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THE EFFECT OF NORADRENALINE ON THE GASTRIC SECRETORY RESPONSE TO HISTAMINE IN THE DOG

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The discovery by Emmelin & Muren (1951) that parasympathetic denervation of the salivary glands sensitizes them to circulating adrenaline suggests that a similar phenomenon might be demonstrable elsewhere in the alimentary tract, notably in regard to the gastric glands. The experiments to be reported here were undertaken as a preliminary study of the effect of noradrenaline on gastric secretion stimulated by histamine before investigating the influence of vagotomy. The confusion which formerly existed regarding the effects on gastric secretion of adrenaline or sympathetic stimulation (Babkin, 1950; Code, 1951) has been partly clarified by the work of Code & Forrest (1954), who found that in conscious dogs provided with Heidenhain pouches, infusion of adrenaline or noradrenaline inhibited a secretion of gastric acid evoked by histamine. The results of the experiments to be described, and the interpretation of them, are in certain respects different from those of Code & Forrest.

METHODS

At a preliminary aseptic operation a metal cannula was installed in the most dependent part of the stomach in each of five dogs. In three of the animals, permanently indwelling polythene cannulae were inserted into the external jugular vein by a simplification of the method of Stroud, Stetson & Rahn (1952). All the animals remained in good health throughout the investigation.

A constant-rate injection apparatus was used for intravenous infusion of histamine and noradrenaline solutions. This consisted of three 20 ml. syringes which were emptied simultaneously at the same rate (approx. 3·6 ml./hr) by a common motor drive. A three-way tap was fitted to each syringe so that the contents of any or all of them could be discharged into the dog at the same time. The syringes contained respectively (1) 0·9% NaCl solution, (2) histamine acid phosphate in 0·9% NaCl solution, and (3) noradrenaline acid tartrate in 0·9% NaCl solution. The histamine solution was infused continuously, together with either of the other two solutions. The noradrenaline solution was turned on at the same time as the saline was diverted into a reservoir, and vice versa, so that the inflow of histamine was unaffected. The solutions from the syringes passed to the dog via a length of fine-bore plastic tubing which either connected with the jugular cannula (see above), or in some experiments was introduced directly into a leg vein through a

wide-bore hypodermic needle which was then withdrawn, leaving the tubing in the vein. The length of tubing between syringes and dog was approx. 50·0 cm, containing approx. 0·5 ml. of fluid. With the discharge rate of the syringes used (3·6 ml./hr), the time elapsing after changing say from saline to noradrenaline infusion before the new solution began to enter the circulation was thus approx. 5 min. This was allowed for in the consideration of the results. Histamine acid phosphate was infused at rates of 0·15–1·5 μg/kg/min for periods up to 5 hr, and noradrenaline at rates of 0·3–1·2 μg/kg/min for periods of 10 min–2 hr.

Samples of gastric juice were titrated for free and total acidity using Töpfer's reagent and phenolphthalein as indicators. Because of the inevitable contamination with saliva, rates of secretion were recorded in terms of m-equiv of acid output.

RESULTS

With the doses of histamine used a flow of acid gastric juice was always obtained. The secretion reached a maximum in the course of half an hour and usually a plateau of secretion was obtained unless the initial rate of secretion was high (0·30 m-equiv HCl/min); in these circumstances, the rate of secretion gradually declined at a uniform rate. During the course of the experiments, one of the dogs tended to become more sensitive to histamine; a response evoked originally by 1·5 μg histamine acid phosphate/kg/min could after six months be produced by a fifth as much histamine.

Noradrenaline in the doses employed always caused a diminution in the rate of gastric secretion (Fig. 1) in all the dogs studied, although the effect was not always as pronounced as in this figure. It was never possible to stop the flow of gastric juice completely with the doses of the two drugs used. When histamine and noradrenaline were given simultaneously from the beginning of the experiment two patterns of inhibition were seen. First (Fig. 2), there was a response in which the secretion reached a plateau in 20–30 min as it normally did, but was only about 20–30 % of the expected level. When the noradrenaline was stopped, the secretory rate rapidly climbed to a new level, approaching that which would be expected if no noradrenaline had been given. The second pattern of response was less frequent, occurring only three times in ten experiments. Here the secretory rate reached a peak just below the expected level in the usual time, but was followed by a decrement (Fig. 3). When the infusion of noradrenaline was stopped, the rate of secretion rose slowly to reach a level equivalent to that expected if the histamine had been given alone. If the infusion of noradrenaline was started a little before the histamine, no qualitative difference could be seen between the new responses and those obtained when the histamine and noradrenaline infusion commenced simultaneously.

