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Augmentation of Gastric Secretion by Cooling the Mucosa of Heidenhain Pouches (40554)

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In an earlier paper (1) we have described an augmentation of acid and pepsin secretion from both innervated gastric mucosa and a Heidenhain pouch following cooling of the mucosa of an innervated pyloric pouch. β-Adrenergic receptors seem to play a part in this. Debas *et al.* (2, 3) have described vagally mediated pyloro-oxyntic reflexes which result in elevations of blood gastrin and/or acid secretion.

In our first series of experiments cooling a Heidenhain pouch in animals with a gastric fistula did not augment pentagastrin-stimulated secretion from the fistula; on rewarming the pouch, however, the fistula secretion was significantly diminished (1). The data reported here are a reexamination of this phenomenon.

Methods. The animals used were five dogs with Heidenhain pouches, four of which in addition had innervated antral pouches of the Pavlov type, and finally six animals which 18 months previously had had their left gastric, right gastroepiploic arteries and accompanying nerves ligated and cut. Three of these animals had Heidenhain pouches and three Pavlov (4). All six of these responded normally to PG.

The fundic pouches were irrigated with water for 60 min at 37°, for a further hour at 5° and finally at 37° again while secretion was stimulated submaximally either with methacholine or pentagastrin.[2] The irrigation system consisted of a rubber tube attached to the pouch cannula instead of the Malecot catheter used earlier (1). The outflow end of the catheter was always 1 cm above the point where the pouch cannula emerged from the abdominal wall. Gastric juice was collected from the fistula only.

The same warm–cool sequence was used in the main stomach without any stimulus, during methacholine and pentagastrin stimulation and also in four animals during irrigation of the antral pouch with 0.5% acetylcholine. In this case water was circulated through a 10-m loop of polyethylene tube which had been inserted through the gastric cannula. Gastric juice was collected from the Heidenhain pouch by the washout technique. This sequence was repeated in the same animals during ganglionic blockade (hexamethonium 50 mg intramuscularly and 5 mg/min intravenously throughout). β-Adrenergic block (propranolol 25 mg intravenously followed by a further 10 mg after 1 hr) and in the four antral pouch animals while the pyloric pouch was irrigated continuously with 0.1 *N* HCl in one series and with ACh 0.25 or 0.5% in saline in another series.

Controls consisted of the 37° irrigation periods before and after cooling, but in addition, to eliminate spontaneous change in secretion with time, in each animal with each stimulus but no other drugs the pouch or main stomach was irrigated for 160 min with 37° water. The effect of cooling was then compared statistically, Student's *t* for paired differences, with any change seen during the same period in the time control (Fig. 1). The figures and tables shown group means, but significant paired differences are marked.

In the experiments with 0.5% acetylcholine blood for gastrin immunoassay was taken at the end of the 5° period and during the last 10 min of the preceding warm period. Gastrin was kindly assayed for us by Drs. T. O'Dorisio and S. Cataland of Ohio State University by their published method (5). This method uses antibody from porcine gastrin raised in guinea pigs and synthetic human gastrin-17 for radiolabeling and as the standard. It has equal specificity for G-17 and G-34 in man and dogs[3] and a sensitivity

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[2] Peptavalon kindly supplied by Ayerst.

[3] Personal communication.

