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Adrenergic Activity and Gastric Secretion (39280)

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An inhibitory action of the sympathetic nerves on the secretory elements of the gastric fundic mucosa is suggested by the increased secretion obtained from sympathetically denervated Heidenhain pouches (1, 2). In addition there have been claims that epinephrine, norepinephrine, and splanchnic nerve stimulation depress the acid secretory response to histamine and pentagastrin (PG) administration (3, 4). Claims have been made that isoproterenol has a similar action against PG (5) and histamine (6, 7), but others contended that the isoproterenol effect varied in direction with the dose of the agent used to stimulate acid secretion (6). If β-adrenergic nerves are inhibitory to gastric acid and pepsin secretion, agents which block β-adrenergic receptors would be expected to antagonize their action.

If β-adrenergic nerves tonically inhibit gastric parietal and chief cells, all forms of stimulated and also resting gastric secretion should be augmented by β-adrenergic blockers.

We propose that the β-adrenergic innervation of the stomach is inhibitory to acid and pepsin secretion and that the failure of PG to stimulate the secretion of pepsin from the usual Heidenhain pouch (sympathetic nerves intact) is not due to the unopposed action of adrenergic nerves.

Methods. Six mongrel dogs, retriever in type, with gastric fistulae and Heindenhain (vagally denervated) pouches were used throughout. The animals weighed between 16 and 18 kg. Isoproterenol, a β-adrenergic agonist, and epinephrine, a mixed α- and β-agonist, when used, were given by continuous intravenous injection as were PG[1] and methacholine when these were used as stimulants of background acid and pepsin secretion. In the feeding experiments the dogs were given their usual daily meal 2 h before the experiment, and collections were made from the pouch only.

The β-blocking agent, propranolol, was administered as a single intravenous bolus.

Gastric fistula and pouch secretions were collected at 10-min intervals, from the fistula by simple drainage and from the pouch by saline washout. Collections were continued until a steady volume and plateau in acid output had been obtained except, of course, following the blocking agents. The last two collections of a treatment period were used in the calculations below. The effect, if any, of the blocking agent was obvious within 30–40 min after the injection. Again, the mean of the last two periods was used. The figures below are the means of these means with standard errors. Significance of change was calculated from paired t test in each case. The mean paired differences and their standard errors are given in Fig. 2 and 3. Throughout the manuscript any effect claimed has been subjected to the t test and has met the 95% probability level. Aliquots were used for titration using the Radiometer automatic titrator. Pepsin was estimated by Anson's method (8) and expressed as units per 10-min of incubation at 37°.

Results. Acid. Acid secretion from both pouch and fistula, when PG was the stimulus, was decreased by isoproterenol. The depression was dose related. This depression was reversed by 25 mg of propranolol (Fig. 1). Epinephrine, 0.5 μg/min, did not significantly depress acid secretion but when followed by propranolol both fistula and pouch acid increased (Fig. 2).

Following methacholine, on the other hand, isoproterenol, 0.125 and 0.25 μg/min, did not depress acid secretion. Addition of propranolol during isoproterenol administration depressed acid secretion from the innervated stomach (Fig. 3).

β blockage during PG stimulation or with

[1] Peptavalon kindly supplied by Ayerst Laboratories.

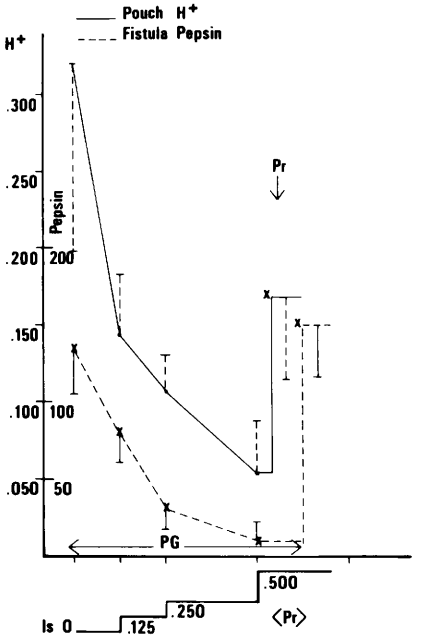

FIG. 1. The effect ± SE of increasing doses of isoproterenol (IS) on pentagastrin (PG) stimulated pouch H^+ and fistula pepsin. At PR the β blocker, propranolol, was given as a single intravenous bolus (25 mg/dog). × = significant propranolol augmentation at $P >$ 95%.

food in the absence of isoproterenol raised pouch acid secretion but otherwise did not influence secretion from pouch or fistula (Fig. 3).

Pepsin. In every instance pepsin secretion followed acid secretion except that in the PG experiments, epinephrine reduced the secretion of pepsin but not of acid from the Heidenhain pouch, and isoproterenol following PG or feeding did not influence pepsin secretion. Following both methacholine and secretin, propranolol augmented pepsin secretion from both Heidenhain pouch and gastric fistula.

Discussion. Isoproterenol and epinephrine depressed PG-stimulated acid and/or pepsin secretion from both Heidenhain pouch and innervated stomach. This depression was reversed by β-adrenergic antagonists. The epinephrine experiments establish that secretion recovers despite the fact that the vasoconstrictor alpha adrenergic effect remains unblocked, suggesting that the observed effects of epinephrine were not due to catecholamine-provoked reduction in gastric mucosal blood flow.

On the other hand, isoproterenol did not bring about any significant change in methacholine-stimulated secretion from either innervated or denervated gastric mucosae. Indeed an augmentation suggested itself since the usual fall off in secretion with time was not seen and β-adrenergic blockage significantly lowered fistula acid and pepsin secretion. The reduction seen in pouch acid secretion just fell short of significance, but pouch pepsin secretion showed enormous variability. Once again it is hard to argue that isoproterenol acts in the first instance by reducing gastric mucosal blood flow since a decline in gastric secretion following β-adrenergic blockage is not a likely consequence of restored gastric mucosal circulation.

