The effect of coingestion of fat on the glucose, insulin, and gastric inhibitory polypeptide responses to carbohydrate and protein[1-3]

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ABSTRACT In the present study we examined the effect of coingestion of 50 g fat (butter) on the postprandial glucose, insulin, and gastric inhibitory polypeptide responses to 50 g carbohydrate (potato) or 50 g protein (low fat veal) in eight normal subjects. The coingestion of fat with either carbohydrate or protein resulted in greatly increased gastric inhibitory polypeptide responses, the effect being more pronounced with carbohydrate. The addition of fat to a carbohydrate meal also reduced the postprandial glucose response. This could have been due to several factors including a delayed glucose absorption, secondary to a fat-induced inhibition of gastric emptying. However, despite the lower blood glucose levels in the presence of fat the insulin response was not reduced, suggesting a potentiation of insulin secretion in the presence of fat. Thus, despite the apparent improvement in glucose tolerance when carbohydrate is ingested together with fat, the accompanying potentiation of insulin secretion could form the basis of long-term changes in insulin sensitivity which accompany alterations in dietary fat intake. *Am J Clin Nutr* 1983;37:941-944.

KEY WORDS Glucose, insulin, gastric inhibitory polypeptide, insulin sensitivity, fat, carbohydrate, protein

Introduction

Epidemiological studies have linked the consumption of high fat, low carbohydrate diets with increased prevalence of diabetes in populations all over the world (1, 2). Although the precise mechanism by which such diets increase the risk of type 2 (or noninsulin dependent) diabetes mellitus remains to be elucidated, it may be related to reduced sensitivity of target tissues to insulin (3–6). Almost 50 yr ago Himsworth established the dietary link between glucose tolerance and insulin sensitivity by showing that those factors which improved glucose tolerance (high complex carbohydrate, low simple carbohydrate, low fat) also increased sensitivity to insulin (7–9). Despite these observations, diets low in carbohydrate and high in fat have been widely used in the treatment of diabetes (10), possibly because they were shown to reduce postprandial hyperglycemia acutely (11).

In the present study we have examined the acute metabolic responses to different dietary components (carbohydrate and protein) by measuring the profiles of glucose, insulin, and gastric inhibitory polypeptide (GIP) in peripheral blood, with particular emphasis on the effects of coingestion of fat. In an attempt to understand better the relationship between acute changes in metabolism and diet, we chose common foods with appropriate constituents: potato (high carbohydrate), low fat veal (protein), and butter (lipid) rather than using purified examples of carbohydrate, protein, and fat.

Materials and methods

Subjects

Eight lean, weight-stable subjects (four women and four men) participated in the study. Their mean age was

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21.5 ± 1.5 yr, weight 66.8 ± 4.0 kg, and body mass index 21.2 ± 1.1 $kg \cdot m^{-2}$. During the study the subjects were on a weight maintaining diet that included at least 250 g carbohydrate each day. They were asked to eat the same evening meal on the night before each test and to abstain from alcohol for the 24 h preceding the test. The studies were performed on an outpatient basis after a 12-h overnight fast. This study was carried out in accord with the updated Helsinki Declaration and was approved by the Ethics Committee of the Alfred Hospital, Prahran, Victoria, Australia.

Metabolic studies

Four test meals were consumed in random order: 50 g carbohydrate (as whole, unpeeled, boiled potato, 284 g) with or without 50 g fat (as butter, 63 g); 50 g protein (as veal, 250 g) with or without 50 g fat (as butter, 63 g). The veal had a fat content of 1.4%, equivalent to 3.5 g in the 250 g meal.

The meals were freshly prepared on the morning of the study and were served within a few minutes. Zero time was taken as the time eating commenced. Blood samples were drawn for glucose, insulin, and GIP measurements in the fasting state and 0.25, 0.5, 1, 1.5, 2, 3, and 4 h postprandially.

Analytical methods

Samples for plasma glucose measurements were collected in fluoride oxalate tubes and analyzed by the glucose oxidase method using a YSI model 23AM glucose analyzer. Plasma immunoreactive insulin concentrations in heparinized plasma were measured using dextran-coated charcoal for precipitation of free hormone after reaction of hormone with commercially available anti-insulin serum (Burroughs-Wellcome). Human insulin (Novo) was used as the standard. Blood samples for GIP measurements were collected in heparinized tubes containing 3 mg Aprotinin (Trasylol) per 10 ml blood. Immunoreactive GIP concentrations in plasma were measured by double antibody radioimmunoassay (12). GIP antiserum exhibited <1% cross-reactivity with cholecystokinin, insulin, pancreatic polypeptide, pancreatic glucagon, porcine gut glucagon-like immunoreactivity, secretin, or vasoactive intestinal polypeptide.

