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MECHANISMS RELATING GASTRIC ACID SECRETION AND MUCOSAL BLOOD FLOW DURING GASTRIN AND HISTAMINE STIMULATION

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SUMMARY

1. Gastric mucosal blood flow (MBF) and gastric acid secretion have been compared and related during the infusion of a wide dose range of gastrin extracts, pentapeptide (Peptavlon, I.C.I. 50123) and histamine.

2. Constancy of increase in mucosal blood flow relative to H^+ secretion was obtained with gastrin stimulation, whereas histamine stimulation produced higher ratios of mucosal blood flow to H^+ secretion, and these ratios declined as each experiment continued.

3. The importance of considering only the increase in mucosal blood flow in relation to acid secreted is demonstrated.

4. It is concluded that the differences shown in the $\Delta MBF/\Delta H^+$ with histamine and gastrin stimulation provide further evidence that the amidopyrine clearance technique measures gastric mucosal blood flow.

INTRODUCTION

The secretion of gastric acid in response to intravenous injections and infusions of histamine or gastrin in cats and dogs has been shown to be correlated with an increase in gastric mucosal blood flow as measured by the amidopyrine clearance technique (Jacobson, 1965; Jacobson, Eisenberg & Swan, 1966; Jacobson, Linford & Grossman, 1966; Jacobson, Swan & Grossman, 1967; Swan & Jacobson, 1967; Moody, 1967; Harper, Reed & Smy, 1968).

Although in general the mucosal blood flow has been shown to vary in the same direction as gastric acid secretion (Jacobson *et al.* 1966, 1967; Cowley, Code & Fiassé, 1969; Reed & Smy, 1968; Moody, 1968) there has

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been no direct evidence as to the nature of the relationship between the two parameters.

It was decided to study the relationship between the increase in mucosal blood flow and the increase in H^+ output above basal levels during gastric secretory stimulation with a variety of doses of pentapeptide (Peptavlon, I.C.I. 50123), crude pyloric gland area extracts (Blair, Harper, Lake, Reed & Scratcherd, 1961) and histamine, as this might produce evidence as to the nature of the mechanism relating mucosal blood flow and gastric acid secretion.

METHODS

The experiments were performed on cats anaesthetized with ether followed by chloralose (80 mg/kg I.V.). The vagus nerves were cut in the neck, and the splanchnic nerves sectioned extraperitoneally in an attempt to minimize the effects of surgical trauma. A wide-bore catheter (i.d. 6·5 mm) was passed into the stomach through an incision in the cervical portion of the oesophagus until the tip lay in the pyloric antrum. The pylorus was occluded with a tape ligature. A nylon catheter was inserted into the left carotid artery, with its tip directed towards the aorta to allow monitoring of arterial B.P. and collection of arterial blood samples.

After completion of the operative procedure, a priming dose of amidopyrine (20 mg/kg I.V.) was given, followed by intravenous infusion of amidopyrine at a rate of 10 mg/kg.hr. An acidified isomolar solution (50 ml. of a 5:1 v/v mixture of 300 m-osmole/l. solutions of mannitol and glycine, brought to pH 3·4 by addition of 0·15 N-HCl) was run into the stomach and replaced at 15 min intervals. A measure of the secreted H^+ was obtained from the increment in titration volume when a sample of the washout fluid was brought to pH 7·0 by 0·02 N-NaOH, combined with the volume of the washout. The amidopyrine concentrations of blood and gastric contents were estimated by the method of Brodie & Axelrod (1950). Gastric mucosal blood flow was measured by the technique described by Harper *et al.* 1968. The amidopyrine content was determined for a 1 or 2 ml. sample of gastric washout collected during each 15 min period and the total amidopyrine output calculated from these figures and the volume collected. From these measurements gastric mucosal blood flow, (MBF) ml./15 min, was calculated as

$$\frac{\text{gastric output of amidopyrine, } \mu\text{g/15 min}}{\text{arterial plasma amidopyrine, } \mu\text{g/ml.}}.$$

Eight groups of experiments were carried out in which sustained gastric acid secretion was stimulated by the I.V. injection (in 1 ml. saline during the first minute of each 15 min collection period) or continuous I.V. infusion of one of the following:

1. Injection of 1–10 μg pentapeptide (I.C.I. 50123 Peptavlon).
2. Infusion of 1–10 μg pentapeptide per 15 min.
3. Injection of 20–30 μg pentapeptide.
4. Infusion of 20–30 μg pentapeptide per 15 min.
5. Injection of 1 mg of a crude gastrin extract (Blair *et al.* 1961).
6. Injections of incremental (1–10 mg) doses of crude gastrin extract.
7. Infusion of 4·5 μg histamine acid phosphate/kg body wt.min.
8. Infusion of 45·0 μg histamine acid phosphate/kg body wt.min.

