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THE SECRETION OF RADIOACTIVE IODIDE BY THE STOMACH OF THE ANAESTHETIZED DOG IN RELATION TO TOTAL GASTRIC BLOOD FLOW AND TO ACID SECRETION

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Lipschitz (1929) was probably the first to draw attention to the fact that the concentration of inorganic iodide in gastric juice was very much greater than that in plasma. The active transport of iodide by the gastric mucosa at physiological plasma-iodide levels has been studied since by many workers using radioactive iodide (see Brown-Grant, 1961, for references). In the majority of these studies no attempt has been made to express the rate of secretion of iodide in terms of the plasma content of iodide. One exception is the work of Howell & van Middlesworth (1956) who obtained values for the clearance of iodide by the stomach of anaesthetized dogs as high as 10–12 ml. of plasma/min after the injection of histamine. This value is of the same order as the rate of total gastric blood flow in anaesthetized dogs reported in an earlier study from this laboratory (Cumming, Haigh, Harries & Nutt, 1963) and it appeared possible that measurement of the gastric iodide-clearance rate might provide an indirect index of the blood flow. Iodide clearance by the stomach and total gastric blood flow have been determined in anaesthetized dogs, both unstimulated and during the infusion of histamine. In addition the effects of adrenaline and noradrenaline on histamine-induced iodide secretion have been investigated and also the action of 5-hydroxytryptamine, both alone and together with histamine. A preliminary account of some of our findings has already been published (Brown-Grant, Cumming, Haigh & Harries, 1963).

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METHODS

Healthy adult mongrel dogs (7·5–17·5 kg body weight) were used. Food was withheld for 24 hr before an experiment but animals were allowed water *ad lib.* The measurement of total gastric blood flow was carried out as described previously (Cumming *et al.* 1963). An intramuscular injection of approximately 20 μc of carrier-free $Na^{131}I$ was given after the operation had been completed and a tape tied round the pylorus. Gastric juice was collected during consecutive 10 min periods by intermittent suction (40–50 mm Hg). At the end of each period the volume of juice aspirated was noted and the stomach was washed out with 30 or 40 ml. of distilled water warmed to 37° C. The juice aspirated was added to the wash-out, the volume made up to 50 ml. and mixed thoroughly. Radioactivity was measured by counting 1 ml. of diluted juice in a well-type scintillation counter. A further 10 ml. of the diluted juice was titrated against 0·01 N-NaOH solution to pH 8·0 to determine the total acid secretion during the 10 min period. Arterial blood radioactivity was determined on 1 ml. samples taken from a cannula in the femoral artery and mixed gastric venous blood was sampled as it passed through the bubble flowmeter. Blood samples were taken about every 20 min during the early part of the experiment when the levels were changing rapidly and every 40–50 min later on when the rate of change was slower (Fig. 1).

The data on radio-iodide secretion was treated as follows. The total activity in the aspirated juice plus wash-out for each 10 min period was determined. The mean arterial blood activity at the midpoint of the collection period was determined by interpolation from a graph such as that illustrated in Fig. 1. *Iodide clearance* refers to the volume of blood required to be cleared completely of radio-iodide each minute to provide the amount of radio-iodide appearing in the total gastric aspirate per minute and was calculated as total activity (counts/100 sec) in a 10 min juice sample divided by estimated activity (counts/100 sec) in 10 ml. of arterial blood. The approximate volume of juice secreted in each 10 min period was known and a value for the juice/blood (J/B) concentration ratio for ^{131}I-iodide could be obtained. The ratio, gastric ^{131}I blood clearance (ml./min) divided by gastric blood flow (ml./min) was also calculated for each 10 min period. This value, which we have chosen to call the *clearance fraction*, gives an estimate of the proportion of the blood passing through the stomach that was actually cleared of iodide. In each experiment values for at least six successive 10 min periods at a given rate of histamine infusion were obtained before the rate of infusion was altered and the values were then averaged.

The arterial blood pressure was recorded on a kymograph from a mercury manometer connected to a cannula in a femoral artery.

Intravenous infusion of histamine acid phosphate (0·3–10·0 μg/kg/min), 5-hydroxytryptamine (5–20 μg of base/kg/min) given as the creatinine sulphate, adrenaline (2–8 μg/kg/min) and noradrenaline (2–8 μg/kg/min) were infused as required by a constant-rate injection apparatus into an external jugular vein.