Data analysis

Two-way analysis of variance, paired *t* test, and "Student's" *t* test were used for statistical comparisons. The area under the incremental postprandial glucose, insulin and GIP curves was calculated by subtracting the area under the basal concentration from the total area under the concentration-time curves which were calculated using the trapezoidal rule.

Results

The glucose responses to the four test meals are shown in **Figure 1**. The glucose response to carbohydrate alone was significantly greater ($p < 0.005$) than that to carbohydrate and fat. As expected, plasma glucose concentration did not change after the protein meal either in the presence or absence of fat.

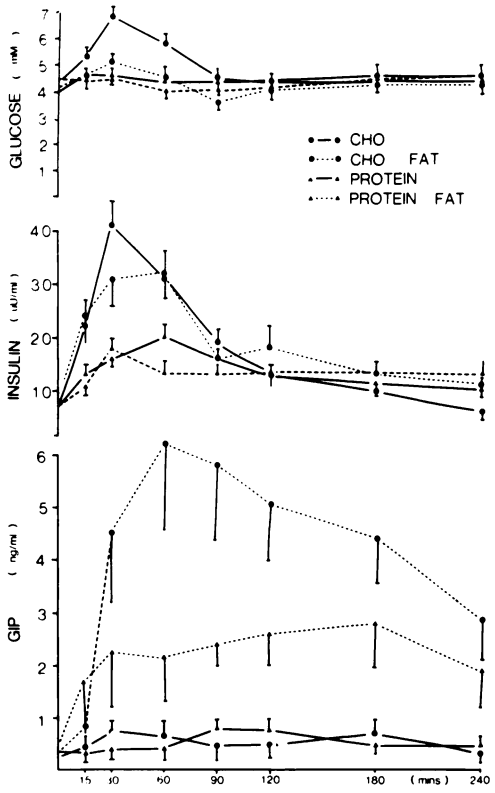

FIG 1. Plasma glucose, insulin, and GIP responses to 50 g carbohydrate ± 50 g fat and 50 g protein ± 50 g fat. Mean ± SEM (n = 8).

The plasma insulin responses to the meals showed a different pattern to that observed with glucose. The insulin response to carbohydrate alone was not significantly different from that to carbohydrate and fat. Similarly, the insulin response to protein, although quantitatively smaller, was not affected by the coingestion of fat.

The results are summarized in **Figure 2** as areas under the incremental curves for 0 to 1 h where it can be clearly seen that the coingestion of fat with carbohydrate greatly reduced the glucose response to carbohydrate ($p < 0.005$) while not significantly affecting the insulin response. When these results are expressed as a ratio of area under the curve (AUC) of insulin to glucose, the effect of fat on the insulin response to glucose or fat becomes even more striking: $^{AUC}insulin/^{AUC}glucose$ = 14.8 ± 2.3 $\mu U \cdot \mu mol^{-1}$ for carbohydrate alone and 46.6 ± 14.2 $\mu U \cdot \mu mol^{-1}$ for carbohydrate plus fat.

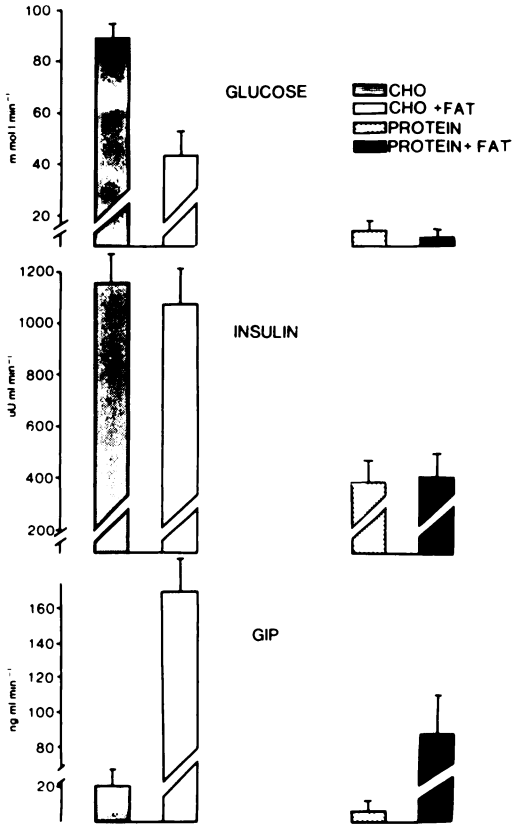

FIG 2. Areas under the incremental curves for glucose, insulin, and GIP for the 1st h after ingestion of 50 g carbohydrate ± 50 g fat and 50 g protein ± 50 g fat. Mean ± SEM (n = 8).

