Hypersecretion of Gastric Inhibitory Polypeptide Induced by Glucose Ingestion in Diabetes Mellitus

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Abstract

The response of plasma immunoreactive gastric inhibitory polypeptide (GIP) to oral glucose loading was determined in 10 normal subjects, 10 patients with mild diabetes mellitus, and 10 patients with moderate to severe diabetes mellitus. In normal subjects the mean fasting GIP was 167±17 pg/ml which rose significantly after glucose loading, reaching the peak value of 513±44 pg/ml at 30 min. In mild diabetic patients, fasting plasma GIP was not significantly different from that in normal subjects. However, the mean peak GIP level following glucose loading was 683±71 pg/ml, significantly higher than that in normal subjects (p<0.05). In moderate and severe diabetics, oral glucose loading caused an abrupt rise in plasma GIP from the basal level of 304±31 pg/ml to the peak of 870±63 pg/ml occurring at 30 min, both of which were significantly higher than the corresponding values in normal subjects (p<0.01). These results suggest that GIP response to oral glucose loading is enhanced in diabetic patients in proportion to the degree of their glucose intolerance.

Gastric inhibitory polypeptide (GIP) is known to enhance insulin secretion induced by glucose and, therefore, is considered to play an important role in the entero-insular axis. Crockett et al. (1976) and Ross et al. (1977) reported that plasma GIP response to oral glucose loading was exaggerated in diabetes mellitus. However, May and Williams (1978) failed to demonstrate the exaggerated GIP response in mild diabetic patients. Moreover, Reynolds et al. (1979) observed significantly diminished GIP response to glucose ingestion in insulin-dependent diabetics. Because of such discordant results, we chose to compare plasma GIP responses to glucose ingestion in mild, moderate, and severe diabetic patients.

Materials and Methods

Subjects

Ten normal volunteers aged 17 to 68, 5 males and 5 females, who had no family history of diabetes were studied. Twenty patients with primary diabetes mellitus were diagnosed by means of the oral glucose tolerance test, excluding endocrine, liver and pancreatic diseases which might cause glucose intolerance. The criteria for diabetes proposed by the Japan Diabetes Association (Kuzuya, 1970) were used to evaluate the glucose tolerance curve: patients with blood glucose concentrations exceeding 160 mg/dl at 60 min and 130 mg/dl at 120 min after oral administration of 50 g glucose are defined as diabetics; those with blood glucose concentrations below 100 mg/dl at 0 min, 140 mg/dl at 60 min, and 100 mg/dl at 120 min are defined as normal. Ten diabetic patients, aged 30 to 71, 7 males and 3 females, with fasting blood glucose levels less than 140 mg/dl and with glucose tolerance curves typical of diabetes were de-
fined as mild diabetics; whereas the other 10 diabetic patients, aged 28 to 68, 5 males and 5 females, with fasting blood glucose levels exceeding 140 mg/dl were defined as moderate and severe diabetics. The mean percent ideal body weight in normal subjects, mild diabetics and moderate and severe diabetics was 103 ± 2%, 109 ± 2% and 112 ± 3%, respectively. No subjects had ever been treated with insulin or received any anti-diabetic medication for at least 6 months before the study.

**Oral glucose tolerance test**

After an overnight fast, 50 g of glucose dissolved in 200 ml of water was ingested by all subjects. Blood was withdrawn before and 15, 30, 60, 90, 120, 150, and 180 min after the glucose loading. Blood was withdrawn from the antecubital vein into heparinized disposable plastic syringes. An aliquot of the blood was used for the determination of blood glucose with a Technicon Auto Analyzer (Hoffman, 1937). Another 2 ml aliquot of blood for GIP determination was placed promptly into chilled tubes containing 2,000 U of Trasylol in a volume of 0.2 ml. The mixture was immediately centrifuged at 4°C and the plasma was separated, frozen, and stored at -20°C until assayed. The remaining portion was centrifuged, and the plasma was separated, frozen, and stored at -20°C for the measurement of insulin. Plasma insulin was measured by the polyethylene glycol method (Desbuquois et al., 1971).

**Radioimmunoassay of GIP**

GIP was measured by the method by Kuzio et al. (1974), with minor modifications. Porcine GIP (Dr. J. C. Brown, University of British Columbia, Vancouver, Canada) was used as the standard and also as the labeled hormone, which was prepared by the Chloramine T method of Hunter and Greenwood (1962). 125I-GIP and 125I were separated on a Sephadex G-25 fine column (0.9 x 30 cm). The fractions showing the least damage were used in the assay. The specific activity of 125I.GIP was calculated to be in the range of 90-200 μCi/μg.