RESULTS

Secretion of iodide by the stomach and the effects of histamine

Figure 1 shows the changes in arterial and gastric venous blood radioactivity during the course of a typical experiment. The highest level of arterial blood activity was generally observed 40–60 min after the injection of $Na^{131}I$. The rate of fall during the course of the experiment was influenced by the level of gastric iodide secretion; where this was persistently high under the influence of large doses of histamine, the fall in arterial blood radioactivity was more rapid. The level of activity in the gastric venous blood was also influenced by the rate of iodide secretion, the arterio-venous difference often increasing when secretion increased and decreasing when the rate of secretion fell. This can be seen in Fig. 1 where noradrenaline decreased and adrenaline increased gastric iodide secretion.

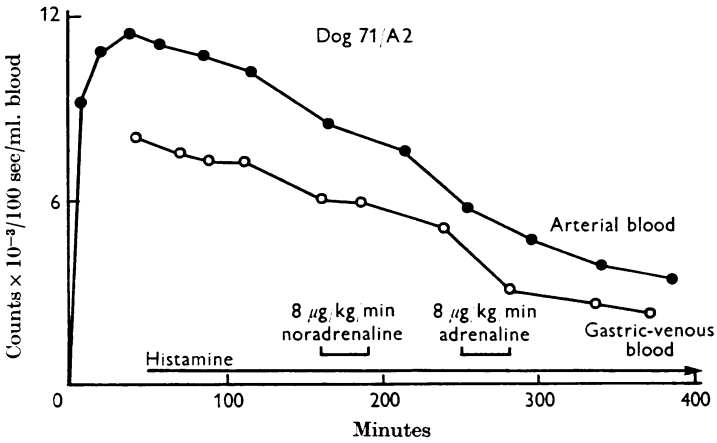

Fig. 1. Changes in arterial and gastric venous blood radioactivity during the course of a typical experiment in which histamine acid phosphate was administered continuously at a rate of 2·5 μg/kg/min. Solid circles are arterial blood, open circles gastric venous blood.

TABLE 1. The effect of intravenous infusions of histamine on the clearance of radio-iodide, the secretion of acid, and the blood flow through the stomach of anaesthetized dogs. Values are mean ± S.E. of mean

	Rate of infusion of histamine acid phosphate (μg/kg/min)				
	0	0·6	1·25	2·5	5·0
Number of dogs	16	4	4	12	9
^{131}I clearance (ml. blood/min)	0·8 ± 0·2	5·6 ± 3·2	5·5 ± 1·5	6·9 ± 1·9	8·6 ± 1·9
Total acid secreted (ml. N/100 acid/min)	0·2 ± 0·1	2·8 ± 1·7	3·1 ± 1·6	5·5 ± 2·1	8·5 ± 2·6
^{131}I cleared / Acid secreted	4·0 ± 0·8	4·2 ± 2·0	3·4 ± 1·8	2·2 ± 0·6	1·6 ± 0·3
'Clearance' / Total blood flow	0·05 ± 0·01	0·26 ± 0·02	0·32 ± 0·06	0·29 ± 0·04	0·38 ± 0·05
Blood flow (ml./min)	16·3 ± 2·0	19·7 ± 9·9	18·2 ± 4·1	20·8 ± 3·8	22·3 ± 3·6

The expected iodide secretion rate calculated from the observed arterio-venous difference and the known gastric blood flow agreed well with the value actually obtained during periods of steady secretion. This implied that the wash-out of radioactive iodide from the stomach was essentially complete and that there was no significant contamination of the gastric venous outflow by blood from any other source.