The plasma GIP responses to each meal are also presented in Figures 1 and 2. The GIP response to carbohydrate and fat was eight times higher ($p < 0.005$) than that to carbohydrate alone. Similarly, the coingestion of fat with protein resulted in a greatly increased GIP secretion ($p < 0.005$). The GIP response to fat ingested with carbohydrate was almost twice as high as that to fat ingested with protein ($p < 0.005$). The GIP concentrations were still elevated 4 h after fat ingestion, whereas 4 h after protein or carbohydrate alone they had returned to base-line values.

Discussion

The major finding in this study was that the coingestion of fat with a carbohydrate meal reduced the postprandial glucose response to the carbohydrate load, but had no effect on the insulin response.

There are several possible factors that could have contributed to the lower glucose response to carbohydrate in the presence of fat. The most likely explanation is a delayed glucose absorption from the small intestine secondary to the fat-induced delay in gastric emptying (13), although the possibility cannot be excluded that an increased hepatic uptake of glucose occurs after the coingestion of fat or even an increased rate of glucose uptake by tissues such as adipose and muscle.

However, despite the reduced blood glucose levels in the presence of fat, the insulin response was not affected. In other situations where blood glucose responses to carbohydrate meals have been reduced (eg, the addition of viscous fiber supplements to glucose [14] or reduced rate of starch digestion [15]) the insulin responses were also markedly reduced. Maintained insulin levels in the setting of decreased glucose levels could be explained in several ways. Although we cannot exclude the possibility that fat ingestion may alter the hepatic extraction of insulin, the simplest explanation would invoke the potentiation of insulin secretion by the coingestion of fat. One possible mechanism by which potentiation of the insulin response to glucose could occur is via GIP. Fat is a potent stimulus for GIP release and GIP has been shown to potentiate glucose-induced insulin secretion (16–18).

Irrespective of the mechanism for the apparent potentiation of glucose-induced insulin secretion in the presence of fat, the results are consistent with the observations of Dobbs et al (19) who reported that the intraduodenal administration of fat to dogs greatly increased the circulating insulin concentration in response to an intravenous glucose infusion, while glucose concentrations remained unchanged. These findings suggest that insulin secretion in response to a given glucose concentration was potentiated in the presence of fat (analogous to our observations in the present study). However, since the glucose concentration did not fall under these circumstances, it is possible that target tissue (hepatic and/or extra hepatic) sensitivity to the action of insulin in facilitating glucose transport was reduced after fat ingestion.

Another major finding of interest in this study concerned GIP secretion. The addition of fat to either the carbohydrate or protein

meals gave rise to a greatly increased GIP response. This confirms previous reports that fat is the most potent dietary stimulant of GIP secretion (20, 21). GIP levels remained elevated for at least 4 h after fat ingestion, which probably reflects slow digestion and absorption of the fat. The possibility that GIP has a role in fat assimilation cannot be excluded. Indeed, a preliminary report of GIP increasing lipoprotein lipase activity in preadipocytes would support such a role (22). The lower GIP responses after fat and protein than after fat and carbohydrate may suggest that protein has inhibited fat-induced GIP secretion. This conclusion is supported by previous findings in which alanine or arginine ingestion was shown to inhibit fat-induced GIP secretion in the dog (23). However, in the absence of information on the GIP response to 50 g fat alone, the lower GIP response after fat and protein relative to that after fat and carbohydrate is difficult to interpret.

These changes found after the coingestion of fat may indicate an acute insulin insensitivity or at least a potentiation of insulin secretion which could form the basis of the insulin resistance associated with the chronic consumption of high fat diets. Thus, despite the apparent improvement in blood glucose levels which occurs when carbohydrate is ingested together with fat, the observation that the insulin levels were not reduced suggests that increasing the fat content of meals would not be beneficial for diabetics.

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