The doses of pentapeptide used were constant in any one animal. Thirty minutes before the infusion of the large dose of histamine an I.M. injection of 50 mg of

mepyramine maleate (B.D.H. Anthisan) was given to minimize the histamine induced fall in blood pressure (Bond & Hunt, 1956).

The acid and mucosal blood flow responses were expressed as the increase in H^+ output (ΔH^+) and increase in mucosal blood flow (ΔMBF) above their appropriate basal values determined before stimulation. All results are expressed as the means $\pm$ S.E. (N) = number of observations. In each experiment the individual ΔMBF and ΔH^+ results have been expressed as the ratio ΔMBF (ml./15 min)/ΔH^+ (μequiv/15) indicating blood flow per unit H^+ secretion.

RESULTS

Blood pressure was monitored in most experiments. Experiments were not carried out in animals in which arterial B.P. was below 60 mm Hg, and results were discarded in the few experiments in which sudden alterations of arterial B.P. occurred. In a group of seven experiments acid secretion, arterial B.P. and MBF were studied during continuous gastrin stimulation. Mucosal blood flow and arterial B.P. were expressed as % of the values observed during the peak acid secretion and were related to time following this peak. The mean B.P. at the peak of secretion was 125 ± 7 (seven) mm Hg. Blood pressure subsequently declined at a slow but significant rate of 0·1% min ($m = \bar{0}{\cdot}102$%/min, $r = \bar{0}{\cdot}5573$, $P = < 0{\cdot}001$, $N = 59$). Mucosal blood flow also diminished during this period ($m = \bar{0}{\cdot}25$% min, $r = \bar{0}{\cdot}6159$, $P = < 0{\cdot}001$). However, there was no correlation between % B.P. and % MBF during this time ($r = 0{\cdot}1953$, $P = > 0{\cdot}1$).

The large dose of histamine (45 μg HAP/kg.min), infused at least 1 hr following the I.M. injection of 50 mg mepyramine maleate, always produced a fall in arterial B.P. In a series of five animals there was a significant fall of B.P. from 119 ± 10 to 76 ± 6 mm Hg within 10 min of starting the infusion. There was no further significant fall in arterial B.P. during the course of the histamine infusion ($m = 0{\cdot}041$ mm Hg/min, $r = 0{\cdot}0745$, $P = < 0{\cdot}1$).

Gastrin stimulation

(*a*) *Pentapeptide stimulation* (P 5)

The pattern of Δacid responses and the corresponding ΔMBF to infusions and repeated single injections of pentapeptide are shown in Fig. 1. When doses of between 1 and 10 μg of P 5 were injected at the beginning of each 15 min collection period in nine cats (Fig. 1*A*) the mean ΔH^+ and ΔMBF responses increased up to the 4th collection period and thereafter remained more or less constant. The mean ΔH^+ response during the 4th collection period was $194{\cdot}0 \pm 31{\cdot}0$ μequiv/15 min, and the mean ΔMBF response $31{\cdot}0 \pm 5{\cdot}7$ ml./15 min (nine). In contrast infusions of 1–10 μg of P 5/15 min throughout the experiment (Fig. 1*B*) produced higher ΔH^+ and ΔMBF responses (mean, $333{\cdot}0 \pm 80{\cdot}5$ μequiv/15 min, and $38{\cdot}0 \pm 8{\cdot}6$ ml./15 min

(seven) in the 4th period, Fig. 1*B*). The general pattern of blood flow and H^+ secretion remained similar to those obtained with the repeated single injections (Fig. 1*A*).

