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Gastric Inhibitory Polypeptide Increases Mesenteric Blood Flow[1] (40222)

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Gastric inhibitory polypeptide (GIP) inhibits histamine-, pentagastrin-, and insulin-stimulated gastric acid secretion (1) and potentiates glucose-stimulated insulin release (2). This recently described gastrointestinal peptide has 43 amino acids and 15 of the first 26 occur in the same position as porcine glucagon while 9 of these 26 are in the same position as in porcine secretin (3). While both glucagon (4) and secretin (5, 6) have been shown to produce mesenteric vasodilation, vascular actions of GIP have not been reported. However, GIP is released from the small intestine in response to intraluminal glucose (7) and fat (8), stimuli which have been previously associated with an increase in mesenteric blood flow (6, 9). Thus, this study was done to investigate the effects of GIP on superior mesenteric and femoral blood flow and also intestinal motility in the anesthetized cat. Our results indicate that GIP increases superior mesenteric blood flow, and possible physiological implications are discussed.

Materials and methods. Cats weighing between 2.0 and 3.6 kg were fasted for 18 hr and then anesthetized with pentobarbital 40 mg/kg. The left femoral artery and vein were cannulated to record arterial pressure and to inject drugs, respectively, after which a laparotomy was performed. Blood flow in the superior mesenteric and right femoral arteries was recorded with noncannulating Biotronex electromagnetic flow meter probes and flow meter. Zero-flow levels were obtained using miniature occluders (10). Mesenteric arterial vascular resistance was calculated by dividing mean systemic arterial pressure by mean superior mesenteric arterial blood flow. Portal venous pressure was not measured as previous glucagon studies showed only small responses, with inappreciable errors introduced if the response was neglected in calculation of mesenteric arterial resistance (4).

Intestinal motility was recorded in four of the cats via saline filled open-tip polyvinyl cannulas which were inserted through the wall of the stomach and directed into either the duodenum or jejunum. The pyloric junction was tied off and intestinal motility (pressure) recorded via Statham pressure transducers (Model P23-AC). Arterial blood pressure, intestinal motility, and superior mesenteric blood flow were continuously recorded on a Grass Model 7C polygraph and the animal's body temperature was maintained at 37–38° with a heating pad.

Gastric inhibitory polypeptide was a kind gift from Dr. John C. Brown, University of British Columbia, Vancouver, Canada. Glucagon was purchased from Eli Lilly and Company.

Results. Gastric inhibitory polypeptide was tested in random doses at least twice in each of six cats. Superior mesenteric blood flow during rest averaged 18.9 ± 2.5 ml/min per kg body wt (range 12.1–26.3). In all animals, iv infusion of GIP produced dose-dependent increases in superior mesenteric blood flow which began within one min and remained elevated for infusion periods of up to 20 min (Figs. 1 and 2). Threshold dose was around 0.25 μg/min. Mesenteric arterial blood flow gradually returned to control after termination of infusion, higher doses requiring periods of up to 15–20 min.

During the superior mesenteric blood flow response, arterial pressure remained essentially unchanged, indicating a fall in mesenteric vascular resistance (Table I). The decrease in mesenteric resistance produced by GIP was similar to that elicited by infusion of low doses of glucagon (Fig. 1). Neither

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GIP nor glucagon affected femoral arterial blood flow. Also, iv infusion of comparable volumes of saline produced no discernible cardiovascular responses.

Little spontaneous intestinal motility was observed in the animals in which it was recorded. However, when present spontaneous activity was inhibited during the period of GIP infusion (Fig. 2).

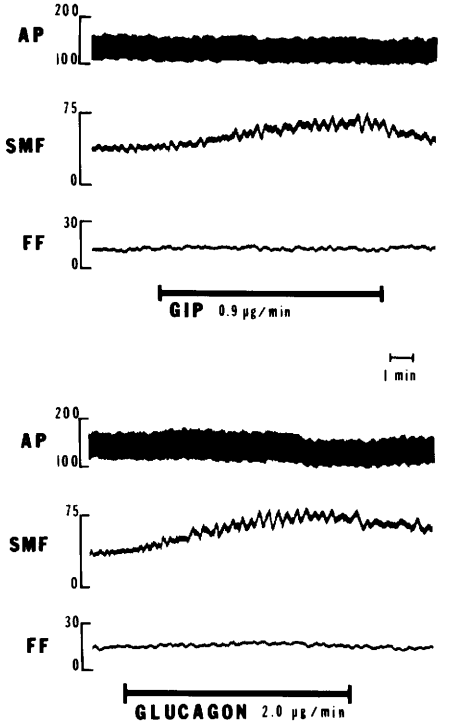

FIG. 1. Top: Intravenous infusion of gastric inhibitory polypeptide (GIP) at 0.9 µg/min produces an increase in superior mesenteric blood flow (SMF), but no change in systemic arterial pressure (AP) or femoral blood flow (FF). Bottom: The vascular response to intravenous glucagon infusion (2.0 µg/min) was similar to that of GIP.

