J. Physiol. (1953) 121, 445–451

GASTRIC SECRETION INDUCED BY HISTAMINE

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(*Received* 17 *January* 1953)

The vessels of the stomach receive only a small fraction of the cardiac output. If histamine acts directly on the stomach it would be expected that a certain rate of gastric acid secretion, produced by an intravenous infusion of histamine, would be maintained by infusing substantially less histamine directly into the arterial supply. However, Thompson & Vane (1953) found that the direct intra-arterial infusion rate had to be as great as the intravenous infusion rate to maintain the same volume of secretion per minute.

A possible explanation of this unexpected result was that when histamine was infused intravenously it accumulated in the blood, whereas when infused into the gastric circulation, it was largely inactivated by the liver.

By comparing the concentrations of histamine in the blood reaching the stomach during intra-arterial and intravenous infusions, we have shown that this is not the correct explanation. The results suggest that histamine-induced gastric secretion depends upon some interaction between histamine and the blood.

METHODS

Cats were anaesthetized with chloralose (70 mg/kg). The coeliac axis was prepared for perfusion of the gastric vessels by the method described in a previous paper (Thompson & Vane, 1953). Blood was withdrawn from the lower end of the abdominal aorta to supply the perfusion machine Type II A or II B (Vane, 1953). The secretion from the stomach was automatically collected over 10 min periods from a cannula inserted into the posterior wall at the pyloric end.

Histamine was infused from a constant output pump into the blood as it entered the perfusion circuit from the aorta, so that blood and histamine were mixed before reaching the cannula in the coeliac axis. Blood samples (4 ml.) were withdrawn from the coeliac cannula.

The concentrations of diffusible histamine in blood were measured by a new method (Born & Vane, 1952). Blood was dialysed against saline, histamine in the dialysate was purified by paper partition chromatography and assayed on the isolated ileum of the guinea-pig.

RESULTS

Table 1 shows the histamine concentrations observed in coeliac blood when histamine was infused intravenously and intra-arterially. During intra-arterial infusion, the histamine concentrations in the coeliac blood could be

calculated from the rate of infusion and the rate of blood flow. The concentrations observed in the blood during intra-arterial infusion of histamine were within 10% of the calculated value. This was within the experimental error of the method of measurement. During intravenous infusions of histamine (15 μg/min) the blood concentrations only rose to a mean value of 5·8 μg/100 ml. blood. These figures are similar to those given by Emmelin (1945) and Ojha & Wood (personal communication) for similar infusions, also in cats. Intra-arterial infusions of histamine at 15 μg/min led to very much higher concentrations in the coeliac cannula. Thus, there was no evidence for an accumulation

TABLE 1. Blood histamine concentrations in anaesthetized cats during different rates of histamine infusion. The blood was taken from the coeliac cannula

Expt. no.	Before histamine infusion	Histamine infusion (15 μg/min I.V.)	Histamine infusion (30 μg/min I.V.)	Histamine infusion (15 μg/min I.A.)	Histamine infusion (30 μg/min I.A.)
1	5·5	10	15	40 (*35 ml./min)	130 (*45 ml./min)
2	5·5	—	15	55 (*25 ml./min)	— —
3	3·1	3·8, 4·6	—	—	—
4	1·6	4·5	—	—	—
5	0·9	5·0	10	—	—
Mean	3·6	5·8	13	—	—

