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COMMUNICATIONS

Investigation of the role of histamine H_1-receptors in the control of gastric acid secretion in the rat

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Studies in the dog and cat have provided indirect evidence that the interaction of histamine with H_1-receptors produces some inhibition of gastric acid secretion. This evidence has been derived from experiments in which dose-response curves have been constructed using both histamine and dimaprit [*s*-[3-(*NN*-dimethylamino) propyl] isothiourea] (a specific H_2-receptor agonist: Durant, Ganellin & Parsons, 1977; Parsons, Owen & others, 1977) in the Heidenhain pouch dog and the anaesthetized fistula cat (Parsons & others, 1977), and in the conscious gastric fistula cat (Carter & Grossman, 1977). In all these preparations dimaprit produced a greater maximum acid response than histamine, and in the dog and conscious cat a significantly greater acid output was obtained in response to histamine in the presence of an H_1-receptor antagonist than with histamine alone.

In the present work the significance of H_1-receptors in the control of acid secretion has been examined in the conscious gastric fistula rat by (i) constructing dose-response curves to histamine (alone, and in the presence of mepyramine) and dimaprit, and (ii) by studying the effect of 2-thiazolylethylamine (a specific H_1-receptor agonist: Durant, Ganellin & Parsons, 1975) on acid secretion.

Female rats of the Wistar strain, approximately 200–250 g, were provided with chronic gastric fistulae essentially according to Lane, Ivy & Ivy (1957) after which at least two weeks was allowed before commencing experiments. Before each experiment the rats were fasted for 18 h, but had free access to water. Each rat was lightly anaesthetized using halothane (Fluothane, ICI Ltd.), and a hypodermic needle inserted into a tail vein. The needle was connected to a motor-driven syringe for intravenous infusions which were given at a rate of 3 ml h^{-1}. While still under anaesthesia the plug was removed from the gastric fistula and the stomach rinsed out with warm 0·9% (w/v) NaCl solution (saline). The rats were then placed in restraining cages and allowed to regain consciousness. Gastric juice samples were continuously collected by drainage and sampled for 6 h at hourly intervals. Acid output (μmol h^{-1}) was determined by titration against 0·1 M NaOH using an automatic titrator (Radiometer type ABU 13). Basal acid secretion was collected for the first hour of each experiment during which time an intravenous infusion of saline was given. The drugs were then added to this infusion as required. For the construction of cumulative dose-response curves using histamine or dimaprit each dose of the secretagogue was infused for 1 h, and the dose was increased in a stepwise fashion over 5 h. The infusion of each dose for 1 h allowed steady rates of secretion to be established.

The drugs used were: histamine acid phosphate (BDH Ltd.), mepyramine maleate (May & Baker Ltd.), dimaprit and 2-thiazolylethylamine (2-TEA) were synthesized in our own laboratories.

Results are expressed as mean ± standard error of the mean. The difference between two means was examined statistically using Student's *t*-test for unpaired data. A P value of less than 0·05 was considered to be significant.

The acid secretory responses to graded doses of histamine (alone, and in the presence of mepyramine, 0·25 μmol kg^{-1} min^{-1}) and dimaprit are shown in Fig. 1. The maximum acid response to histamine alone was

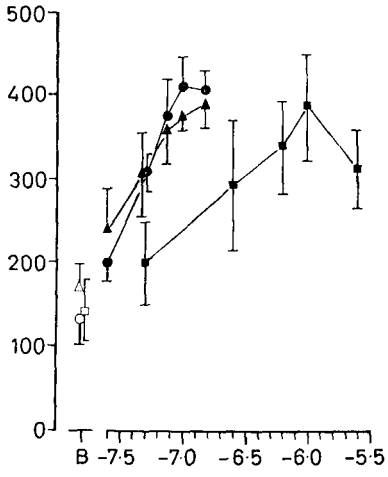

FIG. 1. Dose-response curves to intravenous histamine and dimaprit in the conscious gastric fistula rat; ●—● histamine (n = 6), ■—■ dimaprit (n = 6), ▲—▲ histamine in the presence of mepyramine (0·25 μmol kg^{-1} min^{-1}, i.v., n = 4). The open symbols represent the corresponding basal (B) acid secretion collected in the first hour of each experiment during an intravenous infusion of 0·9% saline, 3 ml h^{-1}. Means and standard errors of the mean are shown. Ordinate: Acid output (μmol h^{-1}). Abscissa: Log_{10} dose (mol kg^{-1} min^{-1}).

* Correspondence.

