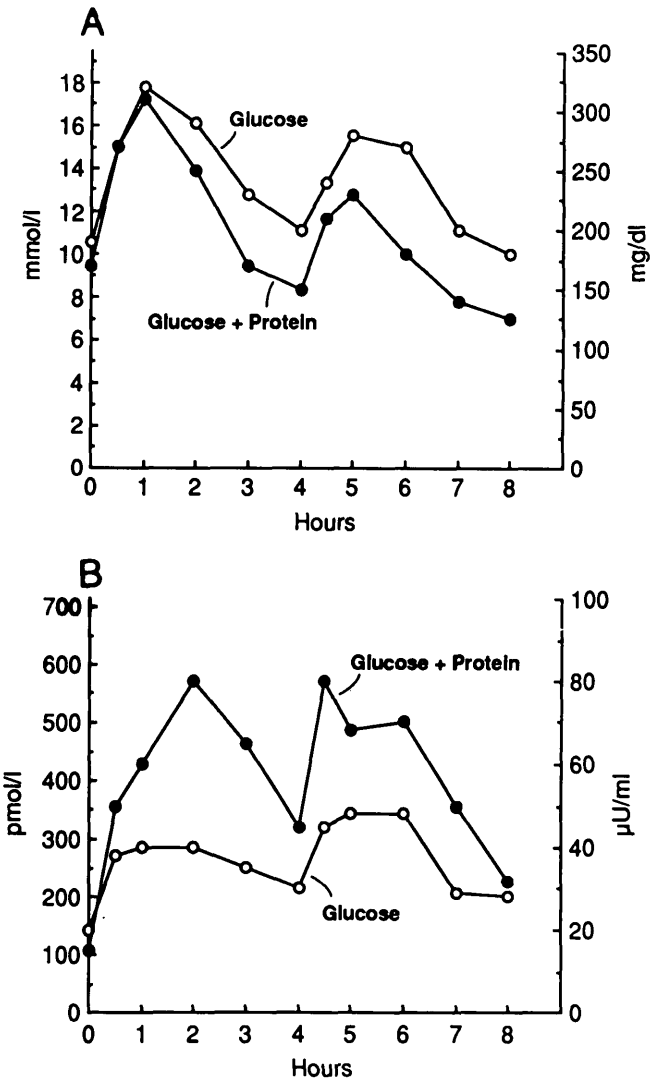

FIG. 5. Effect of glucose alone or glucose plus protein on plasma glucose (*A*) and insulin concentrations (*B*) in non-insulin-dependent diabetic subjects (50 g glucose or 50 g glucose + 50 g protein as lean beef were ingested at 0 and 4 h). Mean fasting glucose 8.6 mM, mean fasting insulin 144 pM (n = 5). From Nuttall et al. (104). © by the American Diabetes Association.

is considered to be 100%, then the added proteins increased the response on average to ~230%. The response was similar for most proteins. However, it was least for egg white (190%) and greatest for cottage cheese (milk protein, 360%) (Fig. 6). The smaller insulin response to egg white protein can be attributed to its relatively poor digestibility (98). All of the proteins reduced the plasma glucose area response to the 50 g glucose dose, except for the egg white protein (49).

These data indicate that ingested protein in general is a rather potent insulin secretagogue in people with NIDDM. This is particularly true when protein is ingested with glucose. The synergistic effect on insulin secretion occurs, although the rise in amino acids is delayed when protein is ingested with glucose (46,48). Preliminary data suggest that the delay in amino acid rise is due to a reduced rate of protein digestion and/or absorption of the resulting amino acids (48).

Because proteins do not raise the blood glucose concentration but strongly stimulate insulin secretion, theoretically at least, an increased protein content of meals for people with NIDDM should be considered if a lower postmeal glucose concentration is a goal (105).

GLUCOSE AND INSULIN RESPONSE TO INGESTED FAT

Nondiabetic subjects. Ingested triglycerides do not stimulate insulin secretion, they also do not affect the circulating glucose concentration when given as a single meal to nondiabetic subjects or subjects with mild NIDDM (106). They do stimulate both GIP and CCK secretion, as indicated previously. Potentially, this could result in greater insulin secretion in the presence of an elevated plasma glucose or amino acid concentration when fats are ingested with carbohydrates and/or proteins. However, this possibility has not been extensively studied.