* Gastric blood flow

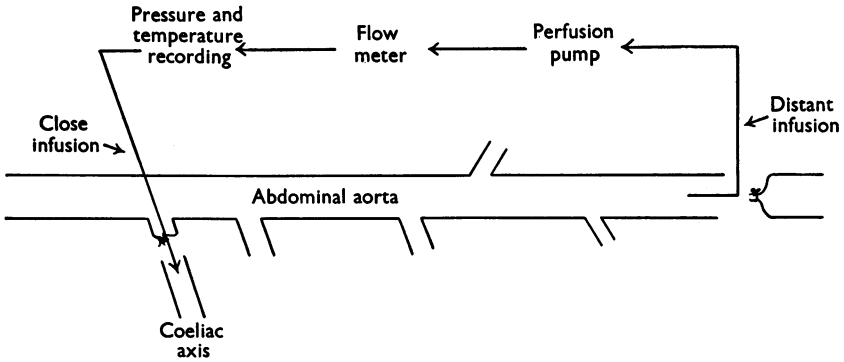

Fig. 1. Diagram showing perfusion circuit and points of infusion of histamine. In the 'distant' position, histamine was infused into the tube connecting the aorta to the perfusion pump. In the 'close' position, histamine was infused into the blood as close to the coeliac axis as possible.

of histamine on intravenous infusions which would explain the rather surprising observation of Thompson & Vane (1953) that as much histamine had to be infused intra-arterially as intravenously in order to cause the same rate of gastric secretion. When their experiments were repeated, using now Type II A and II B perfusion machines, another fact came to light.

Histamine was infused into the external perfusion circuit (*a*) as close to, and (*b*) as far away from, the stomach as possible (Fig. 1). In the close position,

the infusion was made into the coeliac cannula. In the distant position, the infusion was made into the reservoir of the pump.

On 'distant infusion' intra-arterially it was found that 3–5 μg histamine/min, gave as much secretion as 15 μg histamine/min intravenously (four cats). It was then found that whereas an infusion of histamine (1·5–10 μg/min) in the 'distant position' gave a good secretion, the same infusion in the 'close position' gave much less secretion (seven cats). This observation was repeated 12 times (Table 2) and the low rate of secretion from a close infusion was bracketed between high secretions from distant infusions.

TABLE 2. Changes in secretion obtained by infusing histamine at the same rate but into two different parts of the perfusion circuit

		Average secretion (ml./10 min)		
Expt. no.	Histamine dose (μg/min)	Hist. I.R. 1st period (away from stomach)	Hist. I.A. 2nd period (near to stomach)	Hist. I.R. 3rd period (away from stomach)
1	6	1·4	1·0	—
2	3·3	1·7	0·3	1·3
3	10	1·7	0·8	1·4
4	3	2·1	0·7	0·9
5	7·5	1·9	0·3	0·9
6	3	2·8	1·2	1·7
7	3	1·7	0·2	0·9
8	1·5	2·5	1·3	2·2
9	2·0	1·4	0·3	—
10	4·0	2·0	0·4	1·2
11	4·0	1·2	0·4	2·2
12	4·0	2·2	0·2	—

Means: I.R. (21 periods) 1·7 ml./10 min
I.A. (12 periods) 0·6 ml./10 min
I.R., into reservoir; I.A., into coeliac cannula

Fig. 2 shows a typical record. Sometimes at the beginning of an experiment there seemed to be no difference in the secretions resulting from 'close' and 'distant' infusions, but the difference always became apparent when the rate of histamine infusion was reduced. Throughout these experiments the pH of the juice remained low ($\leqslant$1·0) so that the amount of non-parietal secretion was negligible. If indian ink was injected at the 'distant position' into the perfusion reservoir it appeared in the coeliac cannula 5–15 sec later depending on the rate of flow of blood. It was, however, about 1 min before all the ink had disappeared from the external circuit. It seemed, then, that when histamine was infused into the reservoir it became 'activated' in less than 1 min.

It was possible that, when infused into the coeliac cannula close to the stomach, the histamine solution was contained in a thin streamline which was carried by the bloodstream along only one of the major arterial branches and therefore to only a part of the gastric mucosa. The secretory rate might then be lower than that obtained during an infusion into the pump system, wherein

the histamine would be well mixed with the blood and carried to all parts of the stomach, though at a lower concentration.