In all the dogs noradrenaline appeared to cause a regurgitation of bile from the duodenum. This regurgitation was not of constant occurrence, and it varied from dog to dog, being comparatively rare in one and comparatively common in another. Occasionally, when there was regurgitation of bile, the dogs attempted to vomit: there was no obvious correlation between the amount

of bile regurgitated and the occurrence of vomiting. The longer the noradrenaline was given, however, and the greater its concentration, the more likely was bile to be regurgitated.

In these experiments, the heart rate was counted before, during and after the administration of noradrenaline. It was always altered by the noradrenaline. Usually there was a fall in rate of about 15 beats per min during the first

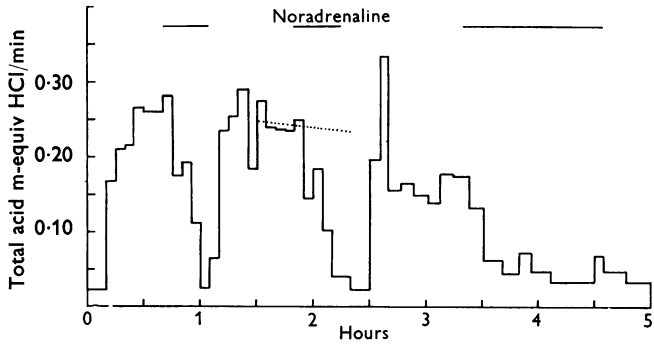

Fig. 1. Inhibition of secretion following three successive administrations of noradrenaline on the same occasion. Dotted line represents extrapolation of the rate of secretion between the 90th and 115th minutes of the experiment to estimate the amount of acid which would be secreted if no noradrenaline were given. Noradrenaline = 1·2 μg/kg/min: histamine acid phosphate = 0·6 μg/kg/min continuously. The calculated percentage inhibitions for the three infusions of noradrenaline are 57, 56 and 52 respectively.

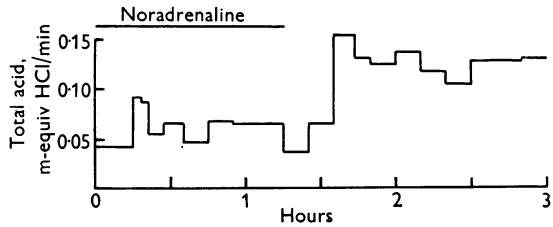

Fig. 2. Inhibition of secretion during the administration of noradrenaline 1·2 μg/kg/min for 74 min. Histamine acid phosphate 0·6 μg/kg/min given continuously.

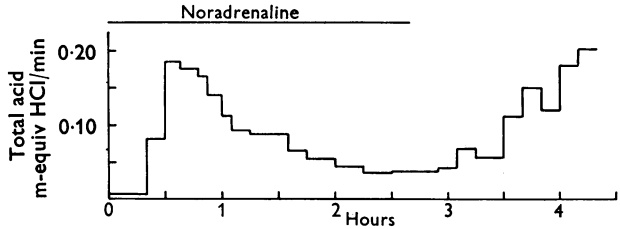

Fig. 3. Inhibition of secretion during the administration of noradrenaline 0·6 μg/kg/min for 160 min. Histamine acid phosphate 10·5 μg/kg/min given continuously.

2 min; less commonly there was a cardiac acceleration of about 20–25 beats per min when the noradrenaline started and this was followed by a fall to the original rate or below within 5 min. When the infusion of noradrenaline was stopped, cardiac acceleration invariably occurred to a rate about 35 beats per min faster than that which obtained before the noradrenaline had been given. This increased heart rate began to decline within 0–3 min.

One of the dogs, before it was accustomed to the experimental procedure, often showed a high rate of resting secretion of high acidity (0·10–0·15 m-equiv HCl/min) which was presumably vagal juice, since the dog was fasting. An infusion of noradrenaline (0·6 μg/kg/min), which would only slightly inhibit a flow of juice of the same acidity produced by histamine in the same dog, was able to abolish this secretion in 5 min, as also did 2 mg atropine sulphate intravenously.

Inhibition and secretion rate

When noradrenaline was infused at a high rate (1·2 μg/kg/min) it was found that the inhibition of acid output in response to histamine was independent of the initial rate of secretion over a wide range (0·05–0·30 m-equiv HCl/min).