The results that we have obtained from forty-five periods of 60 min of observations in experiments on twenty-eight dogs are summarized in Table 1, which is reproduced here from our preliminary communication (Brown-Grant *et al.* 1963). Both iodide clearance and acid secretion are markedly increased above the resting values by the lowest dose of histamine used, the ratio of ^{131}I clearance to acid secretion remaining the same. Progressively higher doses of histamine cause a proportionately greater increase in acid secretion and the ratio falls. A typical example of the effect of histamine on gastric blood flow, acid secretion and iodide clearance is shown in Fig. 2. Characteristically, the volume of juice secreted during the initial control period was low, averaging 0·1 ml./min in this experiment and the J/B ratio for ^{131}I was 8·5. The mean rate of secretion with 0·625 μg of histamine acid phosphate was 0·25 ml./min and the J/B ratio 22·1. Using 1·25 μg of histamine acid phosphate, values were 0·51 and 18·8 respectively. Later in this experiment (not shown in Fig. 2) 2·5 μg of histamine acid phosphate produced secretion at a rate of 1·07 ml./min, J/B ratio 15·4 and 5·0 μg/min a secretion of 1·23 ml./min and a J/B ratio of 14·4.

The effects of adrenaline and noradrenaline on histamine induced secretion

Table 2 summarizes the results of eight experiments on three dogs. The effects on gastric blood flow are in general agreement with those reported previously (Cumming *et al.* 1963). The direction of change in acid secretion and iodide clearance are usually the same but the extent of the change is often quite different.

The effect of 5-hydroxytryptamine (5-HT) given alone

In eleven experiments on six dogs the effect of an intravenous infusion of 5-HT on systemic arterial pressure and on gastric blood flow was measured. Systemic arterial pressure was either unaffected or fell slightly. In nine cases there was no change and in two cases a slight fall in gastric blood flow in response to the infusion of 2·5–10·0 μg/kg/min. In nine of the eleven experiments the effects on acid secretion and iodide clearance were also determined. In all cases the rate of acid secretion before, during and after 5-HT infusion did not exceed 0·002 m-equiv total acid/minute and we consider that there was no significant stimulation of acid secretion. The effect on iodide clearance was small but consistent, an increase occurring in each case and the *clearance fraction* was also increased (Table 3). Table 4 compares the results obtained with 0·625 μg of histamine acid phosphate and 5·0 μg of 5-HT/min. The two drugs have had comparable effects upon iodide clearance and the *clearance fraction* but only histamine has stimulated acid secretion.

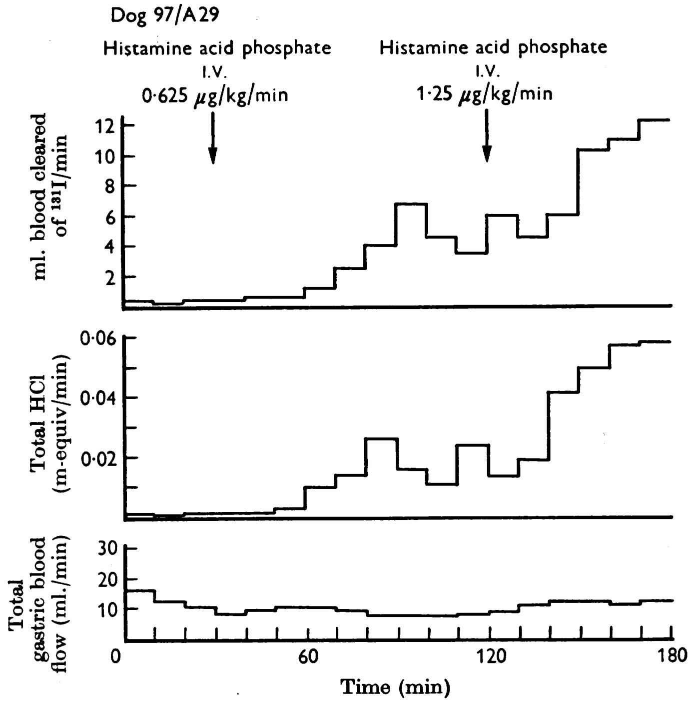

Fig. 2. The effects of infusions of histamine acid phosphate upon gastric iodide clearance, acid secretion and blood flow.

