

Insulin-Lowering Effect of Phenformin Not Mediated by Inhibition of Gastric Inhibitory Polypeptide (40389)

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The oral hypoglycemic drug, phenformin, is known to decrease the plasma insulin response to an oral glucose load in humans (1). This insulin-lowering effect, after oral but not intravenous glucose, is felt by other investigators (2, 3) to result from the high concentration of phenformin absorbed by enterocytes, which decreases their rate of glucose absorption and consequently provides a lesser glycemic stimulus to the β cell.

Recently, evidence has arisen that suggests that gastric inhibitory polypeptide (GIP) is the major gut factor augmenting the insulinotropic effect of oral glucose (4, 5). Since cells releasing this hormone are exposed to high concentrations of ingested phenformin, we investigated the possibility that inhibition of GIP release contributes to the reduced insulin response to ingested glucose during administration of phenformin in humans.

Materials and methods. Seven obese but otherwise healthy adults (125-250% ideal body weight; 5 women and 2 men) participated in this study after their informed consent was obtained. They were given standard oral glucose loads (100 g in 250 ml water) after an overnight fast, following 3 days of preparatory diet (at least 300 g carbohydrate). All subjects had normal fasting glycemia, except for one woman with a fasting plasma glucose level of 270 mg/dl. None was receiving any medication. Blood was collected at baseline and at 15-min intervals for 2 hr after glucose ingestion. Plasma glucose, serum immunoreactive insulin (IRI), and serum GIP were measured by previously described methods (1, 6). A similar study was performed after subjects had received oral phenformin (DBI-TD), 50 mg t.i.d. for 3 days, including the morning of the repeat test.

Plasma glucose, IRI, and GIP responses were plotted as a function of time for each subject during the tests performed before and after phenformin administration. Areas were

then calculated to give the integrated responses above baseline. Statistical evaluation of each individual's response to phenformin

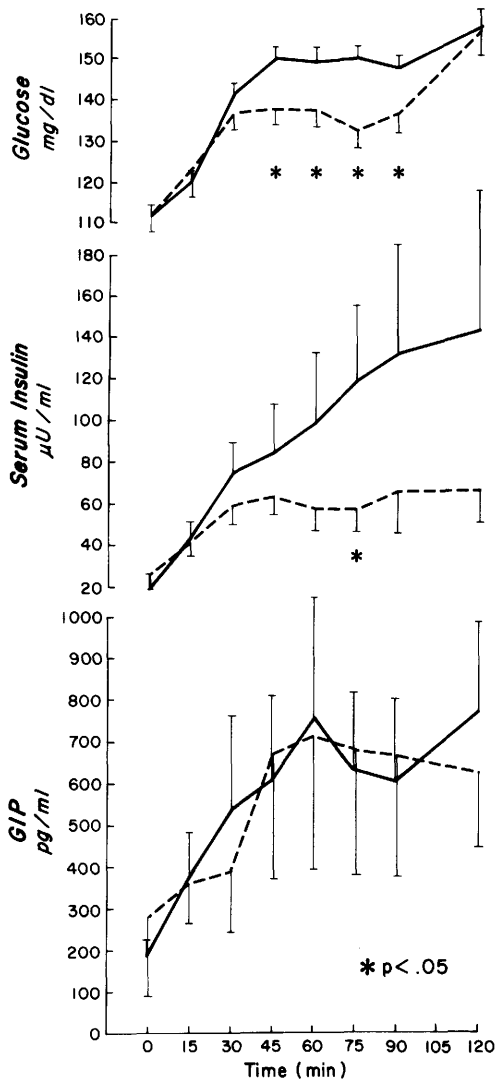


FIG. 1. Mean plasma glucose, IRI, and GIP curves (\pm SEM) after ingestion of 100 g glucose before (solid line) and during (broken line) phenformin treatment in 7 obese subjects.

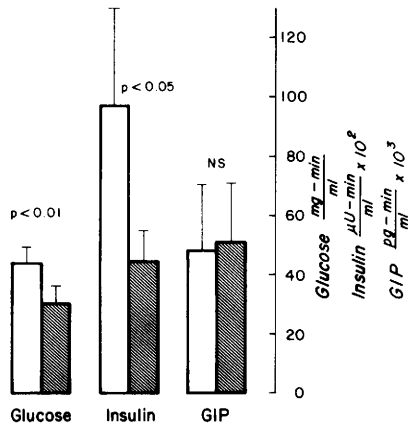


FIG. 2. Total integrated area above baseline beneath the response curves for plasma glucose, serum IRI, and serum GIP after 100 g oral glucose, as measured before and during (hatched bars) phenformin treatment. Results are expressed as mean \pm SEM.

was performed using paired *t* testing.

Results and discussion. Mean plasma glucose and serum IRI responses after oral glucose were decreased during phenformin administration, whereas GIP levels were unaffected (Fig. 1). The mean integrated areas under the curves affirm the statistical significance of the glucose- and insulin-lowering actions of phenformin while showing no effect on serum GIP (Fig. 2). The above values for GIP are similar to those previously reported after oral glucose (6).

This study demonstrates that the GIP response to oral glucose is not reduced by doses of phenformin that significantly lessen the IRI response to the ingested glucose. Therefore, a reduction of GIP levels is not responsible for the decreased IRI response to oral glucose associated with phenformin treatment. Similarly, glucagon, another β -cytotropic hormone, has been shown not to be lowered by phenformin (7, 8).

Since data from our laboratory have previously shown that therapeutic levels of phenformin show no direct inhibitory effect on glucose-induced IRI release from the perfused rat pancreas (9), it appears that the insulin-lowering effect of phenformin after oral glucose is primarily a consequence of a decrease in the glycemic stimulus to pancreatic β cells.

Summary. In 7 obese subjects treated with phenformin, serum insulin and plasma glucose responses to oral glucose were significantly reduced, but serum gastric inhibitory polypeptide (GIP) levels were not significantly changed. These results indicate that the insulin-lowering effect of phenformin on glucose-induced insulin release is not mediated by alterations in GIP levels.

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