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EVIDENCE FOR ANTRAL INHIBITION OF PENTAGASTRIN FROM EXPERIMENTS USING MUCOSAL COOLING*

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SUMMARY

1. The acid secretion of the fundic mucosa in Heidenhain pouches in response to pentagastrin became progressively less as the pouch mucosa was cooled.

2. When a cooled Heidenhain pouch in an animal receiving pentagastrin was warmed, acid and pepsin secretion from the main stomach was depressed. Change from warm to cool produced no obvious effect.

3. In animals receiving pentagastrin continuously, but not in those receiving histamine, lowering the temperature in an antral pouch, or the application of local anaesthetics to its mucosa, increased acid and pepsin secretion from the main stomach when the antral pouch was fully innervated.

4. This effect could readily be abolished by ganglionic and β-adrenergic blockade, but not by bilateral vagal block in the neck, thus suggesting a sympathetically mediated inhibitory mechanism of pyloric origin.

5. The effect of indirect vagal stimulation, using 2-deoxy-D-glucose on secretion from the main stomach, was augmented by pyloric antral local anaesthesia and depressed by antral cooling.

INTRODUCTION

A number of factors have been thought to act directly on gastric secretion from within the lumen of the stomach. Distension (Lim, Ivy & McCarthy, 1925; Magee & Hu, 1975), acid (Iggo, 1957; Johnson, 1972) and a variety of chemicals (Debas & Grossman, 1974) have been studied. In addition, distension has been held to influence serum gastrin levels via a postulated oxyntopyloric reflex (Debas, Walsh & Grossman, 1975).

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In the present experiments, we have changed the temperature in pyloric and in Heidenhain pouches and examined acid and pepsin secretion from both the Heidenhain pouches and the main stomach.

METHODS

Eight dogs were used: four with innervated Pavlov-type pyloric antrum pouches, end to side gastro-duodenostomy and gastric fistulae, and four with Heidenhain pouches and gastric fistulae.

The animals were fasted (18 h) before experiments. To determine the direct effect of Heidenhain pouch cooling on pouch secretion, saline (50 ml.) maintained at the desired temperature was circulated continuously at 25 ml./min through pouch and temperature control bath for 10 min, at which time it was collected and replaced by another sample (50 ml.). The temperature of the circulating fluid was monitored throughout, and varied by less than 1° C. In order to maintain the 5° C perfusate, the temperature-control bath was filled with ice. The temperature was not changed until at least three collections had been made. The means of the last two collections in these experiments were used for calculation. In these experiments, mucosal blood flow was estimated using the tritiated aniline method of Curwain & Holton (1973).

In the other experiments water or normal saline at the required temperature was circulated either through pyloric or Heidenhain pouches, and a temperature bath, at 25 ml./min. Secretion was collected from the gastric fistula. Cooling of the antral pouch was through a self-retaining catheter (Fig. 1). In these experiments, secretion was stimulated throughout by a fixed intravenous infusion of pentagastrin (0·25 or 0·125 μg/min), histamine (2·5 μg/min) or 2 deoxy-D-glucose (50 mg/kg for 20 min). For controls in these animals, the dose of secretory stimulant employed was given on another day for the duration of the usual experiment without alteration of the pouch temperature or use of local anaesthetics, as the case may be. For statistical analysis, paired comparison collection by collection with control was used.

The α- and β-adrenergic blocking agents, phenoxybenzamine and propranolol, were given as 30 and 25 mg I.V. boluses, respectively, at the start of the experiment, followed by a further 10 mg 1 hr later. Pentolinium tartrate, a ganglionic blocking agent, was given intramuscularly, 20 mg initially, followed by an additional 10 mg after 1 hr.

Six months after the original cooling experiments in the antral pouch animals Heidenhain pouches were constructed at a second operation, and the cooling experiment repeated with additional collections, now from the vagally denervated fundic pouch.

In order to determine the extent of the vagal innervation of the antral pouches, motility was measured following 2 deoxy-D-glucose (50 mg/kg.min for 20 min) and I.V. pentagastrin (1 μg/min). In order to measure pouch contractions, the pouch was filled with water through an indwelling catheter which was, in turn, connected to a pressure transducer and a Narco-Bio physiograph. Resting pressure within the system was atmospheric.

The local anaesthetic, lidocaine (2%, w/v, without adrenaline), was used for bilateral vagal block in the neck, and oxethazaine (0·2%, w/v) in citric acid/Na-citrate buffer (0·15 M) at pH 5 for block of the antral mucosa. This was effected by pumping the local anaesthetic solution through the lumen of the pouch at 12 ml./min. Previous work has indicated that oxethazaine is not absorbed and that 0·2% produces satisfactory anaesthetization without side effects. I.V. saline was given throughout each experiment at a rate sufficient to replace the fluid secreted.

