SYMPATHECTOMY AND PROSTAGLANDIN DEFICIENCY DO NOT PREVENT GASTROGENIC HYPERGLYCAEMIA AND HYPERINSULINAEMIA

By

V. Schusdziarra, D. Rouiller and R. H. Unger

ABSTRACT

To examine the mechanism of the recently reported effect of an acidified intragastric test meal on insulin release and glucose homeostasis, a liver extract test meal at either pH 2 or pH 7 was instilled into the stomach of normal dogs and dogs with a chemical sympathectomy or indomethacin-induced prostaglandin deficiency, all of which had a bisected pylorus and gastric fistula. In the normal dogs the instillation of the liver meal at pH 2 elicited a significant rise in plasma glucose, glucagon and insulin levels, while in response to the meal at pH 7 only glucagon rose significantly. This was not altered in chemically sympathectomized dogs, nor during the infusion of indomethacin. In all experiments gastrin or gastric glucagon release in response to the meal at pH 2 was either lower than or similar to the response to the meal at pH 7. These data suggest that the influence of the stomach upon islet cell function and glucose homeostasis does not depend on either adrenergic innervation or the presence of prostaglandins, but rather is mediated by a yet undetermined mechanism.

Recently, we have reported that the intragastric instillation of an acidified liver meal in dogs elicits a rise in plasma glucose and insulin levels, which does not occur in response to a neutral liver meal (Schusdziarra et al. 1979a). This effect was not altered by truncal vagotomy or atropine infusion. The present study was designed to examine the role of adrenergic factors and prostaglandins in mediating this effect, using dogs with a chemically induced sympathectomy and with indomethacin-induced prostaglandin deficiency.
MATERIALS AND METHODS

The studies were performed in 41 mongrel dogs (body weight 21–27 kg). Fifteen dogs were chemically sympathectomized by iv injection of 6-hydroxydopamine (50 mg/kg) as described elsewhere (Gauthier et al. 1972) The completeness of sympathectomy was assessed by fluorescence microscopy according to the method of Falck et al. (1962) in tissue from pancreas and stomach. These dogs were studied 8–10 days after the injection of 6-hydroxydopamine. In 12 dogs indomethacin, an inhibitor of prostaglandin synthesis (Vane 1971; Sanders 1978; Sanders & Ross 1978) was infused at a rate of 2 mg/kg/h starting 2 h prior to the instillation of the test meal.

After anaesthesia (Nembutal®) and laparotomy silastic catheters were placed in the pancreatico-duodenal and fundic veins and in the inferior vena cava of all dogs as described previously (Schusdziarra et al. 1978). The pylorus was bisected to prevent nutrients from entering the duodenum and a gastric fistula was created to provide efflux of gastric contents. After an equilibration period of 1 h after the end of the surgical procedures, 25 ml of a 20 % liver extract test meal (Reheis, Chicago) at either pH 7 or pH 2 was instilled into the stomach.

Frequent blood samples were obtained before and after the instillation of the meal. The blood samples combined 500 KIU/ml Trasylol and 6 mg/ml EDTA.

Plasma glucagon (Faloona & Unger 1974) and insulin (Yalow & Berson 1960; Herbert et al. 1965) levels were measured by radioimmunoassay as previously described using antibody 30K. Plasma gastrin was measured by a modification of a previously described method (Yalow & Berson 1970) using the Pantex® gastrin kit, which reacts equally with G-17 or G-34. The coefficient of variation within the assay was 6 %. The samples obtained after liver extract at pH 2 or pH 7 during one treatment were assayed within the same assay. Plasma glucose levels were determined by the glucose oxidase method employing the Technicon® autoanalyzer.

For statistical analysis Student’s t-test for paired (comparison within groups) or non-paired data (comparison between groups) was employed and values of P < 0.05 or less were considered to be significant.

RESULTS

The instillation of the liver meal at pH 2 into the stomach of normal controls elicited a significant rise in inferior vena cava plasma glucagon, insulin and glucose levels, while in response to the meal at pH 7 only glucagon levels rose significantly (Fig. 1). Similar changes were observed in the pancreatic venous effluent (Fig. 2). In these experiments fundic vein levels of gastrin and gastric glucagon release were significantly lower after the meal at pH 2 than after the meal at pH 7 as shown previously (Schusdziarra et al. 1979b) and summarized in form of the incremental post-prandial values in Table 1.