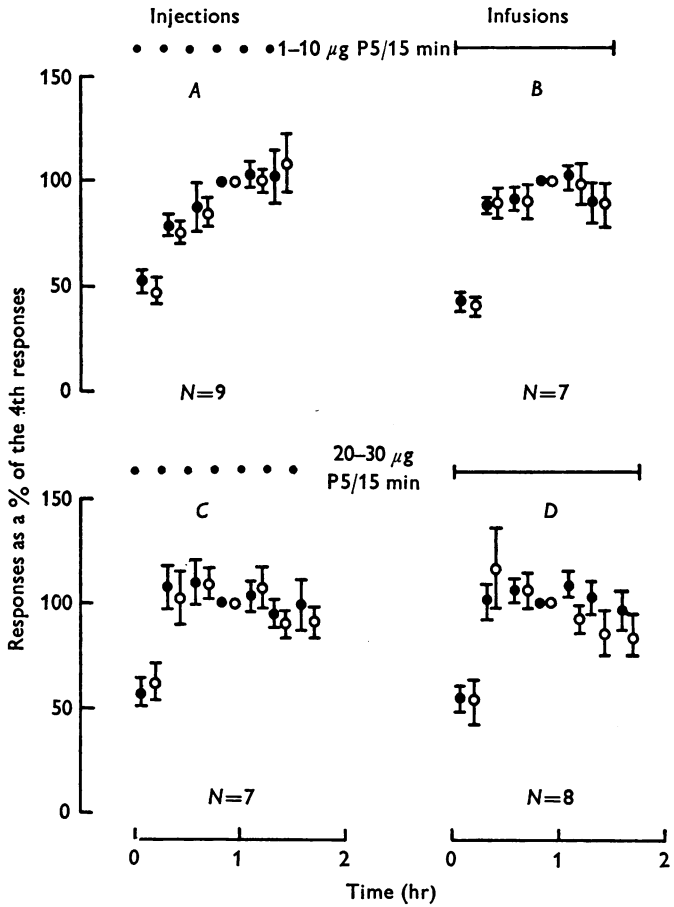


Fig. 1. Comparison of the mean ΔH^+ (●) and the mean ΔMBF responses (○) to injections and infusions of different doses of pentapeptide (P 5). Both mucosal blood flow and H^+ responses are expressed as percentages of the values observed during the 4th 15 min collection period. The bars represent ±1 S.E.

The larger doses of pentapeptide produced slightly different response patterns (Fig. 1*C*, *D*). Repeated injections of 20–30 μg/15 min produced the greatest responses during the 2nd and 3rd periods. There was a mean ΔH^+ response of 340·9 ± 91·8 μequiv/15 min and a mean ΔMBF response of 46·0 ± 15·0 ml./15 min (seven) during the 4th collection period. Once more infusion of this dose range produced greater acid and mucosal blood

flow responses (mean ΔH^+, 619·0 ± 62·5 μequiv/15 min, ΔMBF, 62·0 ± 6·8 ml./15 min (eight) during the 4th period). The maximum responses occurred during the 2nd and 3rd periods.

(*b*) *Crude extracts of pyloric gland area mucosa* (*PGA*)

Repeated injection of 1 mg PGA extract produced the largest responses of acid and mucosal blood flow during the 3rd collection period (Fig. 2*A*), and mean ΔH^+ and ΔMBF responses during the control 4th periods of 358·0 ± 42·0 μequiv and 44·0 ± 8·0 ml./15 min respectively. The other group of experiments using progressively increasing doses of PGA extract was designed to produce a steadily increasing acid output. Mucosal blood flow increased in a similar manner.

(*c*) *Histamine stimulation*

In response to the smaller of the two doses of histamine (4·5 μg HAP/kg.min) the acid and mucosal blood flow responses increased progressively throughout the period studied, whereas the large dose of histamine, 45 μg HAP/kg.min administered following a 50 mg injection of mepyramine maleate, produced only a gradually increasing response after the 3rd collection period (Fig. 2*B*). During the 4th periods the corresponding mean ΔH^+ responses were 435 ± 51 (eight) and 1080 ± 67 μequiv/15 min (ten), and ΔMBF 60 ± 10 (eight) and 475 ± 63 ml./15 min (ten).

The most obvious characteristic of the response pattern to the large dose of histamine is the significantly higher acid and blood flow responses compared with all the other forms of stimulation used (Table 1; differences between the means of all ΔH^+ and ΔMBF responses in the 4th periods and those in the 4th period in response to the large dose of histamine were significant $P < 0{\cdot}01$ in each case).

Mucosal blood flow per unit acid secretion

Over the total time studied (i.e. up to 105 min) there was no significant alteration in ΔMBF/ΔH^+ with time in any of the 'gastrin' stimulation experiments ($P > 0{\cdot}05$ in each case, Table 2). Furthermore, the mean ratios in corresponding periods were not significantly different throughout the groups of gastrin stimulation experiments, with the exception that in certain periods of experiments in which 20–30 μg pentapeptide were infused the ratios were significantly lower than in corresponding periods in some other experiments. These differences are summarized in Table 3. In general the difference occurred in the later part of the experiments.

In contrast to the gastrin stimulation experiments, both groups of histamine experiments show a significant reduction of the mean ΔMBF/