Acid and pepsin were estimated in every sample, the latter using Anson's haemoglobin method (1938). The pepsin units used throughout are mg of tyrosine liberated from haemoglobin by the total pepsin activity in each 10 min collection.

In the experiments using blocking agents and vagal block, blockade was instituted when a secretory plateau had been obtained for hydrochloric acid. The mean of the three samples before blockade was compared with the mean of the first three when a plateau had been obtained after blockade. When 2-deoxy-D-glucose is used, a plateau is not obtained, but peak secretion is seen in the three samples 40–60 min after administration of the drug has started. In these experiments the mean of these three samples after antral cooling was compared in the same animal with the mean for 2-deoxy-D-glucose alone determined on another day.

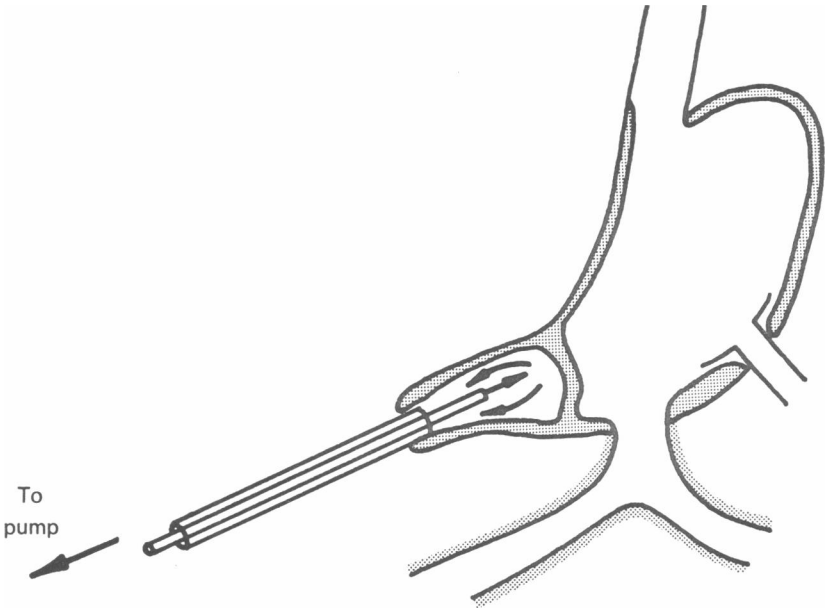

Fig. 1. The antral pouch and the irrigation method.

RESULTS

Within the range studied, 23–44° C, pouch acid secretion varied directly with luminal temperature. Mucosal blood flow and pepsin were not significantly changed within this temperature range (Fig. 2).

Cooling a Heidenhain pouch with water at 5° C for 50 min did not alter either acid or pepsin secretion from the main stomach (fistula). On rewarming the circulated water back to 37° C, however, acid secretion from the main stomach was significantly depressed in comparison to the uncooled pentagastrin controls. Pepsin secretion was depressed also, but significantly so in only one collection period (Fig. 3).

In the antral pouch experiments the mucosa was bathed either at 37° C or at 5° C. In the first set of experiments, the antral pouch was bathed

with ACh (0·5%, w/v) in citric acid/Na-citrate buffer (0·15 M, pH 4) at 37° C and at 5° C (Fig. 4). There was no significant change in fistula secretion of either acid or pepsin.

In the second set of experiments, I.V. pentagastrin at either 0·25 or 0·125 μg/min was the gastric secretory stimulant. In these experiments, changing the temperature of the antral bathing fluid (either water or saline) from 37° C to 5° C significantly increased acid secretion from the main stomach. Pepsin secretion in all four dogs was increased also, but reached significance in only one 10 min collection period (Fig. 4). The increase was larger when the background pentagastrin infusion was

