PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Effect of Vagotomy on the Feedback Inhibition of Pancreatic Secretion

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Chronic experiments on fistulized dogs showed that the pancreatic secretion stimulated by intraduodenal administration of acidified hydrolysine was depressed after bilateral supradiaphragmatic truncal vagotomy, and that the inhibitory influence of exogenous pancreatic enzymes on pancreatic secretion disappeared on postoperative days 10-16. Subsequently, the feedback inhibition of pancreatic secretion was slowly restored, but even 45 days after vagotomy it was still weaker than in intact dogs. It is concluded that the feedback inhibition of pancreatic secretion is centrally controlled from the duodenum via the vagus nerves.

Key Words: *pancreas; secretion; self-regulation; vagotomy*

When pancreatic (PC) secretions are drained from or prevented from being transported to the duodenum, the pancreas responds by hypersecretion, whereas intraduodenal administration of PC secretions or PC enzymes inhibits their secretion by the gland. This feedback inhibition of PC secretion, which is selective [5,12], has been the subject of many experimental and clinical studies [3,5,13]. The evidence obtained points to a fine regulation of PC secretion from the duodenum according to the properties of the duodenal chyme. This self-regulation allows for rapid adjustment of PC enzyme secretion to the composition of duodenal chyme and is involved in the coordination of cavitary and parietal intestinal digestion [4,6].

The feedback inhibition of PC secretion and the stimulation of the latter which occurs when PC secretions are prevented from reaching the duodenum are based on peptidergic (cholecystokinin and secretin) [10,11,13] and M-cholinergic [6] mechanisms. This conclusion stems from the observation that atropine suppresses or substantially reduces the effects of the removal of PC secretions from and their reintroduction into the duodenum. Vagotomy should be expected to alter not only the effects from stimulation of PC secretion [8] but also those arising from its feedback inhibition. The chronic experiments described here were undertaken to confirm this expectation.

MATERIALS AND METHODS

Three dogs with a Basov gastric fistula and a duodenopancreatic fistula [2] that prevents unintended loss of pancreatic juice were used. Tests were started 3-4 weeks after the fistulization operation. PC secretion was evaluated in the fasting animals with an open gastric fistula and was stimulated by intraduodenal administration of acidified (to pH 2) hydrolysine (0.5 ml/kg body weight every 15 min for a total of 4 h). After pancreatic juice had been collected for 2 h, pancreatin was

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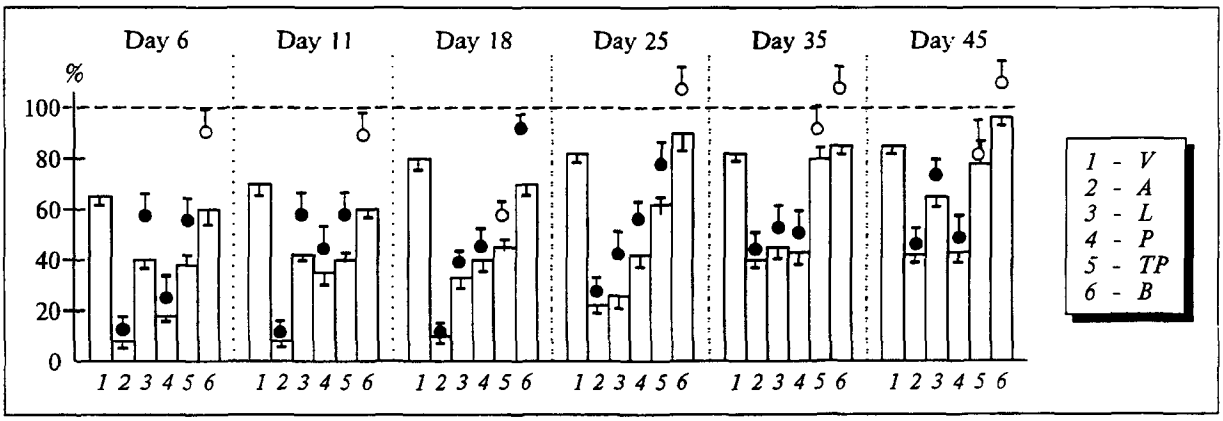

Fig. 1. Effect of vagotomy on pancreatic secretion, as expressed in percent of secretion values before vagotomy (mean results for the three dogs used). *V* = juice volume; *A* = amylase; *L* = lipase; *P* = proteases; *TP* = total protein; *B* = bicarbonate. Activities and concentrations of juice components are indicated by white circles; hourly outputs of the components, by bars; and statistically significant differences from control values, by black circles.

introduced into the duodenum in a dose of 33.3 mg/kg over an hour (a dose level found to markedly inhibit the secretion of all hydrolases by the pancreas); juice collection was continued during that hour and later.