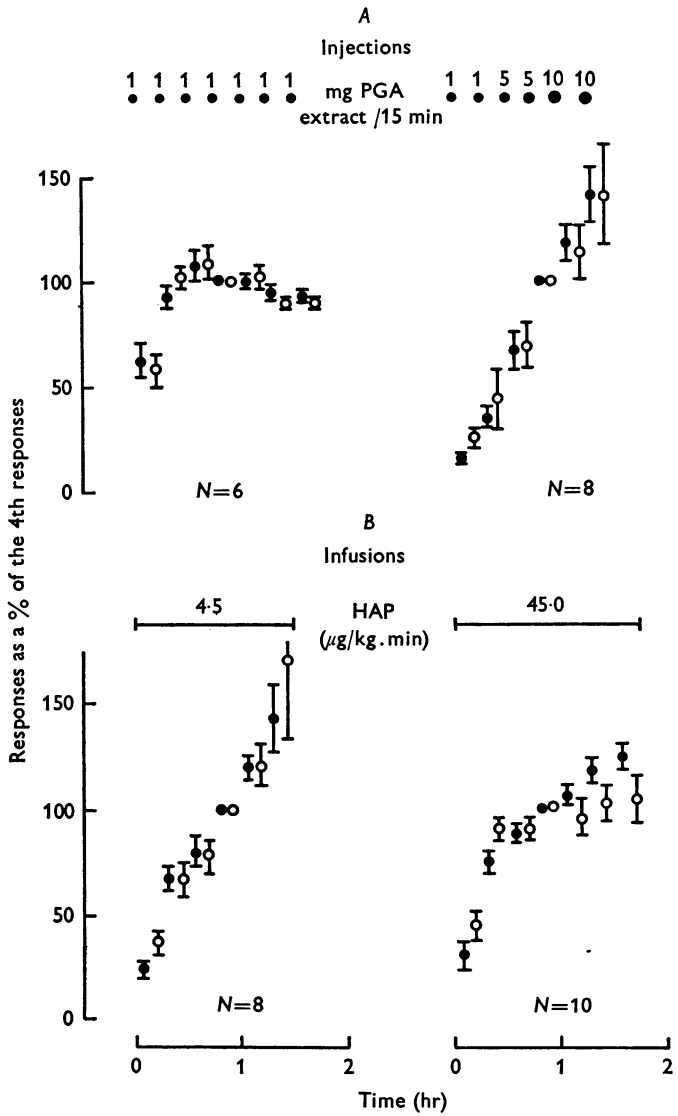


Fig. 2. *A*. Comparison of the mean % ΔH^+ (●) and the mean % Δmucosal blood flow responses (○) to injections of 1 mg/15 min and incremental doses, 1–10 mg/15 min of a pyloric gland area extract (PGA).

B. Comparison of the mean % ΔH^+ (●) and the mean % Δmucosal blood flow responses to infusions of 4·5 and 45·0 μg/kg.min of histamine acid phosphate (HAP). The bars in each diagram represent ± 1 S.E.

ΔH^+ in successive collection periods, $P < 0{\cdot}01$ in each case (Table 2). The mean ratio of each collection period in response to the large dose of histamine was significantly greater than that in corresponding periods with the smaller dose of histamine ($P < 0{\cdot}05$), and with all form of gastrin stimulation ($P < 0{\cdot}05$ in each case).

TABLE 1. Mean ΔH^+ and ΔMBF responses during the 4th periods in each series of experiments

Stimulus			Responses during 4th period				
Material	Route	Dose (μg/ 15 min)	Mean ΔH^+ (μequiv)	S.E. ±	Mean ΔMBF (ml.)	S.E. ±	N
Pentapeptide	Inj.	1–10	194·0	31·0	31·0	5·7	9
Pentapeptide	Infus.	1–10	333·0	80·5	38·0	8·6	7
Pentapeptide	Inj.	20–30	340·0	91·8	46·0	15·0	7
Pentapeptide	Infus.	20–30	619·0	62·5	62·0	6·8	8
PGA extract	Inj.	1000	358·0	42·0	44·0	8·0	6
PGA extract	Inj.	Increments*	555·0	33·0	58·0	9·0	8
Histamine acid PO_4	Infus	4·5	435·0	51·0	60	10·0	8
	Infus.	45·0*	1080·0	67·0	475	63·0	10

* Increments of PGA were 1, 5 and 10 mg, and the doses of histamine acid phosphate were μg/kg body wt.min.

In the absence of significant alteration of $\Delta MBF/\Delta H^+$, either with time, dose of gastrin, or manner of administration within 5 of the 6 'gastrin' experimental groups, these results have been pooled and compared with those obtained in the one exception, i.e. the 20–30 μg pentapeptide/15 min infusions, and the low and high dose histamine experiments (Fig. 3). The $\Delta MBF/\Delta H^+$ of the majority group of 'gastrin' experiments was $0{\cdot}135 \pm 0{\cdot}006$ (227), i.e. 13·5 ml. blood flow per 100 μequiv of acid secreted. Minimal blood flow per 100 μequiv H^+ secreted was observed with infusions of large doses of P 5, the mean ratio being $0{\cdot}095 \pm 0{\cdot}005$ (fifty-three), i.e. a mean 9·5 ml./100 μequiv H^+, in contrast to a mean 47 ml. blood/ 100 μequiv H^+ secreted in response to the large dose of histamine.