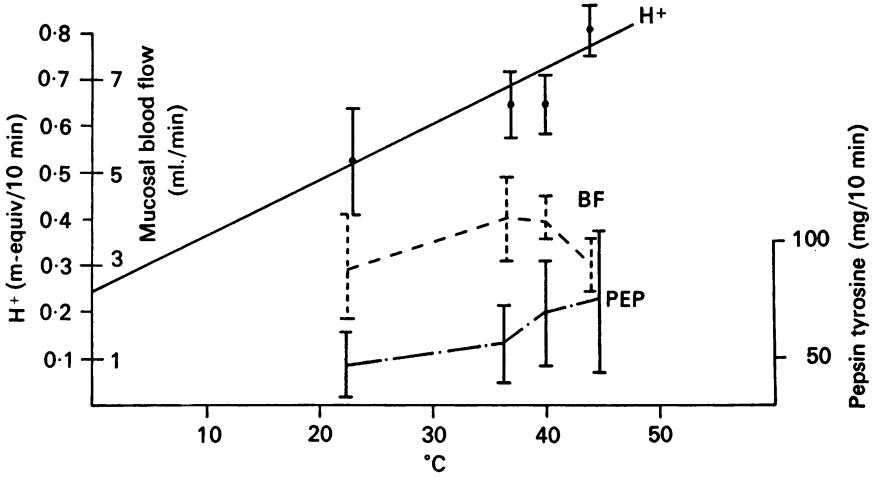

Fig. 2. The calculated regression line and the actual mean acid secretion ± S.E. of mean relating Heidenhain pouch temperature to pouch acid. BF and PEP actual mean mucosal and pepsin secretion, respectively. Regressions for these were not significant. r (H^+) = 0·520. $P < 0·05$. Each point is the mean of two successive observations in four dogs.

0·25 μg/min than when the pentagastrin dose was 0·125 μg/min. The converse was the case with pepsin, and once again the effect was much less dramatic.

Since it seemed possible that antral cooling might result in interruption of receptors, nervous in nature, the effect of local anaesthetic application to the antral mucosa on pentagastrin-stimulated gastric secretion was studied. Oxethazaine (0·2%) produced a marked increase in acid and pepsin from the fistula only. Oxethazaine applied to the antral mucosa during cooling neither enhanced nor depressed the usual gastric secretory augmentation following cooling (Fig. 7).

In an attempt to decide for or against vagal involvement in the stimu-

latory effect of antral cooling, the influence of lidocaine bilateral vagal block in the neck during cooling was examined (Table 3). Bilateral vagal block was accepted when the heart rate increased 50%, the eyelids drooped, and both nictitating membranes relaxed. The validity of these criteria was confirmed by the large drop in gastric fistula pepsin which always followed vagal block. The augmentation of fistula acid by antral

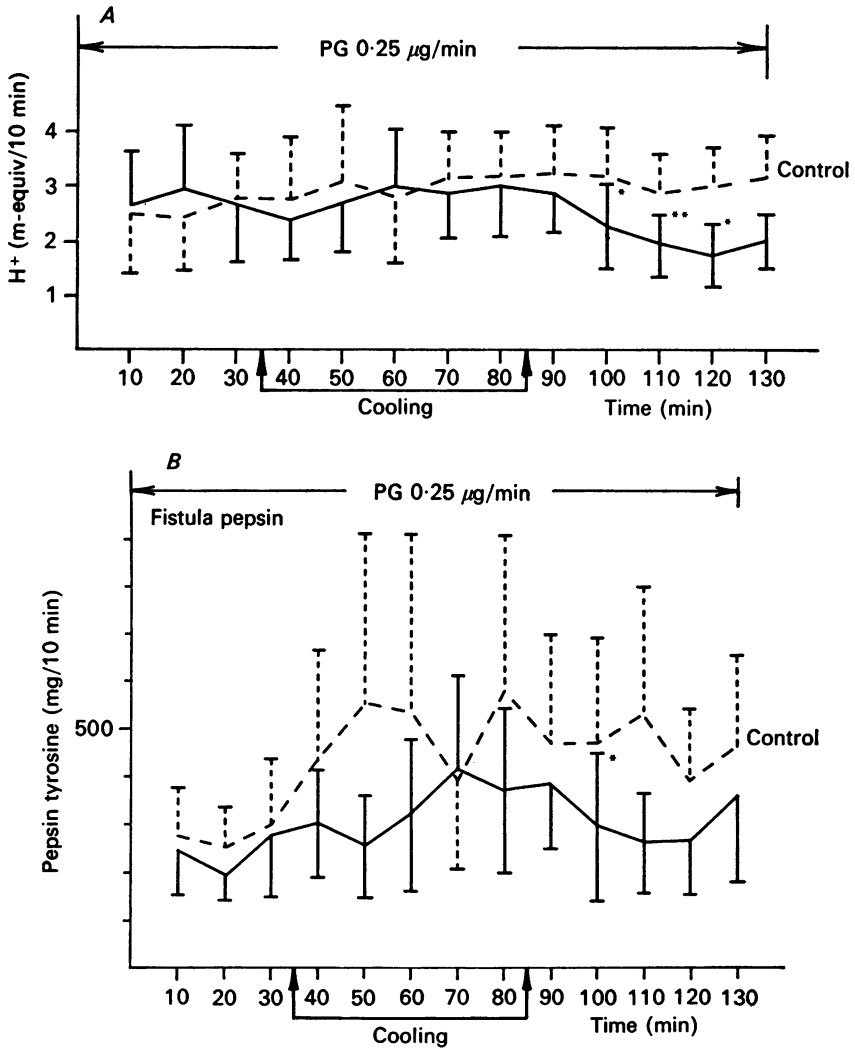

Fig. 3. The effect of Heidenhain pouch mucosal cooling on H^+ secretion (*A*) and pepsin secretion (*B*) from the main stomach. Warm 37° C; cooling 5° C. n = four dogs. *, ** Significantly different from corresponding paired non-cooled control at 0·05 and 0·01 levels, respectively.

cooling was unchanged, but fistula pepsin and pouch acid were significantly diminished.