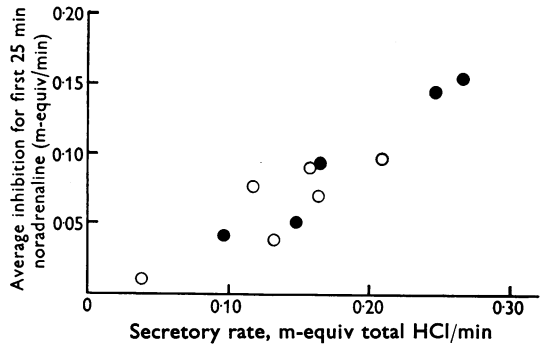

Fig. 4. Inhibition of secretion in m-equiv plotted against initial secretory rate in m-equiv/min. The results are taken from two dogs when noradrenaline was infused at 1·2 μg/kg/min. Open and closed circles represent the two dogs.

In Fig. 4 the inhibition produced by noradrenaline is expressed as the difference between the acid (m-equiv) secreted during a 25 min period immediately before commencing noradrenaline infusion (A) and that secreted during the same period following this (B). When this quantity ($A-B$) is plotted against the rate of acid output (A) (m-equiv), it is seen that a linear relation exists, i.e. $A-B=\text{const.}\times A$. Thus percentage inhibition $\left(\frac{A-B}{A}\times 100\right)$ is independent of the secretion rate (A).

These findings are borne out by expressing graphically the relation between the percentage inhibition of acid output (expressed as described above)

produced by the three infusion rates of noradrenaline used, and the rates of histamine injection in different experiments. As Obrink (1950) has shown, there is a well-defined relation in a given dog between rate of histamine infusion and resultant acid output. Fig. 5 shows that the percentage inhibition of acid output is substantially constant for three levels of noradrenaline infusion over a wide range of histamine infusion rate, although at high values of the latter, some tendency towards a decline in the degree of inhibition produced by noradrenaline appears.

Finally, it is apparent from Fig. 6 that as may be expected, the percentage inhibition of acid output varies with the dose of noradrenaline used.

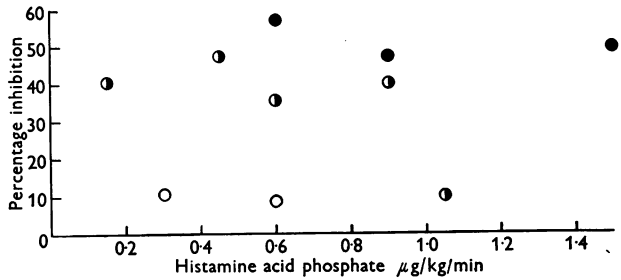

Fig. 5. Dog 'Sandy'. Percentage inhibition of secretion plotted against the dose of histamine acid phosphate administered. ○, noradrenaline 0·3 μg/kg/min; ◑, 0·6 μg/kg/min; ●, 1·2 μg/kg/min.

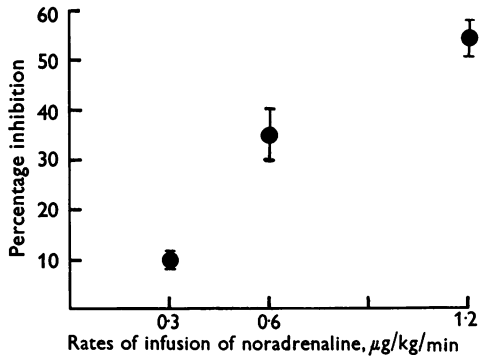

Fig. 6. Dog, 'Sandy'. Percentage inhibition of gastric secretion plotted against the dose of noradrenaline. Secretory rate before infusing noradrenaline was 15–20 m-equiv HCl/min. Vertical lines represent standard errors of means.

DISCUSSION

Opinions expressed in the literature concerning the action of the sympathetic nervous system and adrenaline on the stomach are conflicting (Rogers, Rahe & Ablahadain, 1919; Hess & Gundlach, 1920; von Sirotinin, 1924; Ivy & Javois, 1925). Many other references are cited by Babkin (1950), who also

considers the results conflicting. Code (1951), from a review of the literature, is also driven to the conclusion that whatever effect adrenaline has on the stomach it is a small one. In view of the uncertainty about the effects of adrenaline, it seemed of value to investigate its effects upon the secretion produced by histamine, when a satisfactory flow of juice is assured. Such experiments do not depart too far from physiological conditions, if it is accepted that histamine is the normal stimulant of the oxyntic cells (Babkin, 1938; Emmelin & Kahlson, 1944; Code, Gregory & Hallenbeck, 1947).