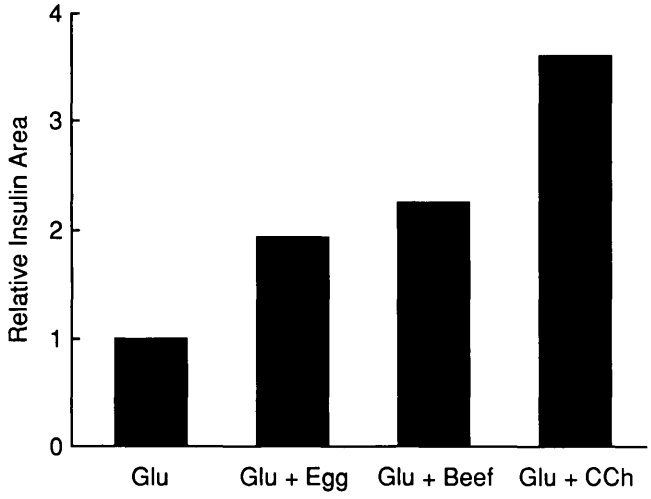

FIG. 6. Effect of various proteins on relative insulin area (mean fasting glucose 8.7 mM, mean fasting insulin 158 pM; $n \geq 9$). Glu, glucose; CCh, cottage cheese. From Gannon et al. (49). © by the American Diabetes Association.

Oral ingestion of 60 g of butter fat ingested as cream did not change the plasma insulin concentration. It did significantly increase the insulin response to a rapid intravenous infusion of glucose given 3 h later. It also resulted in an acceleration of the glucose disappearance rate. Oral glycerol did not potentiate the insulin response. In subjects who had ingested cream, heparin given before glucose eliminated the potentiation of insulin secretion by the fat meal; the reason for this is not explained. Heparin administration was associated with a marked increase in nonesterified fatty acids and a reduction in triglycerides (107). Potentiation of the insulin response to intravenously administered glucose by oral fat ingestion has been confirmed in other studies (108,109).

Ingestion of 50 g butter with 50 g carbohydrate as potato resulted in a greater rise in GIP concentration than when potato was ingested alone, as might be expected. The insulin response was little changed but the glucose rise was considerably attenuated (110). The maximal rise in glucose and insulin was not delayed by the presence of butter in the meal, suggesting little effect of the fat on gastric emptying or on starch digestion and glucose absorption.

We confirmed these results in nondiabetic young males (M.C.G., F.Q.N., S.A. Westphal, E.R. Seaquist, unpublished observations). There was a striking reduction (70%) in the maximal glucose rise, although it occurred at the same time whether or not butter was present. However, the insulin curves were nearly identical (Fig. 7). The 4-h incremental glucose area response was only ~55% of that when potato was ingested alone; the insulin area was 109%. C-peptide data confirmed the insulin results (M.C.G., F.Q.N., S.A. Westphal, E.R. Seaquist, unpublished observations). These data suggest but certainly do not prove that fat-stimulated incretin hormones were important in stimulating insulin secretion. They also raise an additional interesting question. That is, could there be unidentified factors released in response to fat in the meal that accelerate the removal of glucose from the circulation or accelerate its conversion into other metabolites? This could be an independent effect or be mediated through a potentiation of the effectiveness of insulin, i.e., insulin may be more efficient in stimulating glucose clearance from the circulation. Although the kinetics of glucose and insulin change were similar with or without ingestion of butter, it also is possible that the presence of butter merely impaired starch digestion and/or glucose absorption and reduced insulin sensitivity, such that the large amount of insulin secreted did not result in significant hypoglycemia. This is unlikely; nevertheless, these questions remain to be answered in a definitive fashion. Incidentally, in these subjects, the rise in glucose concentration after fat and carbohydrate ingestion was only 0.6 mM. A rise of ≥1 mM has been reported to be