Vagal stimulation was effected using 2-deoxy-D-glucose (50 mg/min for 20 min). Antral cooling during 2-deoxy-D-glucose treatment brought about a marked drop in fistula acid and pepsin. When local anaesthesia was applied to the antral mucosa, however, the stimulatory effects of 2-deoxy-D-glucose on fistula acid and pepsin were augmented (Fig. 8).

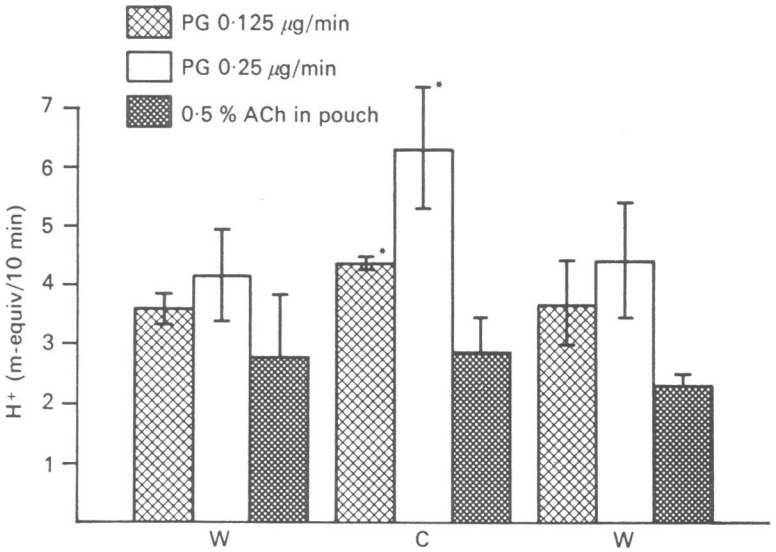

Fig. 4. The effect of antral cooling to 5° C on acid secretion from the fistula and of cooling antral ACh when it is the only secretory stimulus. Each bar is the mean of three consecutive observations before, during and after cooling. Warm (W) 37° C; n = three dogs. Cool (C). * Mean paired difference between cool and warm significant at 95% level. Paired differences for 0·125 and 0·25 μg/min pentagastrin 0·7368 ± 0·1693 and 2·1179 ± 0·4653 H^+ (m-equiv/10 min), respectively ± S.E. of mean.

The PG experiment was repeated after the construction of Heidenhain pouches in antral pouch animals. Cooling significantly raised acid and pepsin secretion from both the Heidenhain pouch (Figs. 5*a*, *b*) and the fistula (Fig. 6). The rise was less dramatic from the Heidenhain pouch and was significant for acid and pepsin during one 10 min collection period only.

After propranolol or ganglionic blockade (Table 1) in these same animals, antral cooling no longer altered acid or pepsin secretion from Heidenhain pouch or gastric fistula. However, propranolol itself raised pouch and fistula acid and pepsin. This was not further raised by antral cooling. When the antrum was rewarmed, fistula acid and pepsin unexpectedly increased further.

Antral cooling did not change histamine-stimulated (2·5 μg/min) acid or pepsin secretion from either pouch or fistula (Table 2).

We concluded that our antral pouches were innervated because their motility increased with 2-deoxy-D-glucose (50 mg/kg), and was not increased in amplitude by pentagastrin (1 μg/min). According to Sugawara, Isaza & Woodward (1969) I.V. pentagastrin increases the amplitude of contractions only when the vagal supply is interrupted.