In thirteen cats (total body wt. = $3{\cdot}46 \pm 0{\cdot}32$ kg) the gastric mucosa was dissected from the gastric muscle immediately post mortem, weighed, and expressed as a percentage of the total body weight. The mean gastric mucosal weight was 0·405 % of the total body weight $\pm$ 0·024 (absolute wt. of mucosa = $13{\cdot}6 \pm 1{\cdot}3$ g (thirteen). The mean resting mucosal blood flow determined before stimulation of acid secretion in these thirteen animals was $1{\cdot}31 \pm 0{\cdot}23$ ml./g wet mucosa.15 min. In seventy-eight cats the resting

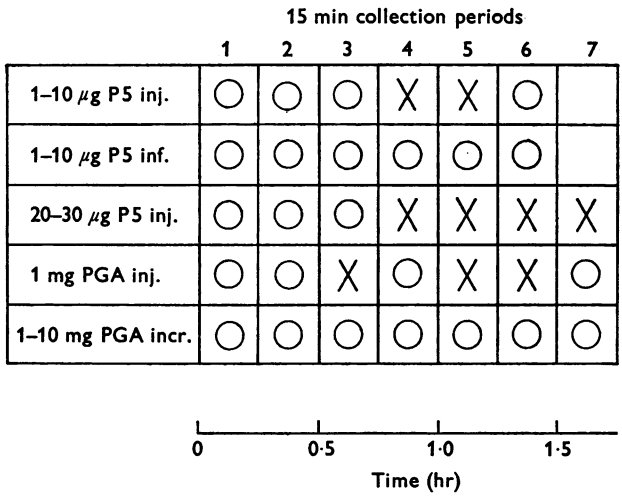
TABLE 2. Relationship between the increase in MBF/the increase in H^+ per 15 min (the $\Delta MBF/\Delta H^+$ ratio) and time

Stimulus									
Material	Route	Dose (μg/ 15 min)	Duration no. of 15 min periods	m	r	P	N	Mean $\frac{\Delta MBF}{\Delta H^+}$	S.E. $\pm$
Pentapeptide	Inj.	1–10	6	0·0005	0·0137	> 0·1	52	0·154	0·009
Pentapeptide	Infus.	1–10	6	0·0021	0·0708	> 0·1	42	0·131	0·009
Pentapeptide	Inj.	20–30	7	$\bar{0}$·0007	$\bar{0}$·0612	> 0·1	47	0·137	0·005
Pentapeptide	Infus.	20–30	7	$\bar{0}$·0051	$\bar{0}$·2380	> 0·05	53	0·094	0·004
PGA	Inj.	1000	7	$\bar{0}$·0007	$\bar{0}$·0325	> 0·1	39	0·128	0·005
PGA	Inj.	Increments*	6	$\bar{0}$·0034	$\bar{0}$·2651	> 0·05	47	0·119	0·006
Histamine acid PO_4	Infus.	4·5*	6	$\bar{0}$·0147	$\bar{0}$·3565	< 0·01	53	0·190	0·011
	Infus.	45·0*	7	$\bar{0}$·0424	$\bar{0}$·4239	< 0·001	64	0·470	0·026

Time in each experiment expressed as number of 15 min periods studied.

* Increments of PGA were 1, 5 and 10 mg, and the doses quoted for histamine acid phosphate were per kg body weight/min.

TABLE 3. Illustration of the difference between the mean $\Delta MBF/\Delta H^+$ in corresponding periods of the 20–30 μg P 5/15 min infusions and all other 'gastrin' stimulation experiments. There was no significant difference between the $\Delta MBF/\Delta H^+$ in corresponding periods when comparing all other groups of 'gastrin' stimulation experiments



× Significant difference between means at 5% level.

○ No significant difference between means.

MBF was 5·74 ± 0·43 ml./kg body wt. 15 min. This is equivalent to a mean resting mucosal blood flow of 1·42 ml./g wet mucosa. 15 min using the above relationship between gastric mucosal and total body weight. In comparison, the mean mucosal blood flow at the height of secretion stimulated by the large dose of histamine in ten cats was 188 ml. ± 21·8/kg body wt. 15 min, equivalent to 46·4 ml./g wet mucosa. 15 min.