411·4 ± 31·5 μmol h^{-1}, and in the presence of mepyramine the maximum response was 388·4 ± 29·1 μmol h^{-1}. Mepyramine did not produce any significant effect on the acid response to histamine [subsequent experiments (Fig. 2) also showed that mepyramine did not affect the basal acid secretion]. The maximum acid responsed to dimaprit was 383·0 ± 65·8 μmol h^{-1}, which was not significantly different from the maximum acid response to histamine. A comparison of the potency of histamine and dimaprit was made by estimating the doses of the secretagogues which gave an acid secretory response of 300 μmol h^{-1}, which is approximately 50% of the maximum stimulated response above the basal secretion. On this basis, dimaprit exhibited 17% of the activity of histamine in the fistula rat, and this result agrees well with observations made in the anaesthetized rat in which dimaprit exhibited 19·5% the activity of histamine (Parsons & others, 1977).

The experiments recorded in Fig. 1 provide no evidence that H_1-receptors influence acid secretion in the fistula rat. Additional experiments were carried out to determine the effect of 2-thiazolylethylamine (2-TEA), a specific H_1-receptor agonist, on acid secretion. The results of these experiments are shown in Fig. 2. Basal acid secretion (during i.v. infusion of saline) was collected for 3 h, and the 2-TEA (2 μmol kg^{-1} min^{-1}) was infused for a further 3 h. Comparison with the corresponding control data showed that 2-TEA significantly inhibited the basal secretion. The effect of mepyramine (0·25 μmol kg^{-1} min^{-1}) on the 2-TEA-induced inhibition is also shown. In the latter experiments basal acid secretion was collected for 1 h, mepyramine alone was then infused for 2 h, and finally mepyramine plus 2-TEA was infused for 3 h. Mepyramine alone had no effect on the basal acid secretion, but the antagonist reversed the inhibition produced by 2-TEA. These results (Fig. 2) indicate that H_1-receptors might be involved in an inhibitory mechanism for acid secretion, although they are at variance with the results shown in Fig. 1.

Previous studies in the cat and dog (where the basal acid output is low) have shown that a significant, albeit small, increase in the maximum acid response to histamine is observed in the presence of an H_1-receptor antagonist, and that an H_2-receptor agonist, dimaprit, gives a greater maximum acid response than histamine alone (Carter & Grossman, 1977; Parsons & others, 1977). In the conscious rat the basal acid secretion is relatively high (Figs 1 & 2), and the secretagogue-induced acid secretion is superimposed on this high basal acid output. Clearly, any change in the basal secretory rate will affect the total acid output during secretagogue administration, and it is therefore likely that the fistula rat is a poor model for comparing maximum rates of acid secretion. On this basis, the failure of dimaprit to stimulate a greater maximum rate of acid secretion than histamine alone, or for mepyramine to potentiate the maximum response to histamine should not be taken as clear evidence that an H_1-receptor mediated inhibitory

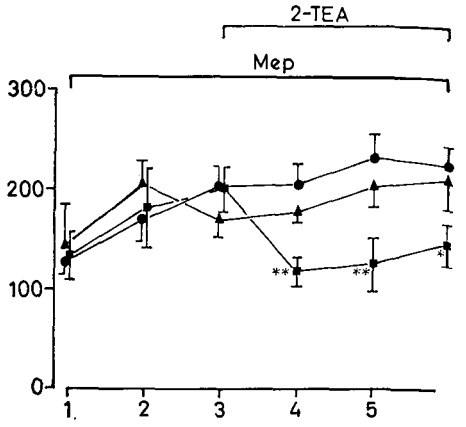

FIG. 2. Acid secretion in the conscious gastric fistula rat during an infusion of 2-thiazolylethylamine alone (2 μmol kg^{-1} min^{-1}, i.v., ■—■, n = 5) and in combination with mepyramine (0·25 μmol kg^{-1} min^{-1}, i.v., ▲—▲, n = 5). The basal secretion during an intravenous infusion of saline, 3 ml h^{-1}, is also shown (●—●, n = 9). * $P < 0.05$, ** $P < 0.01$ represent the degrees of significance of the difference between the basal acid secretion (●—●) and the corresponding acid output during infusion of 2-thiazolylethylamine (■—■). Means and standard errors of the mean are shown. Ordinate: Acid output (μmol h^{-1}). Abscissa: Time (h). 2-TEA: 2-thiazolylethylamine; Mep: mepyramine.

mechanism for acid secretion does not exist in the rat. Indeed, the inhibition of basal acid secretion by 2-TEA, and the reversal of this inhibition by mepyramine (Fig. 2), indicates that such a mechanism does exist, although this result contrasts with the observations of Hirschowitz & Hutchison (1977) who found that 2-pyridylethylamine (an H_1-receptor agonist with 5·6% the potency of histamine: Durant & others, 1975) had no effect on the acid response to 4-methylhistamine (an H_2-receptor agonist with approximately 40% the potency of histamine: Black, Duncan & others, 1972) in the gastric fistula dog.