After chemical sympathectomy, this pH-dependent difference in insulin and glucose response to the meals at pH 2 or pH 7 persisted, while glucagon levels increased similarly in response to either meal (Fig. 1). Within 6 min of the intragastric administration of the liver meal at pH 2, plasma glucose levels rose significantly by about 30 mg/100 ml (Fig. 1), and this was paralleled by a significant rise in pancreatic vein insulin (Fig. 2). Inferior vena cava insulin
Effect of a gastric liver meal upon inferior vena cava plasma glucagon (IRG), insulin (IRI) and glucose levels in normal dogs (pH 7: N = 7; pH 2: N = 7) after chemical sympathectomy (pH 7: N = 7; pH 2: N = 8) and during indomethacin infusion (pH 7: N = 6; pH 2: N = 6). ○ indicates significant difference of $P < 0.05$ vs. baseline levels.

rose significantly at 15 min (Fig. 1). In response to the intragastric liver meal at pH 7 plasma glucose levels rose significantly within 15 min by only 10 mg/100 ml (Fig. 1); this was followed at 20 min by a small but significant rise in pancreatic vein insulin (Fig. 2). However, inferior vena cava insulin levels did not rise significantly (Fig. 1). Inferior vena cava gastrin and gastric vein glucagon levels, are shown in Table 1.

During the infusion of indomethacin, which reduced basal plasma levels of
Effect of gastric liver meal upon pancreatic vein plasma glucagon (IRG) and insulin (IRI) levels in normal dogs (pH 7: N = 7; pH 2: N = 7) after chemical sympathectomy (pH 7: N = 7; pH 2: N = 8) and during indomethacin infusion (pH 7: N = 6; pH 2: N = 6). ⊙ indicates significant difference of $P < 0.05$ vs. baseline levels.

prostaglandin E significantly (Schusdziarra et al. 1979b), again the intragastric liver meal at pH 2 elicited within 10 min a significant 20 mg/100 ml rise in plasma glucose levels (Fig. 1), which was paralleled by a significant rise in insulin. In response to the meal at pH 7 neither insulin nor glucose levels changed significantly from the baseline (Figs. 1 and 2). Pancreatic vein and inferior vena cava glucagon levels were not different in response to either test meal, and gastrin or gastric vein glucagon levels were also unchanged (Schusdziarra et al. 1979b) (Table 1).

**DISCUSSION**

The present data demonstrate that, as previously described (Schusdziarra et al. 1979a), the intragastric instillation of a liver meal at pH 2 stimulates insulin release and raises plasma glucose levels, while the same meal at pH 7 does not. It is unclear if the rise in glucose is the cause for the rise in insulin, or if there
is a mechanism acting on both factors. This effect persists after chemical sympathectomy and during indomethacin induced prostaglandin deficiency. Plasma gastrin, which has been postulated to be part of a “gastro-insular axis” (Unger et al. 1967; Dupré et al. 1969; Kaneto et al. 1969; Creutzfeldt et al. 1970; Rehfeld 1971, 1972; Rehfeld & Stadil 1973) and the gastric glucagon release are either significantly lower or identical in response to the meal at pH 2 compared to the meal at pH 7 (Table 1). This suggests that in response to the acidified gastric liver meal, the stomach activates a mechanism that differs from vagal (Schusdziarra et al. 1979a), muscarinic, cholinergic (Schusdziarra et al. 1979a) or adrenergic pathways and persists during indomethacin-induced deficiency of endogenous prostaglandin E. It is noteworthy in this context that indomethacin infusion inhibits the hyperglycaemic response to glucagon (Schmitt et al. 1979).

The mechanism by which the stomach influences glucose homeostasis and insulin release remains to be determined. Vagal, cholinergic and neutral adrenergic pathways, having been excluded, possible mediation via peptidergic innervation (Uvnäs & Uvnäs-Wallensten 1978; Uvnäs-Wallensten & Uvnäs 1978; Lundberg et al. 1978; Hökfelt et al. 1976; Said & Rosenberg 1976; Uvnäs-
Wallensten et al. 1978); or via certain candidate hormones of the stomach, such of bombesin (Polak et al. 1977; Walch & Dockray 1978), neurotensin (Polak et al. 1976) or substance P (von Euler & Gaddum 1931) may be considered.

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