THE MECHANISM OF VAGAL CONTROL IN HYPOGLYCEMIA-INDUCED PANCREATIC POLYPEPTIDE SECRETION

YUTAKA SEINO, KOZABURO MORI, SUSUMU SEINO, TAKEHIRA YAMAMURA*, TOKU TAKAHASHI*, NOBUYOSHI ITOH* and HIROO IMURA
The Second Division, Department of Medicine, Kyoto University School of Medicine, Kyoto 606, and
*Department of Surgery, Hyogo College of Medicine, Nishinomiya 663, Japan

ABSTRACT
To elucidate the mechanism of hypoglycemia-induced pancreatic polypeptide (PP) secretion, intravenous bolus injections of insulin were given to normal subjects and 4 groups of patients with varying degrees of gastric surgery. In patients with duodenal ulcer, insulin-induced hypoglycemia produced a rapid rise in plasma PP, almost the same as that observed in normal subjects, while the plasma PP response to hypoglycemia was reduced after a selective proximal vagotomy. In duodenal ulcer patients treated by a combined selective vagotomy and antrectomy, the plasma PP response to hypoglycemia was further decreased, with a significantly lower peak level than in patients with untreated duodenal ulcer. Furthermore, the plasma PP response to hypoglycemia was abolished in gastric cancer patients after total gastrectomy with truncal vagotomy. These results suggest that vagal regulation of PP secretion induced by hypoglycemia is at least partially through the nerves of the gastric branch of the vagus.

KEY WORDS vagotomy / antrectomy / gastrectomy / hypoglycemia / pancreatic polypeptide

Recent studies have demonstrated the important role of the vagus in PP secretion (1, 3, 6-8). Adrian et al. (1) have observed that insulin hypoglycemia does not produce a rise in plasma PP in duodenal ulcer patients after truncal vagotomy. It might be presumed that the effect of the vagotomy is primarily on the pancreas due to denervation of the celiac branch. The present study was undertaken to elucidate the precise mechanism of vagal control of hypoglycemia-induced PP secretion by measuring the PP response to meal ingestion in patients with various surgical modifications of the vagal nerves.

MATERIALS AND METHODS
Sixteen patients with untreated duodenal ulcer, 10 males and 6 females aged 28 to 59; 14 duodenal ulcer patients treated by a selective proximal vagotomy, 8 males and 6 females aged 28 to 55; 10 duodenal ulcer patients treated with a combined selective vagotomy and antrectomy, 6 males and 4 females aged 16 to 49; and 11 patients after total gastrectomy with truncal vagotomy for gastric cancer, 8 males and 3 females aged 48 to 68, were studied. As control 10 normal subjects who apparently had no endocrine or gastrointestinal dysfunction, 6 males and 4 females aged 27 to 47, were also studied. As shown in Fig. 1, in patients with proximal selective vagotomy only the branches of the vagal nerve to the area of the parietal cells were cut, whereas in patients with combined selective vagotomy and antrectomy, the gastric vagal branch was cut. In the totally gastrectomized patients, a truncal vagotomy was performed. When tested at least one year after
After an overnight fast and absolute bed rest for at least 30 min, an intravenous bolus injection of insulin (0.2 U/kg) was given to the normal subjects and the 4 groups of patients. Blood was withdrawn from the antecubital vein into heparinized syringes. A 2 ml aliquot of blood for PP determination was placed promptly into chilled tubes containing 2,000 U of Trasylol in a volume of 0.2 ml. The mixture was immediately centrifuged at 4°C and plasma was separated and frozen at ~20°C. Plasma PP was measured by a specific radioimmunoassay previously described by Schwartz et al. (7) employing rabbit anti-hPP serum, hPP as the standard, and bovine PP labeled with ^{125}I by the technique of Greenwood et al. (4). All of these substances were kindly donated by Dr R. E. Chance (Lilly Research Laboratories, Eli Lilly Co., Indianapolis Ind., U.S.A.). In our system the minimal detectable quantity was 30 pg/ml. For comparison within the group, the paired 't' test was used. The 't' test was employed for comparison between unpaired groups.
RESULTS

In normal subjects, the plasma PP level rose significantly from the mean basal level of 30 ± 9 pmol/l (± SE) to a peak value of 287 ± 45 pmol/l following insulin-induced hypoglycemia. In the group of patients with untreated duodenal ulcer, the mean basal PP was 30 ± 6 pmol/l, and the intravenous administration of insulin was followed by a significant elevation of plasma PP with a peak level of 264 ± 39 pmol/l occurring 60 min after the injection (Fig. 2). The remarkable PP response to hypoglycemia was somewhat reduced in patients with selective proximal vagotomy. In patients with a combined selective vagotomy and antrectomy, the plasma PP response to hypoglycemia was further decreased to a mean peak level of 135 ± 45 pmol/l, significantly lower than in untreated patients (P < 0.05). The plasma PP response to hypoglycemia was abolished in patients with a total gastrectomy, as shown in Fig. 2.

As shown in Fig. 3, when the hypoglycemia-induced PP secretion is expressed as the sum of increments above the basal level during a 120 min period (Σ JPP), the PP secretion in patients with selective proximal vagotomy significantly decreased compared to patients with untreated duodenal ulcer (P < 0.01). Σ JPP in patients with combined selective vagotomy and antrectomy was also significantly lower than in untreated duodenal ulcer (P < 0.01), but not significantly different from that in selective proximal vagotomy. Σ JPP in totally gastrectomized patients was nearly abolished, compared to the other 3 groups (P < 0.01).

DISCUSSION

Recent studies (1, 3, 6-8) have indicated that PP secretion appears to be under vagal control. In the present study we have confirmed the previous report that insulin-induced hypoglycemia causes a PP secretion in both normal subjects and patients with duodenal ulcer but that this PP release is absent in patients with duodenal ulcer after a truncal vagotomy (1). In addition, we have extended these findings by demonstrating that the plasma PP response to hypoglycemia is reduced after a selective proximal vagotomy or a combined selective vagotomy plus antrectomy, although it is not completely abolished in either case. The reason for the decreased PP response after these surgical modifications could be the result not only of the vagotomy but also of the removal of certain antral hormones such as gastrin and somatostatin, which are known to affect PP secretion (2, 5). However, since the PP induced by hypoglycemia in patients with a selective proximal vagotomy is not significantly different from that in patients with a combined selective vagotomy and antrectomy, it is unlikely that a permissive antral hormone has a primary role in PP release induced by hypoglycemia. The nearly abolished PP response after total gastrectomy is primarily due, therefore, to the truncal vagotomy in which both the gastric and celiac branches of the vagal nerve are cut. We conclude that hypoglycemia-induced PP secretion is mediated through both the celiac branch of the vagal nerve and also at least partially through the gastric branch of the vagal nerve.

We are grateful to Dr R. E. Chance (Lilly Research Laboratories, Indianapolis), who kindly supplied us with the reagents for hPP radioimmunoassay.

Received for publication 24 April 1981
REFERENCES