The use of pancreatin instead of the natural PC juice of variable composition gathered during the test stabilized the inhibitory influences exerted by duodenal enzymes, thereby eliminating one cause of the variability of the inhibitory effect under study.

After three control tests were performed as outlined above, each dog underwent a bilateral supradiaphragmatic truncal vagotomy. Main tests were run on days 6, 11, 18, 25, 35, and 45 after vagotomy, with note taken of the hydrolysine-stimulated PC secretion and its inhibition by pancreatin.

The measured hourly volumes of collected PC juice were assayed for amylase [9], lipase [2], proteolytic activity [7], total protein (by Lowry's method), and bicarbonate (by titrometry), and hourly outputs of these juice components were calculated.

Table 1. Effects of Vagotomy on Pancreatic Secretion, as Expressed in % of Values before Vagotomy (Average Data for the Whole Observation Period; $M \pm m$)

Parameter of secretion	Activity or concentration	Hourly output
Juice volume	–	78.0±3.6**
Amylase	26.3±6.9**	21.3±6.2**
Lipase	54.8±6.3**	43.0±5.8**
Proteases	46.9±4.6**	37.1±4.9**
Total protein	70.5±6.5**	55.7±7.0**
Bicarbonate	100.7±4.1	5.8±6.2*

Note. *$p<0.01$, **$p<0.001$ in comparison with baseline values.

RESULTS

Mean pancreatic secretion values obtained prior to vagotomy were used as baselines against which the values measured at various times after the operation were compared (Fig. 1 and Table 1). The results confirmed the reported observation that less PC juice is secreted by the pancreas after vagotomy [8]. Decreases occurred not only in juice components that are released in response to a natural meal but also in those whose release can be stimulated, via the duodenopancreatic reflex and endogenous duodenal hormones, by intraduodenal administration of acidified hydrolysine. The decreases in different juice components were, however, unequal. The largest falls were recorded for amylolytic and proteolytic activities and the hourly outputs of amylase and proteases. Falls in the lipolytic activity and in hourly lipase outputs were less marked. The concentrations and hourly outputs of total protein also declined, to varying extents. The bicarbonate concentration, which is controlled by the secretin mechanism, remained unchanged, while the bicarbonate output decreased as a result of diminished juice volume.

The decreases in PC secretion, particularly in that of enzymes, were greatest in the early postoperative period. Subsequently, the secretion slowly increased, although by the end of the observation period (day 45), all juice components, with the exception of bicarbonate, were still at levels significantly below baseline.

In the dogs with intact vagus nerves, intraduodenal pancreatin administration resulted in diminished PC juice volume during the hour of administration and during the next hour (Table 2), with sharp falls in amylolytic activity and amylase output; the lipolytic activity of the juice during