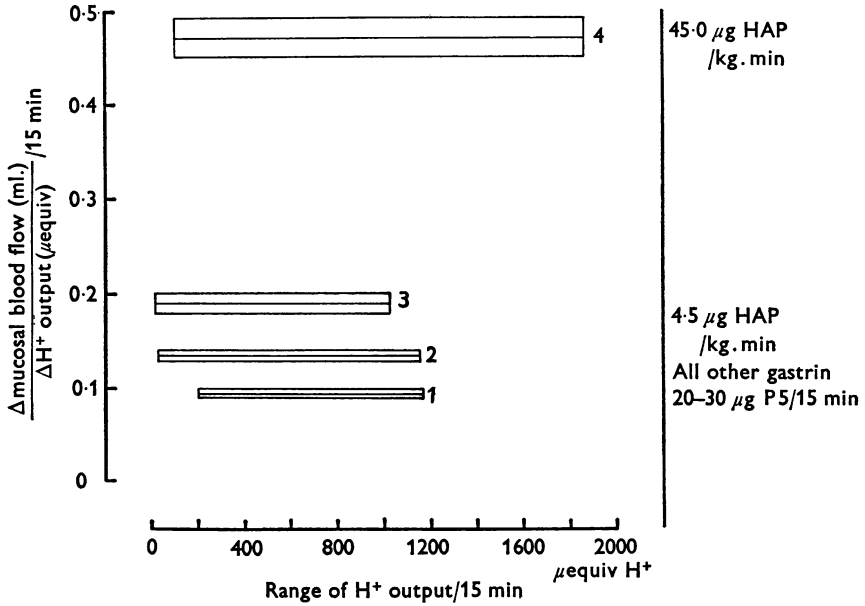


Fig. 3. Comparison of the mean ΔMBF/ΔH⁺ with various forms of gastric secretory stimulation. All results are expressed as the mean ± 1 S.E. and are shown over the range of acid secretion observed for that stimulant.

1. 20–30 μg P 5/15 min infusion (53).
2. Combined data 1–10 and 20–30 μg P 5/15 min repeated injections; 1–10 μg P 5/15 min infusions; 1 mg/15 min injections PGA extract and injections of 1–10 mg incremental doses/15 min PGA extract (227).
3. 4·5 μg histamine acid phosphate/kg. min (53).
4. 45·0 μg histamine acid phosphate/kg. min (64).

The means of each group are significantly different from one another at the 0·05 level.

DISCUSSION

It seems clear that there is no significant alteration in the relationship between the increase in mucosal blood flow and the increase in acid secreted in response to the majority of forms of 'gastrin' stimulation. There is no alteration in ΔMBF/ΔH⁺ during the course of experiments with gastrin stimulation despite a wide range of acid secretory rates within each experiment, and between the various groups (Table 3). Very few of

the corresponding periods show any significant difference in $\Delta MBF/\Delta H^+$ (Table 2). However, if the results are expressed as

$$\frac{\text{the total mucosal blood flow, ml./15 min period}}{\text{the total acid secreted, } \mu\text{equiv } H^+/15 \text{ min period}}$$

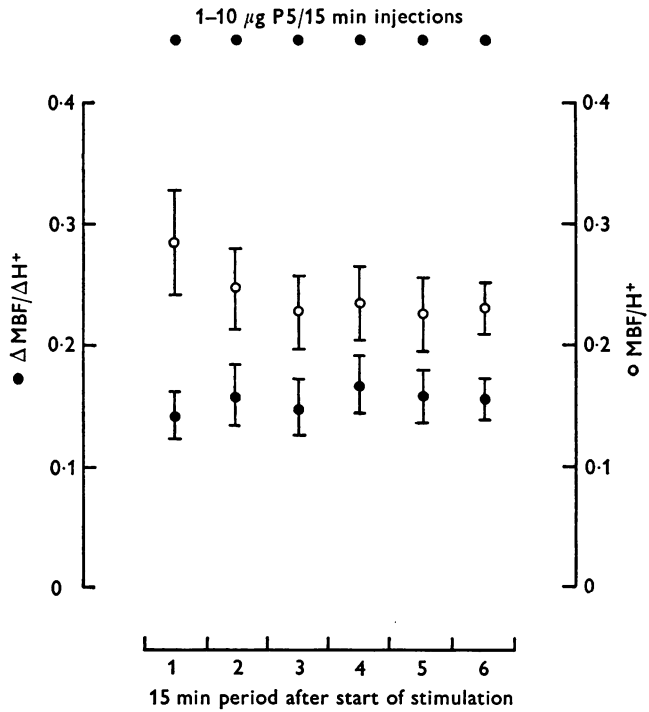


Fig. 4. Comparison of the mean $\Delta MBF/\Delta H^+$ with the MBF/H^+ of the same data during experiments with repeated injections of 1–10 μg P 5/15 min.

there is a very high initial ratio, falling during the first three stimulation periods to a more or less steady level, which is still in excess of the ratio of $\Delta MBF/\Delta H^+$ of the same data (Fig. 4). This illustrates the importance of considering only the ΔMBF in relationship to the secreted acid since the resting MBF is an increasing proportion of the total MBF as the acid secretory rate falls (Harper *et al.* 1968).

In contrast to the constant relationship between ΔMBF and ΔH^+ with various forms of 'gastrin' stimulation, this relationship varied markedly during histamine stimulation. The $\Delta MBF/\Delta H^+$ ratio decreased progressively with time during the infusions of both the large and the small doses of histamine (Table 3), and with the large dose of histamine the ratio was higher in each period than in the corresponding periods with all other

forms of stimulation. It has previously been reported from this laboratory (Harper *et al.* 1968) that the mean increase in mucosal blood flow per unit increase in H^+ was not significantly different when acid and blood flow were stimulated by either a small dose of histamine (4·5–6·0 μg histamine acid phosphate/kg.min) or a variety of doses of crude gastrin extract. These observations were made by calculating the correlation between MBF and H^+ in each experiment and taking the mean of the slopes in each group of experiments. These earlier observations are not confirmed by this study and it is clear that pooling the MBF and H^+ responses throughout an experiment, either in calculating a correlation or in pooling $\Delta MBF/\Delta H^+$, although permissible for gastrin experiments, is not justifiable during histamine stimulation experiments. Nevertheless, during infusion of 45 μg HAP/kg.min the $\Delta MBF/\Delta H^+$ is greater than with all other forms of stimulation throughout the period studied. The mean blood flow per 100 μequiv H^+ secreted was 47 ml.