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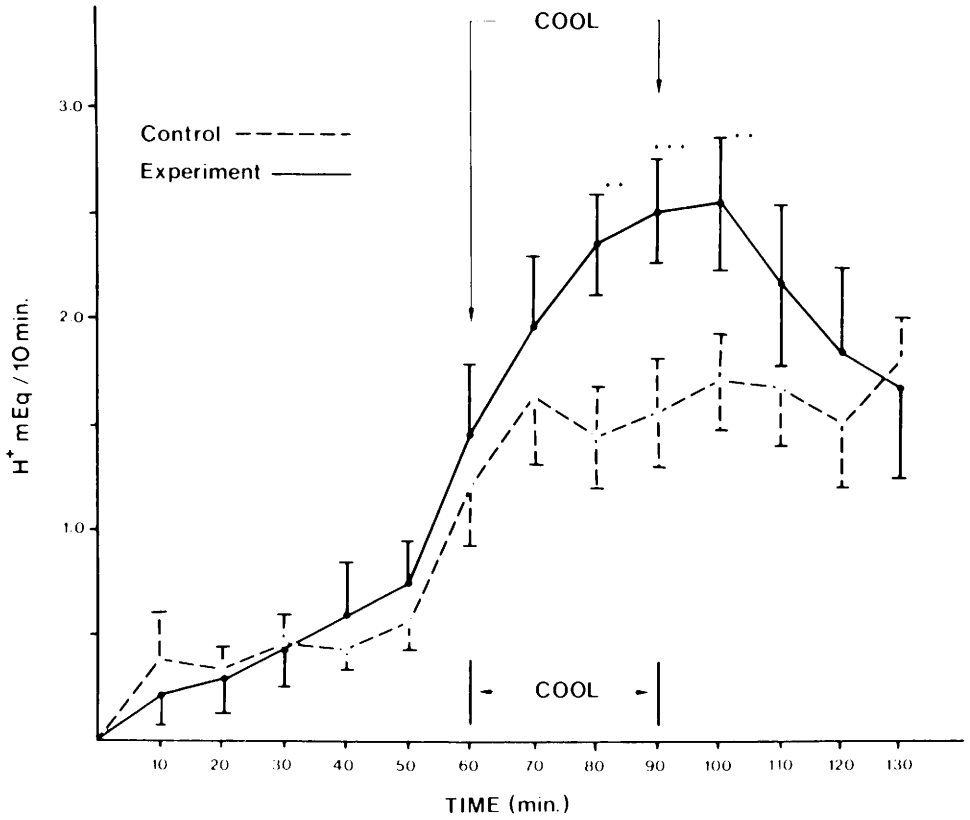

FIG. 1. The effect of cooling a Heidenhain pouch on the PG-stimulated (0.250 g/min from 0 time) acid secretion from the main stomach of five dogs compared with secretion in the same animals without pouch cooling. Each point mean ± SE of one test in each of the five dogs, $^{**}P < 0.02$, $^{***}P < 0.01$ compared with the corresponding control by paired t.

of 2 pg per tube containing 100 μl of serum.

Acid was estimated with a Radiometer automatic machine and pepsin by Anson's (6) hemoglobin method. Acid and pepsin are expressed throughout as totals per collection (10 min) in meq and units, respectively. Pepsin units are milligrams of tyrosine produced from hemoglobin in 10-min incubation at 37°.

Results. Heidenhain pouch cooling during PG administration or in the basal state without stimulation (0.125 μg/min) elevated acid and pepsin secretion from the main stomach significantly (Fig. 1). Rewarming brought about a significant fall.

When 2 μg/min of methacholine was the stimulus, cooling resulted in a marginally significant elevation of fistula acid (Table I).

During hexamethonium (ganglionic) blockade (Table II) Heidenhain pouch cooling did not augment PG-stimulated fistula acid or pepsin. With propranolol pepsin augmentation was abolished (β-adrenergic block) (Fig. 2) and PG-stimulated acid was not increased to a significant extent by pouch cooling (Δ1.6466 ± 0.1874 before, vs 0.432 ± 0.232 with).

Pouch cooling significantly augmented fistula acid and pepsin stimulated by endogenous gastrin, liberated by irrigating the pyloric pouches with 0.25 or 0.5% acetylcholine in saline (Fig. 3).

The mean basal gastrin in the four animals from which blood was drawn was 25.0 ± 6.0 pg/ml of serum. This was raised to 109 ± 29 when the antral pouch irrigant was changed from saline to 0.5% acetylcholine. Cooling (Fig. 4) raised serum gastrin levels slightly in three of four animals (131 ± 17 pg/ml), but the paired t did not reach significance. There

TABLE I. The Effect of Heidenhain Pouch Cooling on Methacholine (2 μg/min Throughout)-Stimulated Main Stomach Secretion (30-min Mean ± SE).