Consideration must be made of the mechanism by which H_1-receptors could be involved in the inhibition of gastric acid secretion. Firstly, there is no direct evidence that H_1-receptors are located on parietal cells, since it has been reported that H_1 receptor antagonists do not affect histamine-stimulated acid secretion in the isolated guinea-pig stomach (Impicciatore, Morini & Bertaccini, 1978), or histamine-induced cAMP accumulation in isolated canine parietal cells (Scholes, Cooper & others, 1976). It is also possible that the interaction of histamine with H_1-receptors restricts gastric mucosal blood flow. However, in the anaesthetized rat 2-pyridylethylamine causes an increase in gastric mucosal blood flow; there is no evidence of a restricted flow (Main & Whittle, 1976). In addition, it has been shown that β-adrenoceptor stimulants inhibit both basal and secretagogue-induced acid secretion in the conscious rat

(Mischer, Pendleton & Staples, 1969; Lundell & Svensson, 1974; Lundell, Nilsson & Svensson, 1976) and that histamine releases catecholamines from the adrenal medulla in the rat; an effect which is blocked by H_1-receptor antagonists (Yoshizaki, 1973). It is therefore possible that the stimulation of H_1-receptors causes release of catecholamines which in turn inhibit acid secretion through the interaction with β-adrenoceptors.

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Reversal of antibiotic-induced muscle paralysis by 3,4-diaminopyridine

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Certain antibiotics can induce respiratory depression during surgery when used in conjunction with some anaesthetics and muscle relaxants (Pittinger & Adamson, 1972). Antibiotics that have been implicated include the aminoglycosides, tetracyclines, polymixins, lincomycin and clindamycin. Reversibility of the antibiotic-induced muscle paralysis by either anticholinesterases or calcium ions is often unpredictable.

Some aminopyridines have powerful facilitatory actions on neuromuscular transmission and can also enhance muscle contractility (Harvey & Marshall, 1977) and we have previously shown that neuromuscular blockade produced by the aminoglycoside antibiotics amikacin and neomycin is reversed by either 4-aminopyridine or 3,4-diaminopyridine (Singh, Marshall & Harvey, 1978b). We have now tested the reversing actions of 3,4-diaminopyridine against muscle paralysis induced by tetracyclines, polymixins, lincomycin and clindamycin.

Experiments were performed on the isolated phrenic nerve-hemidiaphragm preparation of the mouse, mounted in Krebs-Henseleit solution containing 2 g $litre^{-1}$ dextrose, maintained at 32° and gassed with 5% CO_2 in oxygen. Nerve stimulation (rectangular pulses of 0·2 ms duration) at a frequency of 0·05 Hz was alternated with direct muscle stimulation (rectangular pulses of 1 ms duration) at a frequency of 0·05 Hz. Stimulation strength was adjusted to produce maximal twitches. Tissues were exposed to antibiotics in concentrations that produced 80–90% block of indirectly-elicited twitches in 20–60 min. 3,4-Diaminopyridine (0·1 mM) was then added to the tissue bath in the continued presence of the antibiotics and the degree of reversal (expressed as recovery to a percentage of control twitch height) was measured either after 10 min or at the point of maximum recovery. Recovery values are expressed as mean ± standard error of 4–6 experiments.

Polymixin B reduces responses to nerve stimulation whereas responses to direct stimulation are little affected; the neuromuscular block is unaffected by neostigmine and only reversed by high concentrations (10mM) of calcium (Singh, Harvey & Marshall, 1978a). However, we found that 3,4-diaminopyridine restored twitch height to 72 ± 9% in preparations blocked by 0·1 mM polymixin B (Fig. 1a).

Although lincomycin and clindamycin are chemically closely related and both reduce responses to nerve stimulation, clindamycin also reduces responses to direct muscle stimulation (Singh, & others, 1978a). The neuromuscular blocking activity of lincomycin (9·4 ± 0·6 mM) was readily reversible (to 108 ± 7% control) by 3,4-diaminopyridine (Fig. 1b). Clindamycin (2 mM) reduced responses to both nerve and direct stimulation to approximately the same degree, and 3,4-

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