These observations suggest that histamine produces greater mucosal blood flow per unit acid secretion (MBF/H^+) than does gastrin and that this increase in MBF/H^+ is probably related to the dosage of histamine. Bell & Shelley (1968) have reported that following vagotomy, the acid response to histamine in the conscious dog was reduced, whereas the MBF response was unaltered. This contrasted with the reduction of both acid and MBF responses to gastrin after vagal section. Such an effect of vagal section could be argued to cause the apparently greater MBF/H^+ seen with histamine in our studies. However, our results confirm the observations of Swan & Jacobson (1967) in conscious dogs with Heidenhain pouches, and Jacobson & Chang (1969) in dogs with innervated stomachs and gastric fistulae. It seems unlikely that the greater vasodilator effect of histamine depends solely upon the state of innervation of the stomach.

Small doses of histamine (up to 3 μg/kg.min) have almost uniformly been reported to increase MBF (Jacobson, Linford & Grossman, 1966; Delaney & Grim, 1965; Moody, 1967; Bell & Shelley, 1968; Cowley, Code & Fiassé, 1969) and often to increase total gastric blood flow (Peter, Nicoloff, Sosin, Walder & Wangensteen, 1962; Sosin, Bernstein, Peter & Wangensteen, 1964; Leonard, Engle, Peter, Long & Wangensteen, 1964; Harper *et al.* 1968). Reports of the effects of higher doses have seemed to show a reduction of blood flow. Bell & Shelley (1968) showed a parallel rise in MBF and H^+ in the conscious dog with histamine doses up to 1 μg/kg.min. Increasing the dosage to 2·0 μg/kg.min caused a further increase of acid secretion, but no increase in MBF. Willox, Michalyshyn & Kowalewski (1961) showed a profound reduction of gastric venous outflow following injection of 0·5–2·5 mg/kg I.M. whereas Delaney & Grim (1965) reported no change in gastric blood flow when doubling the I.M. dose of histamine in

beeswax from 30 to 60 mg/day. These authors did not measure acid secretion.

It is possible that the larger doses of histamine produced sufficient hypotension to reduce the gastric perfusion in spite of mucosal vasodilatation. The large dose of histamine (HAP, 45 μg/kg.min) was hypotensive in our studies, reducing the arterial B.P. from a mean 119 to 76 mm Hg in one group of animals. In spite of this the MBF/H^+ and the absolute MBF were greater with the large dose of histamine than with either gastrin or small doses of histamine (Table 1).

Mepyramine maleate (50 μg I.M.) was routinely injected before infusion of the large dose of histamine and yet there was a marked fall in B.P. and a rise in MBF (Table 1). It is possible that the fall in B.P. was due to failure of the antihistamine to protect non-gastric, peripheral vascular sites from the vasodilator effect of histamine. Alternatively, it may be that the fall in arterial B.P. was due mainly to the very large dilatation of the gastric mucosa. Such a specific action of histamine on stomach blood vessels would indicate that antihistamines in addition to their well-known lack of effect on histamine-stimulated gastric acid secretion, have little action on histamine-stimulated gastric mucosal blood flow. Schofield, Ingram & Torrance (1967), using liver clearance of iodinated albumin in man as an indirect measurement of gastric blood flow, showed no effect of antihistamine injected alone. Subsequent to infusion of histamine, however, they reported a marked rise in liver blood flow and gastric acid secretion. In contrast, Bell & Shelley (1968), using a heat clearance technique to estimate mucosal blood flow in conscious dogs, showed a marked rise in MBF following injection of mepyramine. Infusion of histamine after the antihistamine caused no further increase in MBF although there was acid secretion. It is difficult to reconcile these apparently contradictory reports of the action of antihistamine. The differences may reside in the techniques used to measure MBF or in the animal preparation.