TABLE 2. The effects of continuous infusions of adrenaline and noradrenaline upon the iodide clearance, acid secretion and blood flow through the stomachs of dogs in the presence of a continuous intravenous infusion of histamine acid phosphate. Values are expressed as percentage change associated with infusion of amine, and relate to the mean of six consecutive 10 min periods before and during infusion of the catechol amines

Dog no.	Dose of histamine acid phosphate (μg/kg/min)	Dose of adrenaline (μg/kg/min)	Dose of noradrenaline (μg/kg/min)	Percentage change in		
				Iodide clearance	Total acid secretion	Blood flow
33	5·0	2	—	+41	+99	+27
2	2·5	8	—	+86	+98	+34
31	1·25	2	—	+85	+167	+179
	1·25	2	—	+56	+120	+52
33	5·0	—	2	+16	+12	−30
2	2·5	—	8	−4	−20	−14
	2·5	—	8	−24	−20	−29
31	1·25	—	2	−20	+5	+5

TABLE 3. The effect of intravenous infusions of 5-HT on the gastric clearance of radio-iodide and the 'clearance fraction' ('clearance'/total blood flow). Values given are the means* of six consecutive 10 min periods, before, during and after cessation of the infusion in each case

		Before infusion		During infusion		After infusion	
Dose of 5-HT (μg/kg/min)	Dog no.	^{131}I clearance (ml. blood/min)	'Clearance' / Total blood flow	^{131}I clearance (ml. blood/min)	'Clearance' / Total blood flow	^{131}I clearance (ml. blood/min)	'Clearance' / Total blood flow
2·5	14	1·23 ± 0·10	0·05 ± 0·01	2·29 ± 0·30	0·06 ± 0·01	1·32 ± 0·04	0·04 ± 0·01
2·5	14	1·32 ± 0·04	0·04 ± 0·01	2·32 ± 0·22	0·23 ± 0·03	—	—
2·5	15	0·26 ± 0·17	0·02 ± 0·01	0·87 ± 0·14	0·08 ± 0·02	0·46 ± 0·11	0·04 ± 0·01
5·0	4	0·54 ± 0·26	0·05 ± 0·01	6·78 ± 1·74	0·34 ± 0·01	4·33 ± 0·30	0·16 ± 0·02
5·0	4	4·33 ± 0·30	0·16 ± 0·02	7·55 ± 1·16	0·45 ± 0·07	6·71 ± 0·77	0·25 ± 0·03
5·0	7	1·84 ± 0·25	0·12 ± 0·02	2·48 ± 0·14	0·29 ± 0·02	2·87 ± 0·25	0·32 ± 0·03
5·0	21	1·14 ± 0·23	0·13 ± 0·03	2·61 ± 0·71	0·20 ± 0·01	2·47 ± 0·49	0·13 ± 0·03
5·0	22	0·58 ± 0·05	0·08 ± 0·01	0·86 ± 0·03	0·13 ± 0·01	0·88 ± 0·16	0·12 ± 0·01
10·0	22	0·88 ± 0·16	0·12 ± 0·01	1·52 ± 0·21	0·14 ± 0·03	1·19 ± 0·16	0·07 ± 0·01

* ± S.E. of mean.

TABLE 4. Comparing the effect of continuous intravenous infusions of 0·6μg/kg/min histamine acid phosphate with that of 5·0μg/kg/min of 5-HT upon iodide clearance, acid secretion and blood flow. Values are mean ± S.E. of mean

No. of dogs	No. of expts.	Drug	^{131}I clearance (ml. blood/min)	Total acid secreted (ml. N/100 acid/min)	^{131}I cleared / Acid secreted	'Clearance' / Total blood flow (clearance fraction)	Total blood flow (ml./min)
4	4	Control	1·1 ± 0·6	0·30 ± 0·11	3·9 ± 1·2	0·05 ± 0·02	21·3 ± 5·3
	4	Histamine	5·6 ± 3·2	2·84 ± 1·70	4·2 ± 2·0	0·26 ± 0·02	19·7 ± 9·9
5	5	Control	1·7 ± 0·4	0·16 ± 0·02	9·3 ± 4·2	0·11 ± 0·02	13·8 ± 3·6
	5	5-Hydroxytryptamine	4·1 ± 1·3	0·16 ± 0·02	30·0 ± 10·4	0·28 ± 0·06	13·1 ± 2·4

