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STIMULATION OF INSULIN SECRETION BY GASTRIC INHIBITORY POLYPEPTIDE IN MAN.[1]

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ABSTRACT. The effect of very highly purified gastric inhibitory polypeptide (GIP) on insulin secretion in man was tested in normal volunteers. Administration of physiological doses of GIP together with glucose by IV infusion resulted in potentiation of the rise in IRI in the blood and improvement in glucose tolerance. It is concluded that GIP is a potent insulinotropic hormone and probably takes part in physiological potentiation of insulin secretion in response to hyperglycemia during absorption of nutrients from the intestine.

Studies with various preparations containing peptides derived from extracts of porcine duodenojejunal mucosa have suggested that the intestinal hormones secretin and pancreozymin-cholecystokinin (PZ-CCK) are capable of potentiating the rise in insulin in the blood in response to hyperglycemia in man (1). In addition to stimulating insulin secretion the very highly purified preparation of secretin and the relatively crude preparations of PZ-CCK (10% PZ-CCK) used in earlier experiments produced significant improvement in glucose tolerance during intravenous infusions of glucose of two hours duration (2). However, studies in the secretion of rat insulin have shown that the stimulatory effect of 10% PZ-CCK is not reproduced with highly purified ("pure") PZ-CCK (3). Gastric inhibitory polypeptide (GIP), recently identified and characterized as an inhibitor of gastric acid secretion in dogs (4,5), is probably a physiological enterogastrone, and is present in 10% PZ-CCK to the extent of 10-15% by weight (6). Studies with very highly purified GIP have shown that the stimulation of increments in immunoreactive insulin (IRI) in the blood in rats by 10% PZ-CCK can be reproduced by administration of GIP in amounts corresponding to those present in effective doses of 10% PZ-CCK (7). We have therefore examined the effects of very highly purified GIP in man.

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MATERIALS AND METHODS

Normal volunteers were tested in the morning after they had fasted overnight. Very highly purified GIP was infused intravenously at the rate of 1 µg/min for a total period of 30 minutes. GIP was prepared according to procedures employed in its identification (4,5) and was more than 95% pure. Infusates contained human serum albumin 1 mg/ml in normal saline or in glucose 10g%. Glucose was delivered at 0.5 gm/min for 60 min. Insulin and GIP in serum were estimated by radioimmunoassay. In the assay for GIP no interfering cross-reaction was detected with glucagon, secretin, vasoactive intestinal polypeptide, gastrin, or pancreozymin-cholecystokinin (6). Plasma glucose was estimated using glucose oxidase in a Beckman glucose analyzer.

RESULTS

In six subjects who received GIP intravenously at the rate used in this study the concentration of GIP in the serum reached a mean peak value of approximately 1 ng/ml by 30 minutes; this concentration is attained in normal subjects after ingestion of glucose (8). The intravenous infusion of GIP in saline at this rate in five normal subjects had no significant effect on plasma glucose or serum IRI concentrations. As shown in the Figure, in six subjects the intravenous infusion of glucose alone caused a