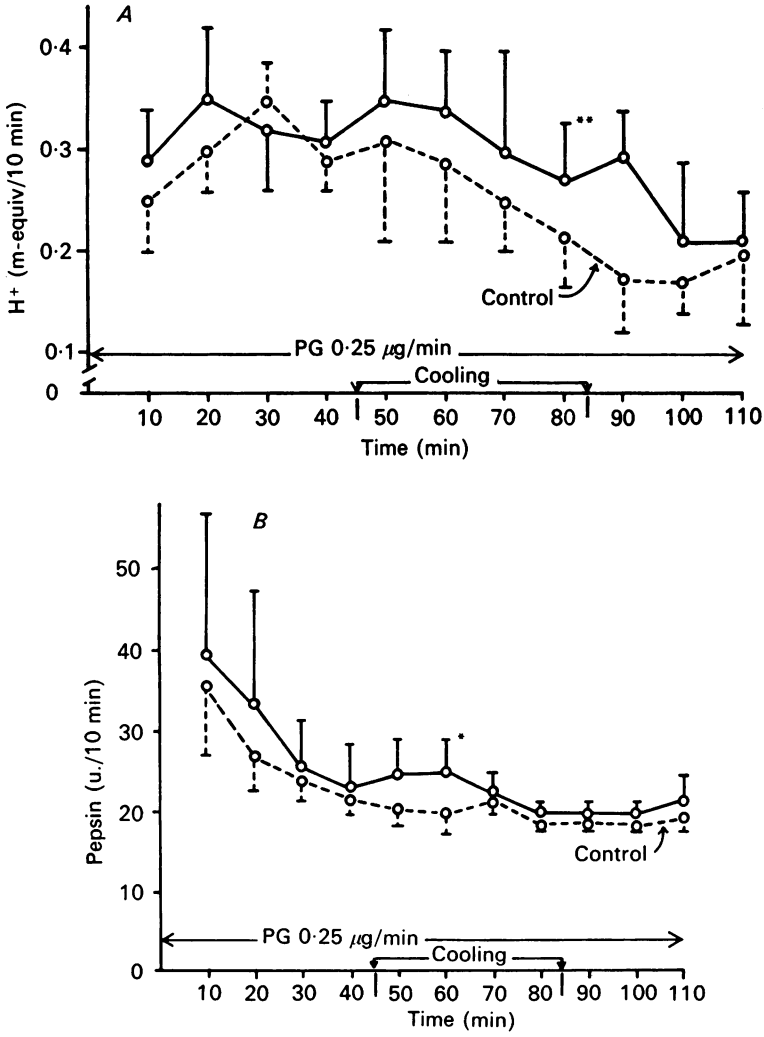

Fig. 5. *A* and *B*, effect of antral cooling to 5° C on pentagastrin-stimulated Heidenhain pouch acid (*A*) and pepsin (*B*) compared with non-cooled controls in the same animals. * $P < 0{\cdot}05$; ** $P < 0{\cdot}01$. Each point mean ± S.E. of mean of one collection from each of three dogs.

TABLE 1. The mean effect ± S.E. of mean of warming (W) and cooling (C) antral pouches on pouch and fistula acid and pepsin secretion in animals previously treated with propranolol (Pro) or ganglionic blockers (GB)

	W		C		W	
	Fistula (acid)	Fistula (pepsin)	Fistula (acid)	Fistula (pepsin)	Fistula (acid)	Fistula (pepsin)
Control	1·648 ± 0·8027	262·8 ± 154·6	2·9571 ± 1·2064	313·5 ± 126·6	3·144 ± 0·7454	274·0 ± 111·3
Pro	3·695* ± 0·8074	373·1 ± 64·4	3·7463 ± 0·8693	401·4* ± 145·7	4·3141** ± 0·6893	532·5* ± 152·6
GB	1·4548 ± 0·2531	132·0 ± 18·7	1·5258 ± 0·4406	89·5 ± 29·0	1·0641 ± 0·3455	82·9 ± 26·7
	W		C		W	
	Pouch (acid)	Pouch (pepsin)	Pouch (acid)	Pouch (pepsin)	Pouch (acid)	Pouch (pepsin)
Control	0·2974 ± 0·0405	26·85 ± 2·67	0·298 ± 0·0485	20·40 ± 1·43	0·2009 ± 0·0377	19·17 ± 0·66
Pro	0·3751** ± 0·0339	33·97 ± 6·83	0·361 ± 0·0704	27·35** ± 1·72	0·3071 ± 0·0787	24·79** ± 0·46
GB	0·3642 ± 0·0715	29·71 ± 3·89	0·3593 ± 0·0764	23·29* ± 1·44	−0·3160 ± 0·0926	23·77 ± 2·02

* Significantly different at the 95% level from the corresponding control figure.
** Significantly different at the 99% level from the corresponding control figure.

TABLE 2. The mean effect ± S.E. of mean of warming (W) and cooling (C) antral pouches on total pouch and fistula acid and pepsin secretion/10 min in animals receiving I.V. histamine (2·5 mg/min). Acid, m-equiv; pepsin, u.