Discussion. The results demonstrate that gastric inhibitory polypeptide (GIP) is a potent vasodilator in the mesenteric vascular bed. It produces dose dependent increases in superior mesenteric blood flow, but has no effect on hind limb blood flow or on systemic arterial pressure (Fig. 1). This selective decrease in mesenteric vascular resistance is similar to reported vascular effects of glucagon (4), and secretin (5, 6). Additionally, GIP shares with secretin and glucagon the ability to decrease small intestinal motility, an inhibitory motor action described previously for GIP on the body and antrum of the stomach (11).

The doses used in this study to achieve sizable increases in superior mesenteric blood flow are somewhat larger on a per kg body weight basis than those reported elsewhere to mimick blood levels or to inhibit gastric acid secretion. For example, in man infusion of

TABLE I.[a]

GIP dose (µg/min)	SMBF (ml/min per kg)	Change in Vascular Resistance (%)
0.45	22.2 ± 2	−14.7 ± 9
0.90	33.4 ± 4	−46.3 ± 4
1.80	44.0 ± 3	−56.0 ± 5

[a] Effect of intravenous infusion of gastric inhibitory polypeptide (GIP) on the mesenteric vascular bed. Superior mesenteric blood flow (SMBF) at rest averaged 18.9 ± 2.5 ml/min per kg body weight. Each dose was tested at least twice in the six different cats. Values are averages ± SE.

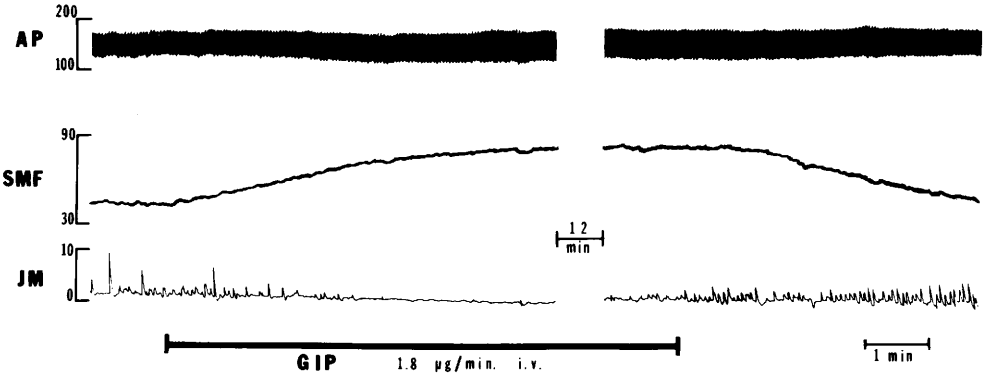

FIG. 2. The superior mesenteric blood flow (SMF) response to gastric inhibitory polypeptide (GIP, 1.8 µg/min) could be maintained for infusion periods up to 20 min. Systemic arterial pressure (AP) did not change, but spontaneous jejunal motility (JM-recorded as intraluminal pressure) was inhibited during the infusion period.

1.0 μg/min for 30 min raises circulating GIP levels to about 1 ng/ml (2) which compare with serum concentrations of more than 1.2 ng/ml seen after a mixed meal (12). In dog, maximum inhibition of pentagastrin-stimulated acid secretion is achieved at infusions of 1.0 μg/kg hr (1). Therefore, the physiological significance of the doses needed to see a systemic effect of GIP on superior mesenteric blood flow is uncertain. Circulating plasma levels of GIP need to be determined in the cat, and the effect of the present doses must be determined on another physiological parameter in this species, e.g. insulin release or gastric acid secretion.

Nevertheless it is possible that GIP exerts a local regulatory action on the mesenteric circulation. The ingestion of hypertonic glucose or its instillation into the small intestine is known to increase splanchnic blood flow (9, 13) and it has been used regularly as an experimental model for the dumping syndrome. Previous investigators have attributed the increase in blood flow to direct effects of hypertonicity on vascular smooth muscle (14, 15), to locally released chemicals as serotonin and bradykinin (16), and also to a nervous involvement (15, 17, 18). However, as intestinal glucose releases GIP (7), the present results suggest that increases in intestinal blood flow observed in the dumping syndrome or following intraluminal glucose may also be mediated at least in part by the release and local action of GIP.

Gastric inhibitory polypeptide was first isolated from a side fraction in the purification process of cholecystokinin–pancreozymin (8), and the impure CCK-PZ available several years ago from the Karolinska Institute contained small amounts of GIP (12). Thus, mesenteric vasodilator effects ascribed to CCK in earlier studies (6) may have included a contribution from GIP.

Summary. Gastric inhibitory polypeptide (GIP) induces dose-dependent increases in superior mesenteric blood flow in the anesthetized cat. There was no concommitant change in systemic arterial pressure or in femoral blood flow indicating a specific decrease in mesenteric vascular resistance.

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