The data reported above illustrate points of the physiology of gastric secretion and of the amidopyrine clearance technique for measuring mucosal blood flow. It is a point of argument that a method depending upon the dissociation of amidopyrine at acid pH will be affected by the amount of acid secreted, and that as the pH falls progressively below the pK of 5 then the clearance will increase. This would give rise to an increase in MBF/H^+ at higher rates of acid secretion. Furthermore, the fact that increased acid secretion is accompanied by a parallel increase in gastric juice volume makes almost inevitable a relationship between either volume or acid secretion and mucosal blood flow as measured by the technique. However, the results reported above show that the relationship between ΔMBF and ΔH^+ remains constant with 'gastrin' stimulation,

whereas with histamine the $\Delta MBF/\Delta H^+$ ratio declines. The $\Delta MBF/\Delta H^+$ ratio obtained with 'gastrin' stimulation remains constant throughout each experiment (Table 3) despite marked alterations in acid secretory response (Table 1), whereas during experiments with the large dose of histamine the mucosal blood flow rapidly reaches a more or less steady level while the acid secretion continues to increase (Fig. 2*B*). Although it is possible that some upper limit to the diffusion of amidopyrine, other than blood flow, could produce this constant, high rate of measured mucosal blood flow, which would as the acid secretion is increasing produce a progressive decline in $\Delta MBF/\Delta H^+$, this seems unlikely since the $\Delta MBF/\Delta H^+$ also falls progressively during stimulation with the low dose of histamine during which time the blood flow, and therefore the amount of amidopyrine crossing the gastric mucosa, is approximately $\frac{1}{8}$ of that during the infusion of a large dose of histamine (Table 1). In addition, the progressive fall in $\Delta MBF/\Delta H^+$ seen during infusions of both large and small doses of histamine owe as much to an initial more rapid increase in mucosal blood flow relative to H^+ secreted as to the reverse situation in the later part of the experiments (Fig. 2*B*).

It could be argued that the initial high $\Delta MBF/\Delta H^+$ ratio with histamine stimulation was an indication of our inability to measure the resting blood flow. Underestimation of this would produce a $\Delta MBF/\Delta H^+$ pattern approaching that seen when the results are expressed as MBF/H^+ (Fig. 4). This is, however, unlikely since there is no decline in $\Delta MBF/\Delta H^+$ during experiments with 'gastrin' stimulated secretion. It does remain possible that the high steady level of mucosal blood flow seen with the large dose of histamine shows the maximum mucosal blood flow response and this would represent some 309 ml./100 g mucosa.min.

In general it would seem that the mechanism responsible for relating the increase in MBF to the amount of acid secreted in response to gastrin stimulation is such that, at the rates of acid secretion studied, the increase in mucosal blood flow per unit acid secreted is constant. The difference between the mean $\Delta MBF/\Delta H^+$ observed with the two doses of histamine (Fig. 3) shows that the relationship alters with the dose of histamine, suggesting that histamine stimulates acid and blood flow separately, the effects being different with different doses. The constancy of the $\Delta MBF/\Delta H^+$ with gastrin stimulation would support the existence of a single mechanism relating H^+ secretion and mucosal blood flow. Similarly the high $\Delta MBF/\Delta H^+$, the decline in this ratio during histamine infusions, coupled with the fact that this ratio has not been observed to fall below the ratio observed during gastrin stimulation (Table 2), probably indicates at least two mechanisms determining MBF under the influence of histamine. Jacobson & Chang (1969) suggested that increased blood flow due to

histamine represented both a direct pharmacological vasodilating property and an indirect metabolic effect secondary to secretion. Our results would support this suggestion in that there is clearly an excessive MBF/H^+ with histamine, which is greater with the large dose of histamine. The failure of the ratio ever to fall below that observed with gastrin would allow the other mechanism seen with gastrin stimulation, of a MBF related to acid secretion. Furthermore, it seems likely that this direct stimulation of mucosal blood flow by histamine is liable to tachyphylaxis, i.e. progressive decline in the presence of a constant stimulus.

In a preliminary account, Reed & Smy (1968) have reported that increasing the gastric mucosal blood flow by infusions of a vasodilator, isopropylnoradrenaline, during acid secretion leads to an increased acid secretion. This may explain the observations that the large dose of histamine produced a significantly higher rate of acid secretion than did the largest dose of pentapeptide (Table 1). This dose of pentapeptide, 20–30 μg/15 min by infusion, is such that a further single injection of 100 μg pentapeptide produced little if any increase in acid secretion. It may be, however, that the excess blood flow associated with the histamine infusion facilitates acid secretion. Moreover, the excess of mucosal blood flow with histamine stimulation would argue against the use of this stimulant especially in experiments designed to evaluate inhibition of gastric secretion, since any inhibition depending upon reduction in mucosal blood flow could well be masked by the high blood flow rates associated with histamine stimulation.

Finally, we observed gastric mucosal blood flow rates between 10 ml. and 300 ml./100 g wet mucosa.min dependent on the stimulant and rate of secretion. It is inappropriate to compare these results with the majority of published figures of gastric blood flow. More often than not the secretory state of the stomach has been ignored; however, the reported range has been from 10 ml./100 g.min in anaesthetized dogs (Moody, 1967) to 52 ml./100 g.min (Delaney & Grim, 1964) in conscious dogs.

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