	W	C	W	
Pouch (acid)	0·3615 ± 0·0619	0·3799 ± 0·1243	0·3644 ± 0·0841	$n = 3$
Pouch (pepsin)	31·2 ± 5·08	26·55 ± 4·49	31·14 ± 8·33	$n = 3$
Fistula (acid)	2·3236 ± 0·8039	2·5329 ± 0·8234	2·6707 ± 1·0083	$n = 4$
Fistula (pepsin)	221·4 ± 43·0	236·6 ± 75·2	384·2 ± 111·9	$n = 4$

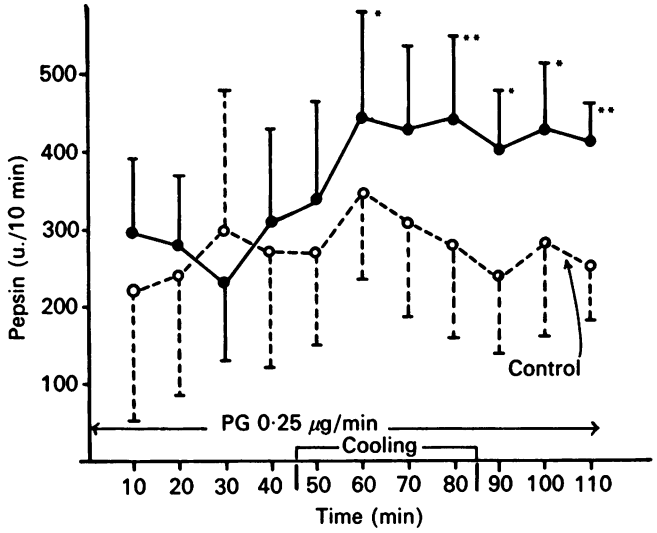

Fig. 6. Effect of antral cooling (5° C) on pentagastrin-stimulated fistula pepsin compared with a non-cooled control in the same Heidenhain pouch animals. *, ** Significant difference from control at $P < 0{\cdot}05$ and 0·01 respectively. Each point mean ± S.E. of mean of one collection in each of three dogs.

DISCUSSION

As expected, direct cooling of the fundic mucosa reduced its responsiveness to pentagastrin, but since cooling did not significantly change mucosal blood flow, direct depression of the secreting cells is the favoured explanation.

Many procedures and disorders which reduce the responsiveness of the fundic mucosa to pentagastrin, e.g. vagotomy (Johnston *et al.* 1973), atrophic gastritis (Ganguli, Cullen & Irvine, 1971) and catecholamines (Hayes *et al.* 1972), also raise serum gastrin levels. If reduced fundic responsiveness triggers the antral G cells, then reduction in fundic pouch sensitivity by cooling should increase fistula secretion.

This hypothesis is not borne out by the results – perhaps because the mucosal area was too small a fraction of the whole and perhaps because the pouches used were Heidenhain. The oxynto-pyloric reflex of Debas *et al.* (1975) was seen only in innervated pouches. A consistent finding, however, was a notable depression in gastric fistula acid secretion and a somewhat smaller and more equivocal one in pepsin secretion on rewarming the Heidenhain pouch. This might mean a more active or a more rapid inhibitory than stimulating oxynto-oxynto or oxynto-pyloro-oxynto mechanism. It could indicate also the dependence of stimulatory (but not inhibitory) mechanisms on vagal innervation. The reflex described by

Debas *et al.* (1975) was stimulatory to blood gastrin levels and required the vagi. Our pouches were Heidenhain, in which case we may have missed a stimulatory vagally mediated reflex and uncovered a sympathetic inhibitory one.