The final volume of the incubation mixture was 1 ml, consisting of 100 μl of 125I-GIP of 3 x 10^6 cpm, 100 μl of standard GIP or unknown serum samples, 100 μl of anti-sera GP-01 (Dr. J. C. Brown; final dilution; 1: 40,000), and 700 μl of diluent buffer (0.04M PO4 buffer pH 6.5, 0.5% BSA, 0.75% Trasylol). Incubation was performed at 4°C for 48 hr. Separation of bound and free fractions was carried out using polyethylene glycol (final concentration were 12.5% (w/v)). B/F values were first examined in the range of pH 6.5-8.0, but no significant change was found. The minimal detectable quantity by this assay was about 60 pg/ml (Fig. 1). Inter-assay variation was less than 17%. The GIP antibody used has been shown to have no significant cross-reactivity with other pancreatic or gastrointestinal hormones. Statistical analysis was performed by either Student’s *t* test or paired *t* test.

**Results**

**Normal subjects** (Fig. 2): Blood glucose concentrations rose from the mean (±SE) basal level of 87 ± 3 mg/dl to the mean peak value of 131 ± 6 mg/dl 30 min after oral glucose loading. The mean basal plasma insulin concentration was 8.7 ± 2.3 μU/ml, which increased significantly, reaching a peak 30 min after glucose administration. The plasma GIP level rose promptly after oral glucose loading, reaching the peak value of 513 ± 44 pg/ml at 30 min, which was significantly higher than the mean...
basal concentration of $167 \pm 17 \text{ pg/ml}$ ($P < 0.01$).

**Mild diabetes** (Fig. 3): In mild diabetic patients, oral glucose loading caused an abrupt rise in plasma GIP from the basal concentration of $238 \pm 33 \text{ pg/ml}$ ($P > 0.05$ vs. normal subjects) to the peak value of $683 \pm 71 \text{ pg/ml}$ occurring at 30 min. The mean peak GIP was significantly higher than the corresponding value in normal subjects ($p < 0.05$). The mean peak plasma insulin concentration induced by glucose ingestion was $38 \pm 6.6 \mu\text{U/ml}$, which was not significantly different from the corresponding value in normal subjects. In this group oral glucose loading elicited a significantly greater rise in blood glucose from the basal level of $105 \pm 8 \text{ mg/dl}$ to the peak value of $184 \pm 15 \text{ mg/dl}$, which occurred 60 min after the glucose loading.

**Moderate and severe diabetes** (Fig. 4): In this group of diabetics, fasting blood glucose levels were markedly elevated to the mean value of $203 \pm 25 \text{ mg/dl}$. Oral
Fig. 4. Plasma IR-GIP, insulin, and blood glucose levels induced by 50 g oral glucose administration in 10 moderate and severe diabetics. Closed circle and solid line represent means ± SEM in moderate and severe diabetics. Broken line shows the mean level in normal subjects. (*P < 0.05, **P < 0.01)

glucose loading elicited no significant response of plasma insulin. The mean fasting GIP level was 304 ± 31 pg/ml, which was significantly higher than that in normal subjects (p < 0.01). Glucose ingestion caused a greater rise in plasma GIP than in normal subjects. The mean peak plasma GIP in these patients occurred 30 min after glucose ingestion and was 870 ± 63 pg/ml, which was significantly higher than that in normal subjects (p < 0.01).

Discussion

Crockett et al. (1976) and Ross et al. (1977) have demonstrated that plasma GIP response to oral glucose loading is exaggerated in untreated diabetic patients. The present study confirms these observations and further demonstrates that plasma GIP response to glucose ingestion is enhanced even in mild diabetes. May and Williams (1978), however, reported no enhancement of GIP response to oral glucose loading in mild diabetes when compared with normal subjects. The reason for this discrepancy is not clear, but differences in blood glucose and plasma insulin levels during oral glucose loading may be important; the diabetic subjects studied by May and Williams (1978) had milder glucose intolerance and more circulating insulin.

The mechanism responsible for the exaggerated GIP response to glucose ingestion, though not clear at present, deserves consideration. Recent studies (Brown et al., 1975; Crockett et al., 1976; Ross et al., 1977) have suggested that the augmented GIP release to glucose ingestion in diabetics may be the result of attenuated insulin secretion. In the present study we have observed that plasma insulin response to glucose is significantly impaired in moderate-to-severe diabetics, and even in mild diabetics insulin release is delayed and inappropriate for the amount of circulating glucose. Therefore, our findings that GIP response to oral glucose loading is increased in proportion to the severity of impaired insulin secretion lend support to this hypothesis. The effect of insulin on GIP secretion, however, is still controversial and inconclusive. Creutzfeldt et al. (1980) have demonstrated that the infusion of insulin alone or together with glucose significantly suppresses the GIP rise after fat ingestion, but does not alter the GIP response to oral glucose in juvenile diabetes. On the other
hand, Sirinek et al. (1978) reported that insulin is capable of attenuating the GIP response to glucose in a negative feedback fashion in dogs. The final answer must await further studies on this problem.

Recently, Reynolds et al. (1979) have reported that there is a significantly lower response of GIP secretion to oral glucose loading in insulin-dependent diabetics than in normal subjects. This contrasts with the results of our present study. But our diabetic subjects were untreated, and findings seen in well established diabetes are not necessarily characteristic of the early stages of the disease.

We conclude, therefore, that impaired insulin secretion accompanied by hyperglycemia probably, at least in part, contributes to the hypersecretion of GIP in diabetic patients.

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References