If β-adrenergic receptors exercise tonic depression of gastric secretion one would expect that blockers of β-adrenergic receptors would result in increased secretion no matter what the stimulus. This is possibly the explanation for the significant increase in PG- or food-stimulated Heidenhain

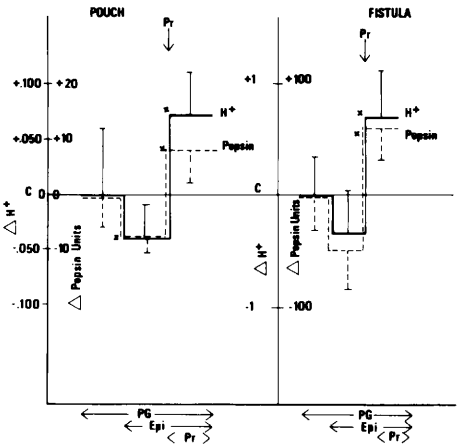

FIG. 2. The effect of epinephrine (Epi) on pentagastrin stimulated pouch acid and pepsin (left) and fistula acid and pepsin (right) and the effect of propranolol (25 mg) given at PR. All the points are mean difference per 10 min from control (C) ± SE in mEq for H^+ and milligram of tyrosine from hemoglobin substrate for pepsin. × = significant propranolol augmentation at greater than 95% probability level. Epi, 0.5 μg/min.

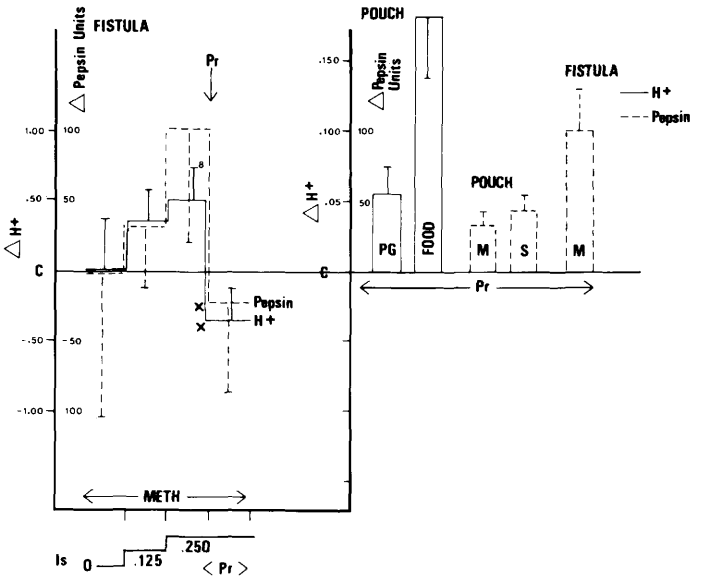

FIG. 3. Left: The effect of increasing doses of isoproterenol (IS) on methacholine (Meth)-stimulated fistula acid and pepsin and of propranolol (25 mg) given at PR. × = significant propranolol depression at 25 mg. $P > 95\%$. Right: The effect of propranolol on pouch and fistula acid and pepsin secretion stimulated by pentagastrin (PG), food, methacholine (M) and secretin (S). In these experiments no exogenous catecholamine was given. All the bars represent significant increases greater than 95% probability. Each bar represents a separate set of experiments on six dogs each. Points both right and left are mean change from control (C) per 10 min, in milliequivalents for H^+ and milligrams of tyrosine from hemoglobin substrate for pepsin.

pouch acid secretion following propranolol. This confirms the findings of Evan and Lin (9). In these experiments β-adrenergic receptor blockade did not influence fistula secretion arguably because of the dominance of vagal influence. The failure of PG or gastrin to stimulate Heidenhain pouch pepsin secretion cannot be due to suppression by β-adrenergic nerve fibers since Heindenhain pouch pepsin secretion was uninfluenced by β-adrenergic blockage.

Blockade of β-adrenergic receptors did not augment acid secretion when given with methacholine or secretin, but did augment pepsin secretion from both innervated and denervated gastric fundic mucosae. Thus, in the Heidenhain pouch, when using substances which unlike PG or gastrin do stimulate pepsin secretion, evidence for tonic β-adrenergic receptor inhibitory activity was obtained. This and the data obtained from the Heidenhain pouches are further evidence that methacholine and secretin act differently from gastrin to stimulate pepsin secretion. Indeed, there is good evidence (10, 11) that pentagastrin or gastrin actually antagonizes cholinergically or secretin-stimulated pepsin secretion: Attractive ideas are that the cells of origin of cholinergically stimulated pepsin secretion are different from those of gastrin-stimulated pepsin secretion or that one mechanism involves pepsinogen I and the other pepsinogen II.

Based on the fact that β-adrenergic blockade augments pentagastrin- and food-stimulated acid secretion from the Heidenhain pouch but not methacholine-stimulated acid secretion, we conclude that gastrin acts differently from cholinergic nerves or agents not only on the chief but also on the parietal cell as we have previously suggested (12).

Summary. Isoproterenol infusions depress pentagastrin (PG)-stimulated secretion of acid and pepsin from both gastric fistulae and denervated (Heidenhain) pouches in conscious dogs. It was not found to do so if methacholine replaced gastrin. Propranolol reversed the isoproterenol depression of PG stimulation but had no effect on isoproterenol plus methacholine

except on the fistula where both acid and pepsin were depressed. It is felt that PG and methacholine act by differing mechanisms both on chief and parietal cells.

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