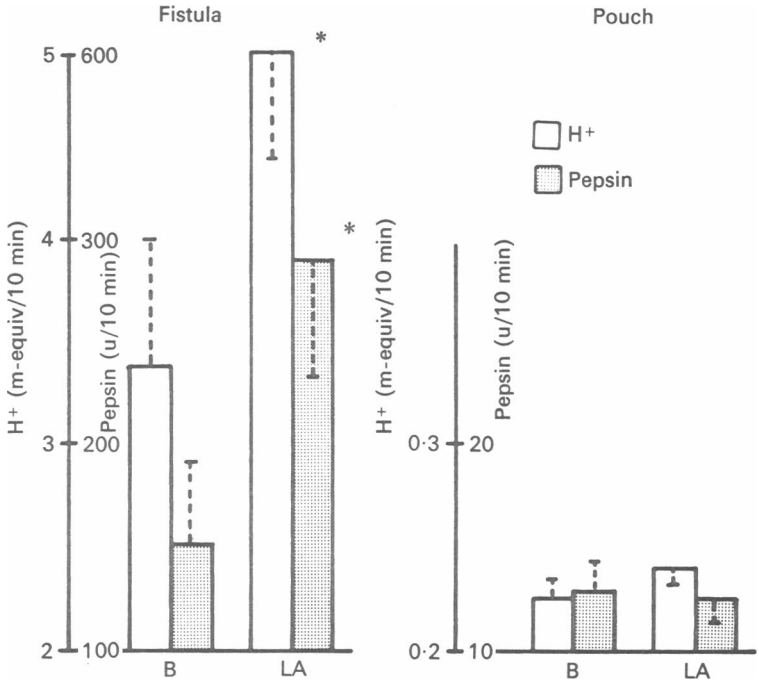

Fig. 7. Mean effect ± S.E. of mean of local anaesthesia, LA, (oxethazaine) to the antral pouch mucosa on the secretory response of the gastric fistula and Heidenhain pouch to pentagastrin (0·25 μg/min). Each bar is the mean of three successive observations. * Paired difference from before (B) significant at $<5\%$ level. Significant paired mean differences from B ± S.E. of mean: H^+ 1·7625 ± 0·4926. (m-equiv/10 min; pepsin 139·1 ± 40·7 (u./10 min). $n = 4$.

If the antral mucosa is the source of an inhibitor released when the fundic mucosa is warmed after cooling, an increase in fistula acid and pepsin secretion should be seen in pentagastrin-stimulated animals, when the pyloric antrum is depressed. This is what we have seen repeatedly in four animals in which we have physiological evidence of vagal innervation of the pyloric antral pouch, whether we cooled the antral mucosa or blocked it with a local anaesthetic. It has been seen also in Heidenhain pouches constructed later in these same animals. It might be argued that a self-retaining catheter, such as we have used in the antrum, must release endogenous gastrin and that this release is facilitated by low temperatures.

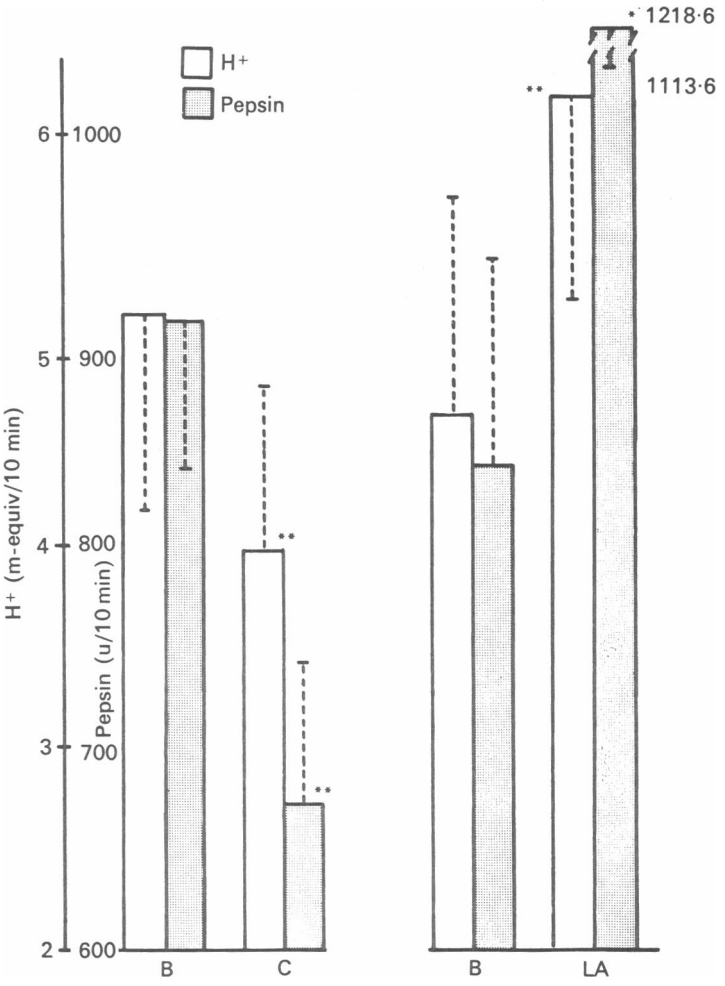

Fig. 8. Mean effect ± S.E. of mean of cooling (C) (left) and mucosal anaesthetization (LA) (right) of the antral mucosa on acid and pepsin secretion from the gastric fistula in animals receiving I.V. 2-deoxy-D-glucose. Each bar represents the mean of the three samples from 40–60 min after receiving 2-deoxy-D-glucose. The controls are for the same period without antral cooling. Mean paired differences (** and *) significant at the 98 and 95% probability level, respectively. Paired differences ± S.E. of mean significantly different from before (B) are as follows. Left fistula H^+ 1·1453 ± 0·1629. Fistula pepsin 673·9 ± 52·4. Right (local anaesthesia) fistula H^+1·5463 ± 0·3392. Fistula pepsin 373·9 ± 99·7. H^+ (m-equiv/10 min). Pepsin (u./10 min). n = four dogs.