The effect of 5-HT on histamine induced secretion

In twelve experiments on eight dogs the effects of 5-HT (5–20 μg/kg/min) on blood pressure and gastric blood flow during histamine infusion were examined. The effects seen were minor and inconsistent. In a further twelve experiments on five dogs no consistent effects on blood pressure or gastric blood flow were obtained nor was acid secretion or iodide clearance noticeably affected. In two cases a moderate depression of acid secretion was accompanied by a similar fall in iodide clearance. We were not able to reproduce the dramatic decrease in acid secretion reported by Black, Fisher & Smith (1958). It was our impression that when acid and iodide secretion were depressed it was in animals that were hypoxic during the infusion owing to bronchoconstriction. Deliberate mild hypoxia (induced by giving 5–10 %/O_2 in N_2 through the tracheal cannula) produced a similar transient depression in both acid and iodide secretion. The infusion of 5-HT during the breathing of 95 % O_2 failed to inhibit acid or iodide secretion in three experiments, but as the inhibition was not obtained consistently in animals breathing air no certain conclusions can be drawn from these observations.

DISCUSSION

The results obtained by the infusion of different doses of histamine, in particular the ratio ^{131}I clearance/acid secreted in Table 1, show that although histamine in low dosage stimulates both secretory processes larger doses have a proportionately greater effect on acid secretion. There is a tendency for a fall in the estimated J/B ratio to occur with an increasing volume of secretion. This was seen in many experiments and has been noted previously by other workers (see Brown-Grant, 1961, for references). It suggested to them that an iodide-rich secretion was being diluted by an increasing volume of iodine-poor acid secretion and that the two secretory processes were independent. Similarly, in experiments where the effects of adrenaline and noradrenaline on histamine-induced secretion were studied, the changes in acid production and iodide secretion, though generally in the same direction, were not of the same degree. This may be further evidence that there are two distinct secretory processes. The most striking dissociation of iodide and acid secretion was obtained when 5-HT was infused. A constant stimulation of iodide secretion was observed (Table 3) with no effect on acid production. The volume of secretion produced was small and difficult to measure accurately; the apparent juice/blood ratio for ^{131}I in these samples was often above 100 and sometimes as high as 150. The significance of the results obtained with 5-HT is difficult to assess. Our reason for giving 5-HT was the circumstantial evidence (see

Brown-Grant, 1961) that the secretion of iodide is a function of the mucus-secreting cells of the gastric mucosa and the report (Black *et al.* 1958) that 5-HT causes a massive secretion of mucus by the stomach of the dog. In only one of our experiments did we observe any gross evidence of increased mucus secretion during 5-HT infusion and this was in a dog which experienced severe respiratory difficulty during infusion due to clinically apparent broncho-constriction. We did not, however, use such high doses of 5-HT in our experiments as Black *et al.* did because we wished to avoid such episodes. Some stimulation of iodide secretion was always observed, but this was with fairly large doses (Table 3) and the effectiveness was low compared with that of histamine (Table 4). The effects of 5-HT on histamine-induced secretion of acid and iodide were inconsistent.

The relation of iodide clearance to blood flow is of interest. Clearly, the increase in iodide secretion at low levels of histamine is disproportionate to changes in total blood flow and the *clearance fraction* increases markedly from 0·05 to 0·26. Under the conditions of our experiments, however, even when 10 μg of histamine were infused giving clearance rates of 10–12 ml./min, values above 0·45 were never obtained consistently. Iodide clearance values never approximate to total blood flow and so cannot be used to obtain an indirect estimate of total gastric blood flow. It is of interest, however, that the value of the *clearance fraction* at a steady rate of secretion must represent a minimal value for the proportion of the total gastric blood flow passing through the capillaries of the mucosa.

SUMMARY

1. The gastric clearance of radioactive iodide, acid secretion and total gastric blood flow have been measured in anaesthetized dogs.

2. Low doses of histamine increased the rate of acid secretion and iodide clearance comparably but at higher doses acid secretion was increased to a greater extent than iodide secretion.

3. The effects of adrenaline and noradrenaline infusions on histamine-induced acid and iodide secretion were in general the same but the extent to which the two processes were affected was not usually the same.

4. 5-Hydroxytryptamine stimulated iodide secretion by the stomach, producing a small volume of secretion of very high iodide concentration relative to the blood; no effect on acid secretion was observed. No consistent effects of 5-hydroxytryptamine on histamine-induced acid or iodide secretion were observed.

5. These findings support the view that iodide and acid secretion are separate and distinct processes.

6. During vigorous histamine-induced secretion the fraction of the

total gastric blood flow passing through the mucosal capillaries must be at least 0·3–0·4.

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