In the experiments described, histamine had been introduced into the blood stream through a hypodermic needle pushed through the wall of a piece of pressure tubing. By infusing indian ink in this way into an artificial perfusion circuit it was found that laminar flow did occur. However, the position and size of the streamline depended upon several factors: (*a*) the position of the tip of the infusion needle in relation to the cross-section of the perfusion tube;

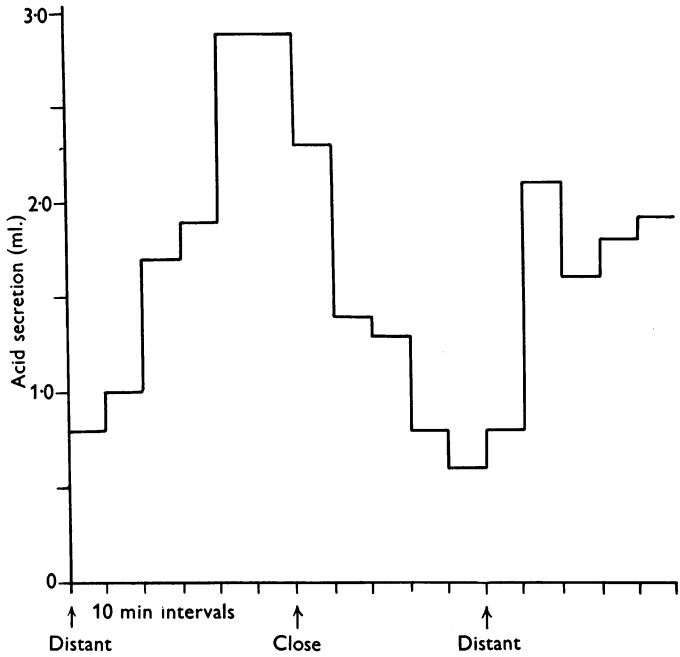

Fig. 2. The secretion resulting from 'distant' and 'close' infusion of histamine. During the 'distant' infusion the secretory rate increased to 2·8 ml./10 min. On close infusion it fell to 0·6 ml. On changing back to distant infusion, the rate again increased.

(*b*) the direction of entry of the infusion needle into the tube; and (*c*) the shape of the perfusion cannula. Different perfusion cannulae had been used and the position of the infusion needle was decided purely by chance. Therefore it seemed improbable that streamlining could account for the results. However, in order to break up any streamlines, a mixing device was included in the perfusion circuit so that the blood was thoroughly mixed just before it entered the stomach. This consisted of a small Perspex tube (Fig. 3), constructed so that the direction of flow of blood through it was abruptly changed several times. When the device was included in an artificial perfusion circuit an infusion of indian ink showed that it produced turbulence.

The secretion obtained by the distant infusion of histamine was compared with that obtained by infusing histamine into the mixing device 'close' to the stomach. Table 3 shows that in five cats, even though the mixing device was present, histamine infused into the perfusion circuit far from the stomach gave more secretion than histamine infused near the stomach. Streamlining, therefore could not account for the effect.

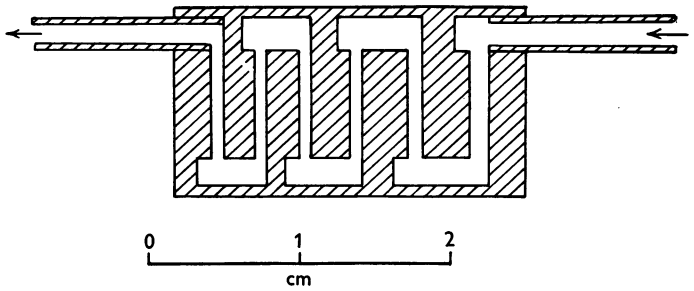

Fig. 3. The mixing device. This was made from Perspex and, when included in the perfusion circuit, caused turbulent flow.

TABLE 3. Changes in secretion obtained by infusing histamine at the same rate far from (I.R.) and near to (I.M.) the stomach.