	Warm	Cool	t	n
H^+ (meq/10 min)	0.746 ±0.369	2.400 ±0.261	3.20[a]	4
Pepsin (units/10 min)	483.3 ±204.4	1149.6 ±144.5	2.5	4

[a] Significant $P < 0.05$.

was no significant correlation between change in serum gastrin and augmentation of secretion during cooling.

If Heidenhain pouch cooling promotes augmented pyloric gastrin secretion the expectation is that the augmentation of secretion could be diminished by acidification of the pyloric pouches (Fig. 2). When this was done with PG as the stimulus augmentation of acid and pepsin remained undiminished.

TABLE II. Effect of Ganglionic Blockade (Hexamethonium) on PG (0.125 μg/min Throughout)-Stimulated Secretion from the Main Stomach during Heidenhain Pouch Cooling (30-min Mean ± SE).

	Warm	Cool	Δ		n
H^+ (meq/10 min)	0.598 ±0.264	0.321 ±0.046	−0.278 ±0.225	NS[a]	5
Pepsin (units/10 min)	139.3 ±58.0	63.6 ±9.0	−75.5 ±53.4	NS	5

[a] t for paired Δ not significant.

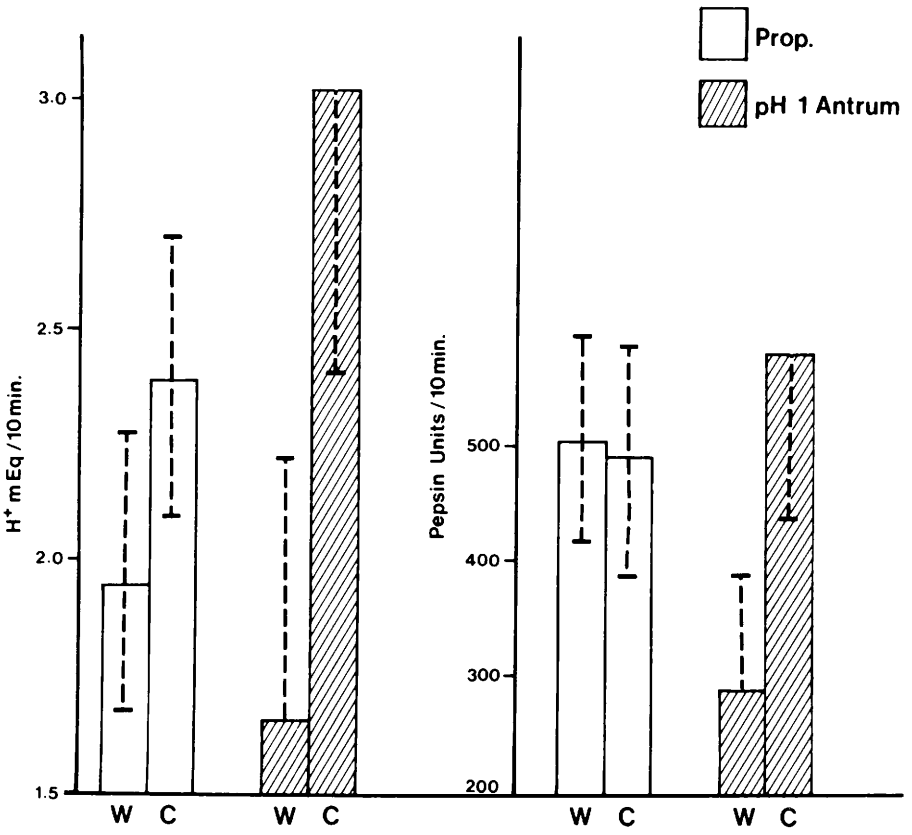

Fig. 2. The effect of β-blockade (prop.) and antral acidification on the augmentation of PG-stimulated (0.250 μg/min iv) acid and pepsin secretion from the main stomach during cooling of the Heidenhain pouch (C = 5°; W = 37°). The differences between warm and cool with antral acidification are significant by paired comparison. With propranolol they are not. Each bar mean of one experiment in each of five dogs ± SE.