The inhibition of secretion recorded by Thompson & Vane (1953) with adrenaline was attributed by them to an effect on the rate of flow of blood through the stomach. In the experiments described in this paper, it was noticed that the heart rate recovered from the effects of the infused noradrenaline within a short period of time, and in no instance was the heart rate abnormal 5 min after the noradrenaline had been stopped. However, the effect of the noradrenaline on gastric secretion was often much more prolonged, the secretion commonly being inhibited up to 60 min after injection of noradrenaline had ceased. There is insufficient evidence to say whether or not the length of time for which gastric secretion was suppressed after the noradrenaline had been discontinued depended upon the length of time for which the noradrenaline had been administered, but where secretion was inhibited for a long time after stopping noradrenaline, it was usually after this drug had been given at 1·2 μg/kg/min. With noradrenaline infusions of 0·6 μg/kg/min a prolonged effect after noradrenaline seemed less likely to occur. Since Emmelin (1955) has shown in the anaesthetized cat that when adrenaline is used to diminish salivary blood flow, and hence salivary secretion, the blood flow through the gland returns to normal long before the gland recovers its secretory power, it is conceivable that the blood flow through the stomach returns to normal some time before gastric secretion is re-established at its previous level.

Code & Forrest (1954) also produced inhibition of histamine-induced secretion in unanaesthetized dogs by means of noradrenaline, but secretion was collected from Heidenhain pouches and not from the whole stomach. They suggested that noradrenaline acted by virtue of its vasoconstrictor effect, and in support of this stated that secretion of juice rapidly returned to normal when an infusion of adrenaline or noradrenaline was stopped. Inspection of the figure in their paper, however, where adrenaline (0·67 μg/kg/min) was given for 2 hr, shows that 30 min after the adrenaline infusion had been discontinued there was still no sign of an increase in the secretory rate from the stomach. The secretory rate from the pouch had not regained its original level 1½ hr later. Code & Forrest cited Brun (1945) in support of their suggestion that the effect of adrenaline or noradrenaline on gastric secretion is purely vascular. Brun, however, states that, whereas the effect of adrenaline on gastric vessels is marked, the effect passes off in 3–4 min.

Another reason for doubting whether the effect of adrenaline on gastric secretion is purely vascular is that adrenaline is very dissimilar in its inhibitory potency when acting upon secretions of gastric juice of different origin. The observation in one of the dogs used in this study that a resting secretion, possibly vagal in origin, was much more readily inhibited than was a histamine-induced secretion of the same acid strength in the same dog, indicates at least that the mechanism of inhibition against different types of gastric secretion is not the same. If noradrenaline acted purely by diminishing blood flow, then it would be reasonable to suppose that the degrees of inhibition produced by noradrenaline on various types of gastric secretion would be comparable. This contention is supported by Linde (1950), who found that adrenaline (50 μg intravenously), whilst having no effect on histamine-induced secretion in cats, was able to abolish vagal secretion almost entirely. That vagal secretion is fairly easily inhibited by sympathetic influences is suggested by Babkin, Schachter & Nisse (1944); also Hess & Gundlach (1920), who did produce some inhibition of secretion with adrenaline, observed it most frequently when the adrenaline was given in the first or cephalic phase of gastric secretion.

From the results given, and the relevant observations of others, it seems doubtful whether the effects of noradrenaline on gastric secretion are purely vascular in character.

SUMMARY

1. Gastric secretion was stimulated in dogs with chronic gastric fistulae by histamine acid phosphate in doses of 0·15–1·5 μg/kg/min intravenously.

2. Noradrenaline in doses of 0·3–1·2 μg/kg/min for periods of 10 min to 2 hr invariably caused a fall in the rate of secretion of gastric juice.

3. The doses of noradrenaline used also tended to cause a regurgitation of bile from the duodenum, but this regurgitation was not constant.

4. Noradrenaline nearly always made the heart rate decrease, but on a few occasions it caused a cardiac acceleration before the heart rate fell. When the noradrenaline was stopped there was invariably a cardiac acceleration, but the pulse rate returned to normal within 5 min.

5. Inhibition of gastric secretion persisted up to 60 min after the noradrenaline infusion was stopped.

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