		Average secretion (ml./10 min)				
Expt. no.	Histamine (μg/min)	Hist. I.R. 1st period	Hist. I.M. 2nd period	Hist. I.R. 3rd period	Hist. I.M. 4th period	Hist. I.R. 5th period
1	2·5	3·2	2·5	4·2	1·9	—
2	5·0	2·9	0·7	1·9	—	—
3	1·3	—	1·2	1·5	0·4	0·9
4	0·5	1·7	1·0	1·3	—	—
5	1·0	3·3	2·3	3·0	—	—

I.R., into reservoir; I.M., into mixing device.

DISCUSSION

It was found that when histamine was infused into the arterial blood supplying only the stomach, the gastric secretory rate depended upon the place where the infusion was made. The secretion obtained by infusing histamine close to the stomach was significantly less than when it was infused far from the stomach.

This difference was not accompanied by changes in the rate of gastric blood flow and could not be explained by inadequate mixing of blood and histamine when the infusions were made close to the stomach. It seemed, therefore, that if histamine was in contact with blood for a short time (about 1 min) before reaching the stomach the rate of secretion was greater than if the duration of contact between blood and histamine was reduced to the shortest possible.

What is the significance of this result? It is not known how histamine stimulates the stomach to produce acid secretion, but for many years it has

been assumed that histamine has a direct action upon the parietal cells of the gastric mucosa (Kahlson, 1948; Babkin, 1950). Evidence in favour of this assumption is that isolated gastric mucosae of certain species produce acid secretion in response to histamine applied to the serosal surface (Delrue, 1930, 1933; Gray, Adkinson & Zelle, 1940; Gray & Adkinson, 1941; Teorell & Wersäll, 1945; Davies, 1946; Edwards & Edwards, 1948; Patterson & Stetten, 1949; Davies, 1951).

However, the concentrations of histamine used were much higher than those needed to produce secretion *in vivo*. The possibility remains that, in order to produce secretion, histamine has to interact with a constituent of the mucosa or the bathing fluid. Moreover, most of the work on isolated gastric mucosa has been done with that of the frog which seems to differ from the mucosae of other animals. In the summer, an isolated piece of frog's mucosa will secrete spontaneously without the addition of histamine to the bathing fluid. This secretion cannot be due to any diffusible secretagogue originally contained in the mucosa, for the bathing fluid can be changed many times without any alteration in the rate of spontaneous secretion (Davies, personal communication).

Our results suggest the possibility that histamine acts *indirectly* upon the secretory cells of the stomach. An interaction between histamine and blood may be necessary before secretion can occur. The interaction needs some time to become effective.

Different kinds of interaction are possible. Blood may act upon histamine to produce the secretagogue. Histamine may liberate a substance from a constituent of blood which may produce secretion or increase the secretion produced by histamine. Again histamine may form a complex with a constituent of blood and thus remove an inhibitor of secretion.

It is commonly supposed, and there is some evidence, that antihistamine drugs compete with histamine for the same 'receptors' in tissue cells, and by combining with these 'receptors' abolish the action of histamine (Alonso, Adams, Goddard, Jaeger & Litchfield, 1948). If this were so then it would be expected that antihistamine drugs would abolish the action of histamine at all sites where histamine has a direct action. But the antihistamine drugs have no inhibitory effect upon histamine-induced gastric secretion. Indeed, they potentiate it (Loew & Chickering, 1941; Burchell & Varco, 1942; Hallenbeck, 1943; McElin & Horton, 1946; Emmelin & Frost, 1947; Wood, 1948; Gilg, 1948; Linde, 1950). These facts may perhaps also be regarded as evidence for an *indirect* action of histamine on gastric secretion.

SUMMARY

It was found that the rate of acid secretion from the perfused stomach of the cat depended upon the site of infusion of histamine. If the histamine was

allowed to mix with the blood for ½–2 min, the resultant secretion was greater than if the histamine was mixed with the blood for as short a time as possible.

Our thanks are due to Dr G. S. Dawes for many useful discussions. During this work, one of us (J. R. Vane) was in receipt of a grant from the Medical Research Council and latterly of a Stothert Research Fellowship from the Royal Society.

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