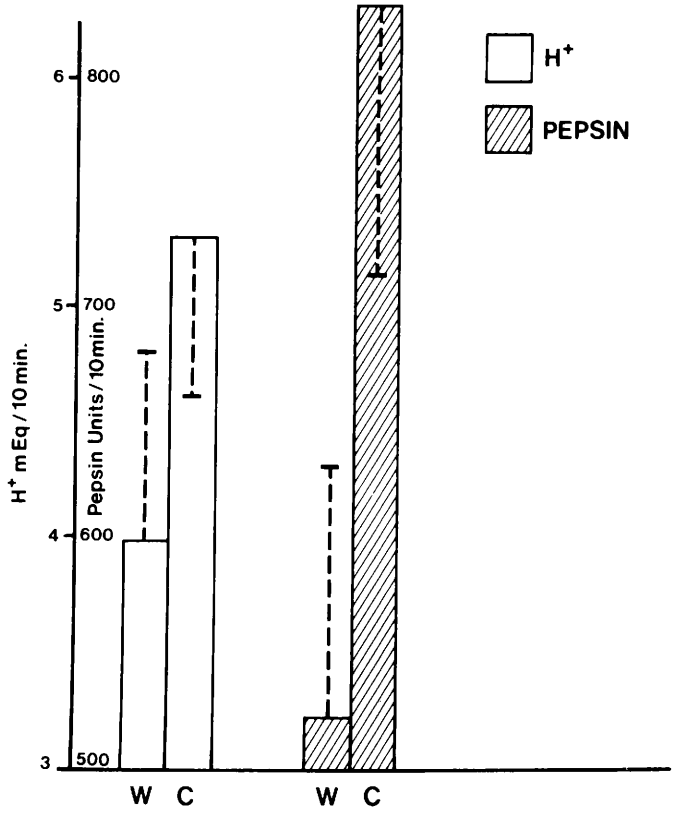

FIG. 3. The effect of changing Heidenhain pouch temperature from 37° (W) to 5° (C) on acid and pepsin secretion from the main stomach caused by bathing the antral mucosa with 0.25% ACh (P pepsin <0.01, P acid <0.05 by paired t).

In the six dogs with previously ligated left gastric and gastroepiploic arteries and accompanying nerves (7) neither Pavlov nor Heidenhain pouch cooling altered fistula acid or pepsin secretion (Fig. 4).

Main stomach cooling (*Table III*). Unstimulated and PG-stimulated pouch secretions were increased by cooling the main stomach. In the latter case an insignificant elevation in gastrin was seen. Since PG was given throughout it is unlikely that it masked possible significance. Acid secretion stimulated either by endogenously released gastrin (acetylcholine in the antral pouch) or by methacholine was not significantly increased by main stomach cooling although in the latter case a large but irregular increase was seen.

Cooling increased methacholine-stimulated pepsin significantly. Since neither endogenous gastrin nor PG stimulate pouch pepsin (8), augmentation of pepsin when these were used was neither expected nor seen.

Discussion. The present experiments have shown that depression of the sensitivity of a part of the fundic mucosa to secretory stimulants by cooling (1) increased acid and pepsin secretion from the remainder of the fundic mucosa whether either mucosa was vagally innervated or not (i.e., from main stomach or Heidenhain pouch). It is likely that cooling of the mucosa was less effective in the main stomach than in the pouch, which may account for the failure of the former to augment either methacholine- or antral-stimulated secretion significantly (Table III). Main stomach cooling did, however, augment both PG-stimulated and basal secretion from the Heidenhain pouch.

This apparent fundic feedback seems to require the integrity of structures traveling with either the left gastric or right gastroepi-