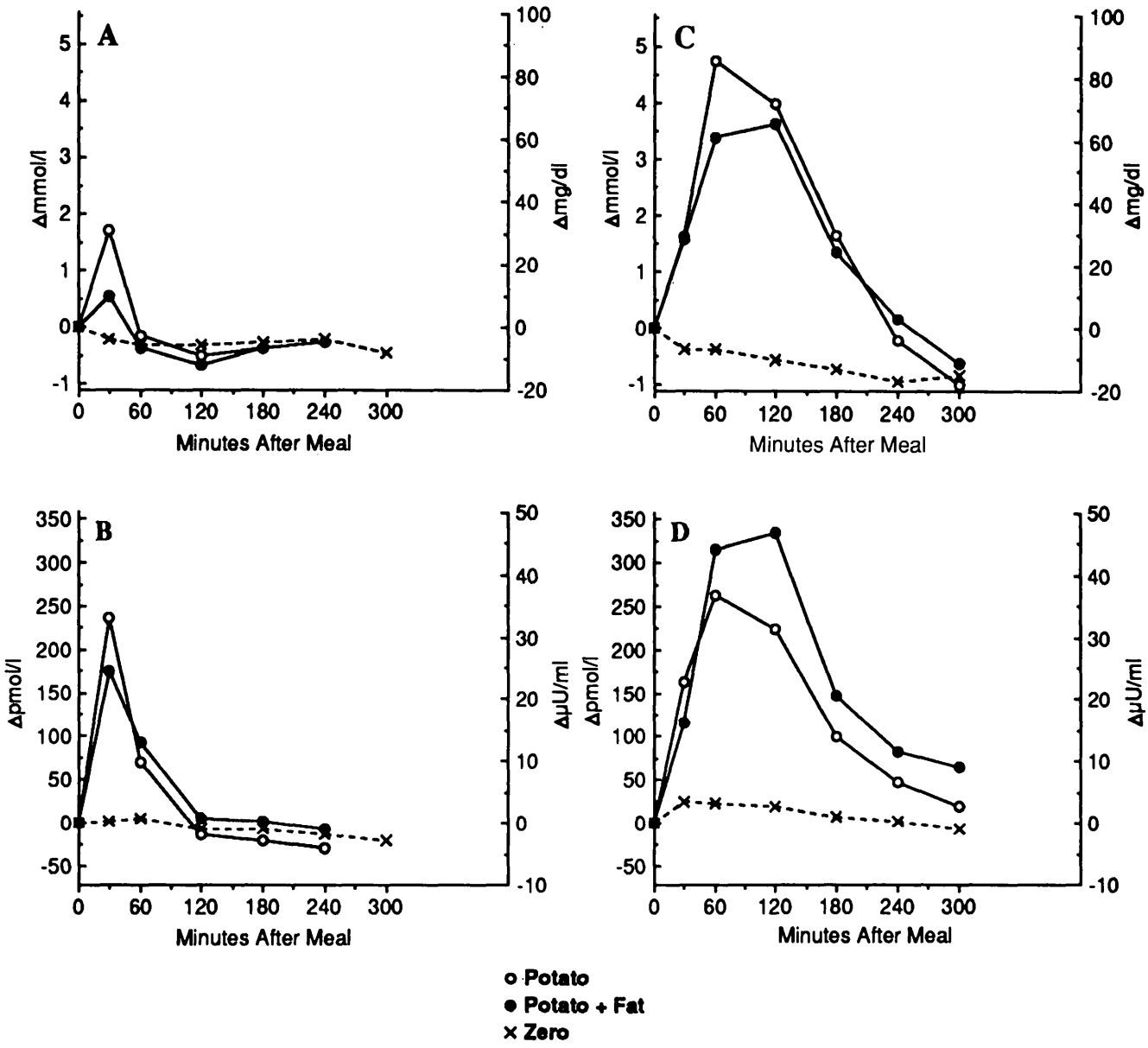

FIG. 7. Glucose and insulin responses to ingestion of 50 g starch (potato) or 50 g starch plus 50 g fat (butter) by nondiabetic or non-insulin-dependent diabetic subjects (mean fasting glucose 5.2 mM [93 mg/dl] in nondiabetic subjects, 7.6 mM in diabetic subjects; mean fasting insulin 101 pM [14 μU/ml] in nondiabetic subjects, 194 pM in diabetic subjects). *A*: effect of fat on plasma glucose (nondiabetic subjects n = 10). *B*: effect of fat on serum insulin. *C*: effect of fat on plasma glucose (non-insulin-dependent diabetic subjects n = 6). *D*: effect of fat on serum insulin.

required for GIP to potentiate glucose-stimulated insulin secretion in nondiabetic people (112–114). This suggests other incretins were playing a large role here.

