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SHORT COMMUNICATIONS

Gastric Inhibitory Polypeptide: Effect on Glucose-Induced Insulin Release from Isolated Rat Pancreatic Islets *in Vitro*

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Summary. Gastric Inhibitory Polypeptide (GIP; 1 or 10 μg/ml) potentiated glucose-induced (8 or 16.6 mM) insulin (IRI) release from isolated rat pancreatic islets. Basal release was unaffected. The threshold concentration of glucose necessary for GIP to modulate IRI release was between 6 and 8 mM. GIP had no effect on IRI release from islets submitted to a maximal glucose stimulus (25 mM).

Key words: Gastric inhibitory polypeptide, insulin release, isolated rat islets, enteroinsular axis.

Gastric inhibitory polypeptide (GIP), a 43 amino acid polypeptide from porcine duodenal mucosa [1, 2], known to inhibit acid secretion from the stomach [3], was recently shown to stimulate insulin (IRI) release *in vivo* [4]. Purified porcine GIP administered intravenously with glucose to normal man augmented IRI secretion and improved glucose tolerance [4].

We have studied whether GIP is able to stimulate IRI-release *in vitro*. A marked stimulatory action of GIP on glucose-induced IRI-release from isolated rat pancreatic islets was found.

Materials and Methods

Fed, male Wistar rats (200–250 g) were used throughout the study. Bovine serum albumin (lot ORHD 20) was purchased from Behringwerke A.G., Marburg, ^{125}I-porcine-insulin (specific activity 150–200 mC/mg) from Farbwerke Hoechst A.G., Frankfurt. Crystalline rat insulin was a gift from Novo Research Institute, Copenhagen, Denmark. GIP (lot 26–6–74 B and 30–4–75 G) was obtained as previously described [1, 2].

Islets were isolated from rat pancreas by collagenase [5] 2 hrs after intraperitoneal administration of 0.6 ml pilocarpine hydrochloride (2% w/v) to decrease the content of proteases in the pancreas [6]. Incubations were performed as previously described [7] with the concentrations of glucose and GIP as indicated in Table 1. The insulin content of the medium was determined by radioimmunoassay with rat insulin as reference standard [8]. IRI release was expressed as ng/10 islets/45 min.

Table 1. *Stimulatory effect of gastrointestinal polypeptide (GIP) on glucose-induced insulin (IRI) release from isolated rat pancreatic islets. Mean values ± SEM are shown with the number of individual observations in parentheses. An asterisk indicates a significant difference from the respective control value ($P < 0.01$). Values for "P" were calculated by Student's "t" test based on nonpaired comparisons*

Glucose (mM)	GIP (μg/ml)	IRI release (ng/10 islets/45 min)
2.0	----	5.4 ± 0.5 (29)
2.0	10	6.1 ± 0.5 (26)
6.0	----	12.3 ± 1.0 (20)
6.0	10	13.9 ± 0.8 (20)
8.0	----	34.2 ± 3.5 (35)+
8.0	10	49.1 ± 3.3 (45)+
16.6	----	66.1 ± 1.7 (60)
16.6	1	71.8 ± 1.6 (60)+
16.6	10	80.6 ± 2.3 (60)+
25.0	----	76.3 ± 2.3 (26)
25.0	10	80.5 ± 4.9 (26)

Results

GIP had a stimulatory effect on glucose-induced IRI release (Table 1). In the presence of 8 or 16.6 mM glucose GIP (1 or 10 μg/ml) significantly increased IRI release from isolated rat pancreatic islets. "Basal insulin release" was unaffected, i.e., insulin output from islets incubated at a non-stimulatory glucose concentration (2 mM) with or without GIP (10 μg/ml) was identical. In the presence of a low stimulatory glucose concentration (6 mM) no additional effect of GIP on IRI release was seen. This indicates that the threshold concentration of glucose, necessary for GIP

to modulate IRI release *in vitro,* is between 6 and 8 mM. GIP (10 μg/ml) had no additional effect on IRI release from islets exposed to a maximal glucose stimulus (25 mM).

Discussion

The hypothesis of the existence of an enteroinsular axis has been suggested by the observation that the oral administration of glucose causes a greater rise in serum insulin levels than intravenous administration of glucose [9, 10]. It is at present unclear which of the gastrointestinal hormones or factors are part of the enteroinsular axis, i.e., which of the various gastrointestinal hormones is enhancing the assimilation of orally administered glucose via increased IRI release [11]. All known gastrointestinal hormones have been studied for their ability to stimulate IRI release *in vitro* and/or *in vivo.*

To test the IRI releasing capacity *in vivo,* gastrointestinal hormones are usually injected simultaneously with an i.v. glucose load. Before a gastrointestinal hormone can be considered a "physiological" stimulator of IRI release one has to prove that a pure preparation was used and that the hormone was injected in quantities that do not elevate serum levels above the ones reached after oral administration of glucose [11].

GIP seems to meet these criteria. A highly purified GIP preparation was shown to increase IRI release in man [4]. The dose of GIP infused in these studies elevated serum immunoreactive GIP levels not higher than 1 ng/ml, well within the range which can be achieved by physiological stimuli for GIP release [12, 13].

GIP is not only a modulator of glucose-induced IRI release *in vivo* but stimulates significantly glucose-induced IRI release *in vitro* (Table 1). The threshold concentration of glucose necessary for GIP to stimulate IRI release *in vitro* seems to be between 6 and 8 mM. GIP had no additional effect on IRI release from islets exposed to a maximal glucose stimulus (25 mM).

The concentration of GIP necessary to stimulate IRI release from rat islets *in vitro* (Table 1) is much higher than the serum concentration necessary to stimulate IRI release *in vivo* [14]. This does not seem to be caused by a major degradation of GIP during incubation since recovery studies showed only minor loss of immunoreactive GIP during the 45 min incubation period. However, during enzymatic isolation islets are submitted for 20 min to the action of collagenase and proteolytic enzymes derived from pancreatic exocrine cells. This might cause alteration in membrane structure possibly explaining the decrease in sensitivity of the B-cell's secretory mechanism towards the action of GIP.

Our findings on the stimulatory effect of GIP on glucose-induced IRI release *in vitro* are compatible with the concept that GIP might be a likely candidate for the gastrointestinal factor which, via stimulation of IRI release, enhances the assimilation of orally administered glucose.

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