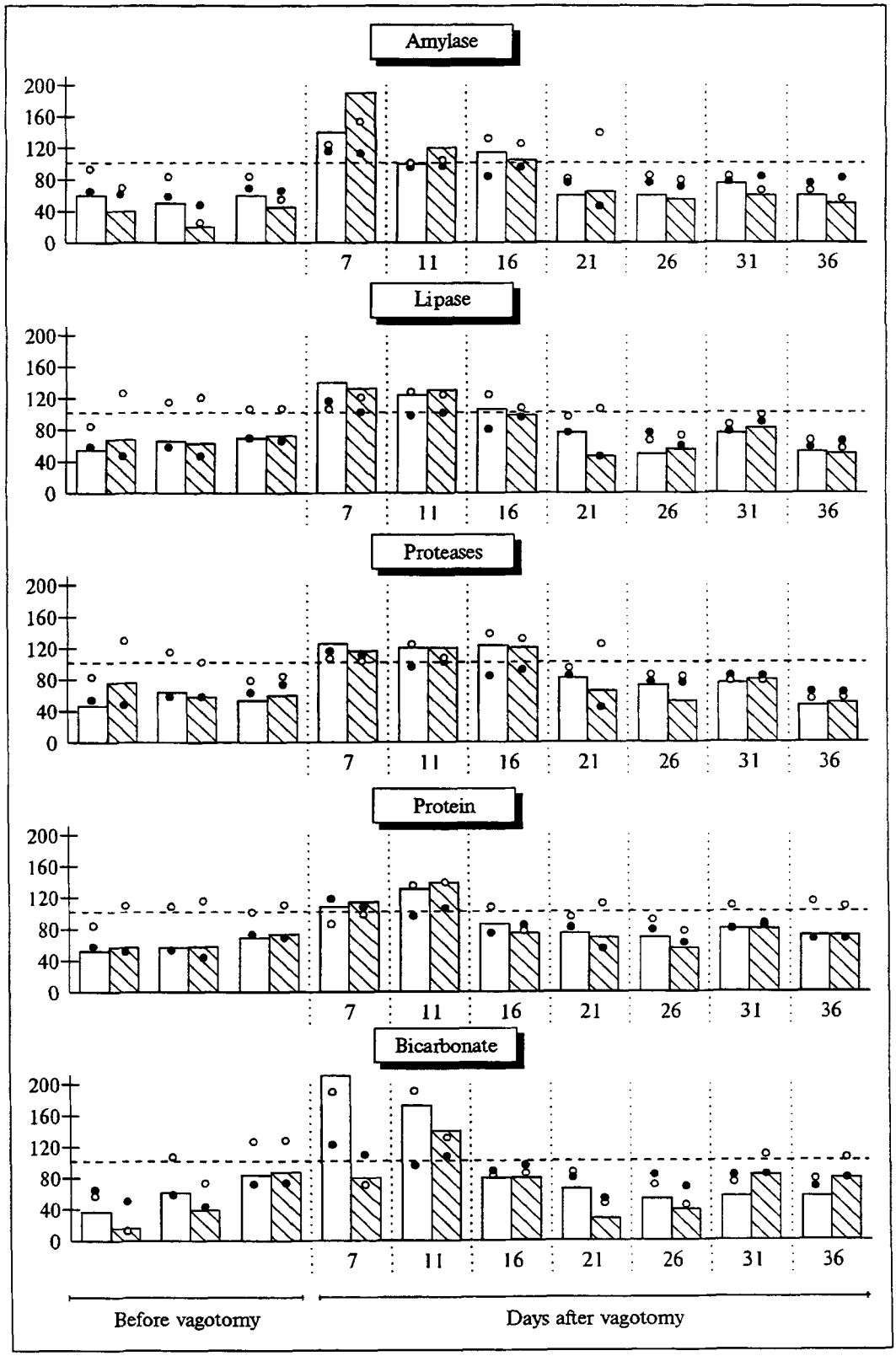

Fig. 2. Inhibition of hydrolysine—stimulated pancreatic secretion in a dog before and at different times after vagotomy, as expressed in percent of secretion values before intraduodenal administration of pancreatin. Here and in Fig. 3: secretion during the hour of pancreatin administration is indicated by white bars and that during the subsequent hour by dark bars; activities and concentrations of juice components are denoted by white circles and hourly outputs of the components by black circles.

these two hours remained unchanged, but the lipase output declined because of diminished juice volume. Similar results were obtained for proteases, total protein, and bicarbonate.

After vagotomy, as indicated by the averaged data presented in Table 2, the sole parameter that decreased was the volume of PC secretion during the hour of intraduodenal pancreatin administration, with