No facilitation was seen, however, when we cooled ACh which had been placed in the pyloric pouch.

The increases seen in gastric fistula acid secretion after pyloric mucosal cooling were approximately 50%, whether pentagastrin was given at the rate of 0·125 or 0·25 ng/min, thus suggesting that the inhibition of antral origin is related directly, either to the potency of the stimulus or to the acid secreted.

TABLE 3. The effect of vagal block, α-adrenergic blockade and mucosal anaesthesia on the augmented response to pentagastrin produced by antral cooling. Each figure is the mean ± S.E. of mean of the last three observations of four following each procedure. $n = 4$ throughout

(*a*)

	Warm	Cool	Cool ↓
Pouch (acid)	0·2711 ± 0·0666	0·3159 ± 0·0959	0·1571 ± 0·0518*
Pouch (pepsin)	37·03 ± 3·33	37·15 ± 3·87	30·54 ± 1·55
Fistula (acid)	2·1856 ± 0·5737	4·7964 ± 0·7281**	3·5305 ± 0·2222
Fistula (pepsin)	340·9 ± 54·3	573·2 ± 99·2*	282·2 ± 18·3*

↓ Block of both cervical vagi.

(*b*) Pentagastrin (0·5 μg/min)

	Cool	Cool ↓
Pouch (acid)	0·3203 ± 0·1055	0·3635 ± 0·1447
Pouch (pepsin)	27·66 ± 2·94	31·44 ± 3·66
Fistula (acid)	4·2053 ± 0·2757	4·5606 ± 0·1799
Fistula (pepsin)	437·8 ± 49·7	441·8 ± 35·5

↓ I.V. phenoxybenzamine (30 mg).

(*c*) Oxethazaine (0·2%). pH 5. Topical application to the antral mucosa. Pentagastrin (0·5 μg/min) ($n = 4$)

	Cooling	Cooling + oxethazaine
Pouch (acid)	0·3098 ± 0·0783	0·3385 ± 0·1428
Pouch (pepsin)	20·54 ± 2·14	20·24 ± 2·62
Fistula (acid)	5·3545 ± 0·7115	4·7244 ± 0·5352
Fistula (pepsin)	375·2 ± 79·4	362·8 ± 85·2

* Significantly different at the 95% level from the corresponding fig. in the column to the left.

** Significantly different at the 99% level from the corresponding fig. in the column to the left.

The effect of antral cooling on pepsin secretion was bizarre, in that the augmentation was related inversely to the dose of gastrin.

The postulated pyloric inhibitory mechanism seems to be independent of central vagal connexions, since bilateral lidocaine block in the neck did not abolish augmented fistula acid response to cooling. Vagal block might

be expected to reduce pepsin secretion from the innervated gastric mucosa. The reduction in acid secretion from the Heidenhain pouch after vagal block, and the small and insignificant reduction in secretion from the fistula, might represent a decrease in endogenous gastrin.

The secretory response to histamine was unaltered by antral cooling. This makes it possible to say that antral cooling, or local anaesthetization, augmented only hormonally stimulated secretion. With 2-deoxy-D-glucose, local anaesthesia augmented gastric fistula secretion. Pyloric pouch cooling during 2-deoxy-D-glucose stimulation, on the other hand, depressed acid and pepsin from the main stomach and pepsin from the pouch by 38% which, however, was not enough to reach significance in only three dogs. Since cooling was found not to modify the ability of antral ACh to stimulate gastric secretion, it was concluded that cooling blocks the vagal supply to the G cells while local anaesthesia blocks the mechanism which reduces the action of gastrin on the secreting mucosa. This view would be more substantial if local anaesthesia had significantly augmented 2-deoxy-D-glucose-stimulated acid secretion from the Heidenhain pouches, but once again significance was not quite reached.

The suggested pyloric inhibitory mechanism uncovered by cooling and local anaesthesia could be either hormonal or nervous. We favour a sympathetically mediated mechanism because we do see occasional, though small effects on the Heidenhain pouch which has full sympathetic innervation, and also because propranolol increases secretion to the extent that cooling of the pyloric mucosa no longer produces augmentation. The increase in fistula secretion in these animals on rewarming the antral pouch was unexpected, and is unexplained at the moment. Augmented acid secretion following β-blockade has been observed before (Evan & Lin, 1970; Magee, 1976). Recent work has shown that β-adrenergic stimulants are potent inhibitors of pentagastrin-stimulated acid and pepsin secretion but not of methacholine (Magee, 1976) or histamine (Curwain & Holton, 1972). As far as it has been tried, cooling, local anaesthesia or propranolol do not interfere with, or modify, one another on acid and pepsin secretion, which supports a common mechanism.

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