NIDDM subjects. In preliminary studies, we found a different response in people with untreated NIDDM with the same study protocol and foods. In these subjects, the plasma glucose curves were similar whether butter was present in the meal or not. This is in contrast to the smaller glucose response in nondiabetic subjects when butter was ingested with the potato. However, the insulin-area response was ~45% greater. This additional rise in insulin appears to occur with amounts of fat as small as 5–15 g (unpublished observations). These data support the concept that starch digestion and/or glucose absorption rates were not affected by the presence of butter in the nondiabetic subjects. They also suggest that potentiation of an insulin effect on glucose disposal is not occurring in the NIDDM subjects, i.e., the efficiency of glucose disposal is not being facilitated. In less detailed studies, Estrich et al. (66) also reported little difference in the plasma glucose response to 50 g glucose when 40 g of avocado oil was ingested simultaneously. In addition, the insulin response appeared to be little different in these NIDDM subjects whether or not fat

was ingested, although values were not obtained in all subjects.

Our data in NIDDM and the data obtained in nondiabetic subjects need to be confirmed with other dietary sources of glucose or glucose itself. Different dietary fats also should be studied.

Incidentally, in nondiabetic subjects, 50 g butter ingested with 50 g protein (veal) was reported not to affect the insulin response when compared with the modest insulin response to the protein ingested alone (108). This also needs to be confirmed in more extensive studies. We are not aware of similar studies in untreated subjects with NIDDM.

NONESTERIFIED FATTY ACIDS

In people with untreated mild to moderately severe NIDDM, fructose, galactose, or protein ingestion all result in a highly significant decrease in serum nonesterified fatty acid concentration (49,78; unpublished observations) and thus alter the circulating fuel mixture available for oxidation. This occurs, although the circulating glucose concentration is little changed. An increase in nonprotein is likely, but has not been *RQ* studied in these subjects.

CONCLUSIONS

The studies reviewed indicate that the quantitative insulin response to various absorbed nutrients differs considerably in people with mild to moderately severe NIDDM compared with healthy people. The reasons for these differences are incompletely understood. Because of the differences, some caution should be exercised when applying information obtained in healthy subjects to NIDDM subjects.

It also is becoming increasingly clear that there are interactions between different ingested nutrients that result in metabolic responses that cannot be predicted from those of the individual nutrients. These interactions make the prediction of the metabolic response to a defined mixed meal potentially difficult. However, with the knowledge we have obtained from the study of individual macronutrients and constituent foods and an improved but still incomplete knowledge of the interaction of these foods on insulin secretion, we have been able to largely account for the glucose and insulin-area responses observed after the ingestion of a single defined mixed meal (115). We also were able to explain a smaller glucose area response and greater insulin response to the defined mixed meal compared with that of 50 g glucose in the same NIDDM subjects, although the mixed meal contained more potential glucose (68).

We are convinced that with additional investigations it will be possible to explain quantitatively not only the glucose and insulin responses to defined mixed meals, but also other metabolite responses such as fructose, galactose, amino acids, lactate, triglycerides, and nonesterified fatty acids. Such studies should provide some insight into the mechanisms by which fuel storage and utilization are regulated in the postprandial state. They also should provide some insight into the regulation of other hormones important in fuel metabolism such as glucagon, cortisol, and growth hormone and possibly catecholamines in healthy people and in those with NIDDM. For example, we have clearly shown an increase in serum cortisol in nondiabetic people after ingestion of mixed meals high in protein (116). We were not able to confirm a significant rise in growth hormone, although ingested protein was perviously reported to stimulate secretion (100,117).

Studies of the metabolic response to individual absorbed macronutrients and defined foods and the effect of incorporation of them into mixed meals also should provide a basis for the development and evaluation of diets for people with NIDDM in long-term studies. Overall, it is hoped that investigations such as reviewed herein ultimately lead to dietary recommendations for people with NIDDM that are based on firm scientific data.

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