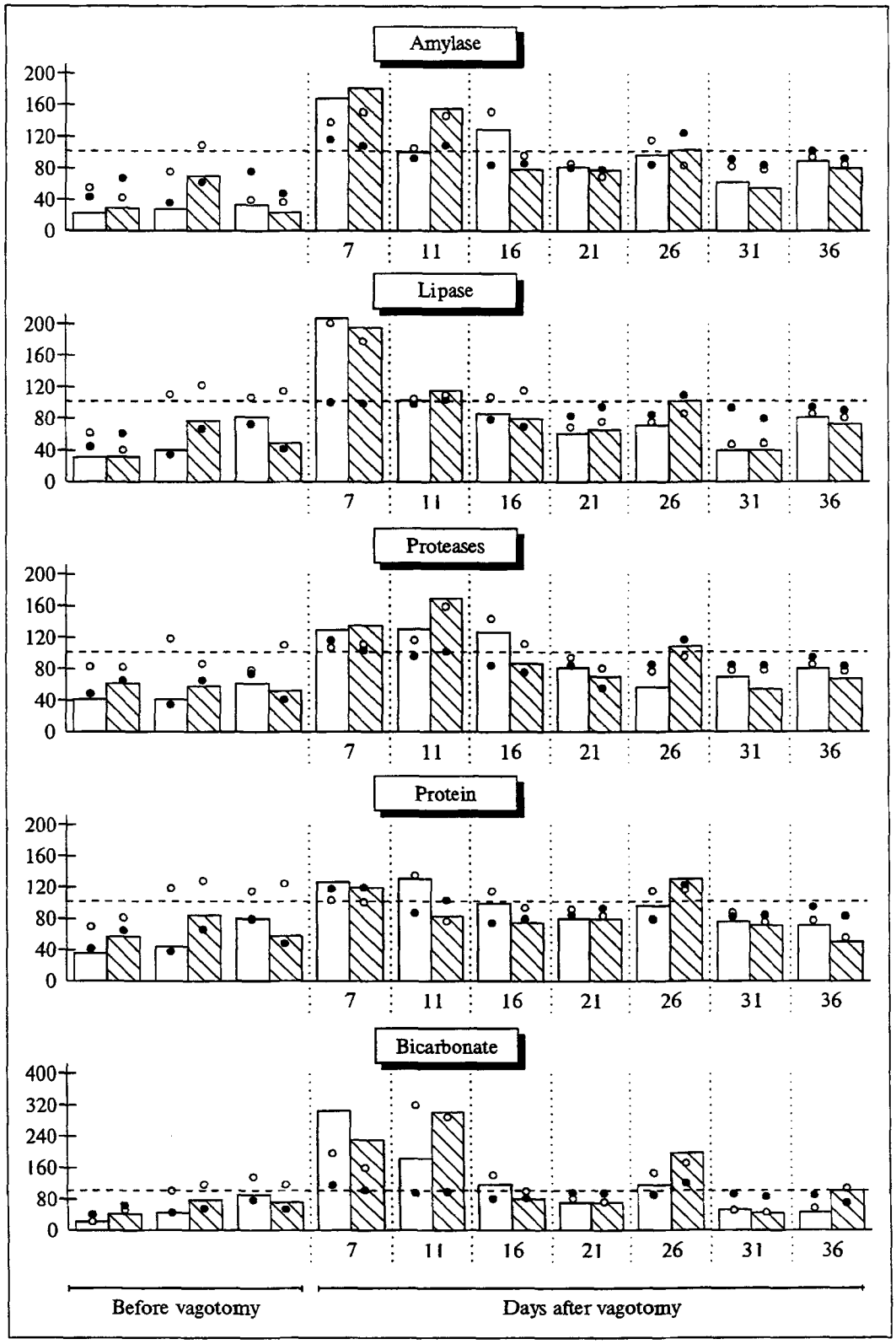

Fig. 3. Inhibition of hydrolysine–stimulated pancreatic secretion in another dog before and at different times after vagotomy, as expressed in percent of secretion values before intraduodenal administration of pancreatin.

little or no change in any of the juice components either during the hour when pancreatin was administered or during the subsequent hour.

A different picture emerged when the postoperative course of the inhibitory effect produced by intraduodenally administered pancreatin was followed (Figs. 2 and 3). Shortly after the operation, the inhibitory effect was either absent or paradoxical in that PC secretion increased rather than decreased in response to pancreatin administration. The period

Table 2. Inhibition of Pancreatic Secretion during the Hour When Pancreatin Was Injected Intraduodenally (A) and during the Subsequent Hour (B) in Dogs before and after Vagotomy, Expressed in Percent of the Secretion Values before Pancreatin Injection ($M \pm m$)

Parameter of secretion	A		B	
	before vagotomy	after vagotomy	before vagotomy	after vagotomy
Juice volume	70.1±6.9*	89.3±4.4*	67.5±4.6*	90.4±9.5
Amylase	74.3±5.5* 51.9±5.8*	104.0±7.3 95.2±10.1	64.6±9.6* 45.2±6.6*	103.4±9.1 96.6±11.8
Lipase	100.4±5.7 69.7±6.8*	99.2±9.8 81.4±13.7	103.3±9.1 69.3±6.0*	112.6±8.1 84.2±11.1
Proteases	90.2±8.1 62.6±5.3*	99.0±7.6 94.8±7.2	95.6±9.8 62.5±3.8*	96.2±8.0 87.5±10.0
Total protein	100.5±6.0 68.4±7.4*	100.7±6.3 95.4±7.4	110.0±5.9 72.5±3.6*	95.7±7.4 87.5±8.9
Bicarbonate	85.4±10.8 60.4±8.5*	106.2±24.4 94.4±20.5	80.1±11.3 49.1±8.3*	94.0±19.2 100.0±20.6

Note. Figures in the numerator are the activity or concentration of juice components and those in the denominator are their hourly outputs. The asterisk denotes a significant difference from the baseline value taken as 100%.

during which no inhibitory effect was observed ranged approximately from 10 to 16 days for most of the secretion parameters under study. This period was followed by one during which the inhibitory response of PC secretion to intraduodenal pancreatin underwent complete or partial recovery.

The results of this study indicate that the peripheral mechanism by which PC enzymes from the duodenum exert inhibitory influences on enzyme secretion by the pancreas can operate with reasonable efficiency only when a long time has elapsed after vagotomy but not shortly after this operation which eliminates the central vagal control over the feedback regulation of PC enzyme secretion. This may explain in part why the feedback inhibition of PC secretion in acute tests differs in magnitude from that observed in chronic experiments like ours.

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