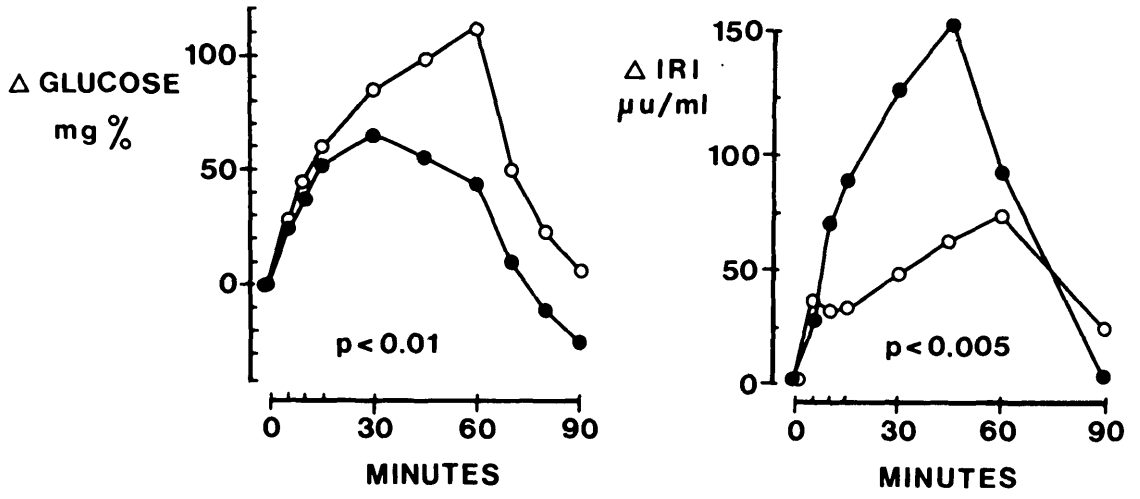

Figure. Mean changes in plasma glucose and serum IRI in 6 subjects receiving IV glucose alone (open symbols) or IV glucose with GIP (solid symbols). P values refer to the significance of paired differences in incremental areas through the period 0-60 minutes.

progressive rise in the mean serum IRI concentration to a peak attained at 60 minutes. When GIP was added to the glucose infusion the rise in IRI in serum in the same subjects was greater in every case. The effect of GIP was evident early in the course of infusions, and in spite of variability of insulin responses among the subjects, the mean of paired differences in incremental IRI was significant at 15 minutes ($p < .05$). When GIP was administered IRI in serum attained a peak shortly after termination of delivery of the peptide at 30 min., and fell sharply between 40 and 60 min., suggesting that the insulinotropic effect of GIP is short-lived. The mean integrated increase in IRI during infusion of glucose with GIP was more than 200% that evoked by glucose alone: in terms of the mean of paired differences this was statistically significant ($p < .005$). When GIP was added to the glucose infusion the mean rise in plasma glucose fell below that produced by infusion of glucose alone at 30 minutes when the mean of paired differences was statistically significant ($p < .05$). The integrated increase in glucose through the period of infusion of glucose on the occasion when GIP was administered was reduced to 66% that produced by glucose alone: in terms of the mean of paired differences this was statistically significant ($p < .01$).

DISCUSSION

In the present study highly purified GIP was administered in doses slightly smaller than those now known to have been present in the crude preparations of PZ-CCK used in earlier studies in man. Administration of the hormone produced no subjective effects in the volunteers and resulted in a rise in the concentration of GIP in serum within the range observed in normal subjects after ingestion of glucose. On administration of the peptide to fasted subjects the small mean increment in IRI in serum was not statistically significant, and there was no detectable change in the concentration of glucose in plasma. Administration of the same dose of GIP together with glucose greatly potentiated the rise in IRI in the serum during hyperglycemia, and significantly improved

the glucose tolerance curve. These effects of GIP correspond to those of 10% PZ-CCK administered in doses containing similar amounts of GIP. We therefore conclude that GIP is the major active agent present in 10% PZ-CCK that affected insulin secretion in earlier studies of the effects of this preparation on the response to intravenous infusion of glucose.

The results of these experiments demonstrate that porcine GIP administered intravenously together with glucose in normal man, in doses that produce increments in GIP and glucose in the blood within the ranges observed after ingestion of standard loads of glucose, leads to potentiation of insulin secretion and improvement of glucose tolerance. The magnitudes of these effects suggest that this hormone is capable of accounting for a major part of the differences in insulin secretion and glucose tolerance observed in comparisons of effects of administration of glucose by intravenous and enteric routes in man (9, 10). While the effects of very small doses of secretin on insulin secretion with disproportionate improvement in glucose tolerance in man (11) suggest that this hormone may also contribute effects in the so-called entero-insular axis, evidence related to the secretion of this hormone in response to intestinal absorption of glucose is conflicting (12,13). Furthermore, evidence of the occurrence of effects of humoral secretions of the intestine on the disposal of glucose by means not simply related to their actions on the endocrine pancreas (14,15) implies that the physiological role of intestinal hormones in the regulation of the metabolism of glucose may be highly complex. Nevertheless the present observations suggest that GIP is a major component of the entero-insular axis operating in response to absorption of glucose from the gut, and indicate the importance of characterizing the functions of this hormone in carbohydrate metabolism in man in health and disease.

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