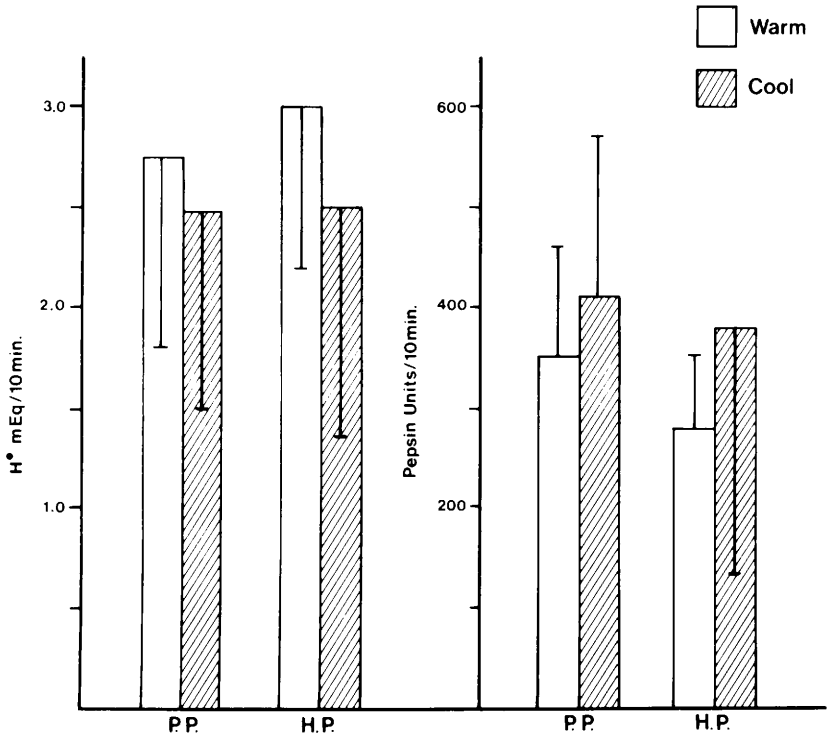

FIG. 4. The lack of significant effect of changing Heidenhain pouch (HP) and Pavlov pouch (PP) temperature on main stomach secretion stimulated by 0.25 μg PG/min in three animals each, following ligation and section of the left gastric vessels and accompanying nerves.

TABLE III. THE EFFECT OF COOLING THE MAIN STOMACH ON SECRETION OF ACID AND PEPSIN FROM THE HEIDENHAIN POUCH[a]

	H^+		Pepsin		Gastrin (pg/ml)	
Procedure	Warm	Cool	Warm	Cool	Warm	Cool
Basal	0.056 ± 0.013	0.089 ± 0.020*	36.9 ± 5.9	33.2 ± 7.4		
PG	0.268 ± 0.054	0.314 ± 0.061*	36.7 ± 4.6	32.1 ± 3.14	57.7 ± 8.8	73.3 ± 11.3
Methacholine	0.233 ± 0.070	0.336 ± 0.100	96.0 ± 13.1	113.7 ± 5.77*		
Antral ACh 0.5%	0.225 ± 0.031	0.251 ± 0.060	25.6 ± 0.4	24.1 ± 0.9		
	H^+ (meq/10 min)		Pepsin (units/10 min)			

[a] Each figure 30-min mean ± SE.
* $P < 0.05$.

ploic arteries or both, since it was absent when they were severed. Its suppression by propranolol and hexamethonium implies involvement of a β-adrenergic component and a synapse.

Such a facilitatory feedback could result either from an increase in the sensitivity of the noncooled mucosa to PG and methacholine, an increase in antral gastrin secretion, or both. Compensatory gastrin release was unlikely in the present experiments because cooling augmentation was still seen at an antral pH of 1 and because we have been unable to detect any significant elevation of serum gastrin on cooling either pouch or main stomach mucosa.

Gastrin release is not totally excluded, since in the conditions of depressed fundic secretion in which serum gastrin is elevated the entire secreting mucosa is affected (9). Perhaps a partial depression such as ours is offset by the hypersensitivity of the remaining mucosa, hence the equivocal gastrin results.

We postulate a fundo-fundic feedback by

which decreased sensitivity of fundic mucosa results in hypersensitivity of the remaining normal mucosa to endogenous gastrin, pentagastrin, methacholine, and the stimuli involved in basal secretion. The fact that propranolol raised secretion, which we have noted before (1), and that the effect of cooling was diminished after it plus the augmentation of basal secretion, raises the possibility that this feedback may be in the nature of a depression of an existing β-adrenergic inhibitory system.

In earlier experiments (1) we failed to demonstrate this feedback because as we subsequently discovered the structures accompanying the left gastric and right gastroepiploic arteries had been injuried in several of the animals used.

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