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# *N*-Methyl, 5-Methyl Histamine Evokes a Higher Maximal Rate of Gastric Acid Secretion than Histamine (39924)

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Histamine H2 receptor antagonists counteract those actions of histamine, such as stimulation of gastric acid secretion, that are not blocked by the older antihistaminics, histamine H1 receptor antagonists (1). Accordingly, histamine receptors are now classified on the basis of which of these two types of blockers counteract the action in question. By this classification, stimulation of gastric acid secretion by histamine is an H2 action since it is inhibited by H2 but not by H1 antihistaminics. Similarly, analogs of histamine with histamine-like action can be classified according to the degree of selectivity they show for H1 or H2 receptors. Two monomethyl derivatives of histamine, one with a methyl group on the imidazole ring, 5-methyl histamine (2), and one with a methyl group on the side chain nitrogen, *N*-methyl histamine (3), have been shown to have selectivity for histamine H2 receptors including gastric acid secretion. We report here that the dimethyl derivative corresponding to each of these two monomethyl histamines evokes higher maximal acid secretion than histamine in cats with gastric fistulas.

*Methods.* *N*-methyl-2-(5-methyl-4-imidazolyl)ethylamine (in this presentation called *N*-methyl, 5-methyl histamine and abbreviated DMH for dimethyl histamine) was synthesized and purified by methods that will be described elsewhere. Preliminary studies showed that DMH was about 1000 times more potent for an H2 action, stimulation of auricular rate, than for an H1 action, contraction of guinea pig ileum (4). The tests reported here were done in cats (3- to 9-kg body weight) with plastic cannulas in the stomach forming a permanent gastric fistula (5). Gastric juice was collected continuously and divided into 15-min samples. Acid concentration was measured by electrometric titration to pH 7.0 with 0.2 *M* NaOH. All drugs were given intravenously through an indwelling catheter inserted into a leg vein at the start of each test. Each dose of stimulant was given for 30 min and was immediately followed by the next higher dose. The significance of differences between means was determined by Student's *t* test for paired values.

*Results.* The first set of tests (Fig. 1A) compared acid secretory responses to graded doses of DMH and histamine. The maximal response to DMH was significantly ($P < 0.02$) greater than to histamine.

The second set of tests (Fig. 1B) compared the acid secretory response to graded doses of histamine given alone with the response to the same doses of histamine given against a background of a constant dose of a histamine H1 receptor antagonist, pyrilamine. The maximal response to histamine plus pyrilamine was significantly ($P < 0.02$) greater than to histamine alone.

The third set of tests (Fig. 1C) compared the acid secretory response to graded doses of DMH alone with the response to DMH given against a background of a constant dose of histamine. The dose of histamine was double the dose needed for maximal response. The maximal response to DMH was significantly lower ($P < 0.02$) in the presence of the background dose of histamine than with DMH alone. The maximal response to DMH plus histamine was similar to the maximal response to histamine alone (Figs. 1A and B).

*Discussion.* These findings are compatible with the hypothesis that, in addition to histamine's well-known action on H2 receptors to stimulate acid secretion, it also acts on H1 receptors to inhibit acid secretion. When the H1 inhibitory effect was largely avoided either by using an H1 blocker with



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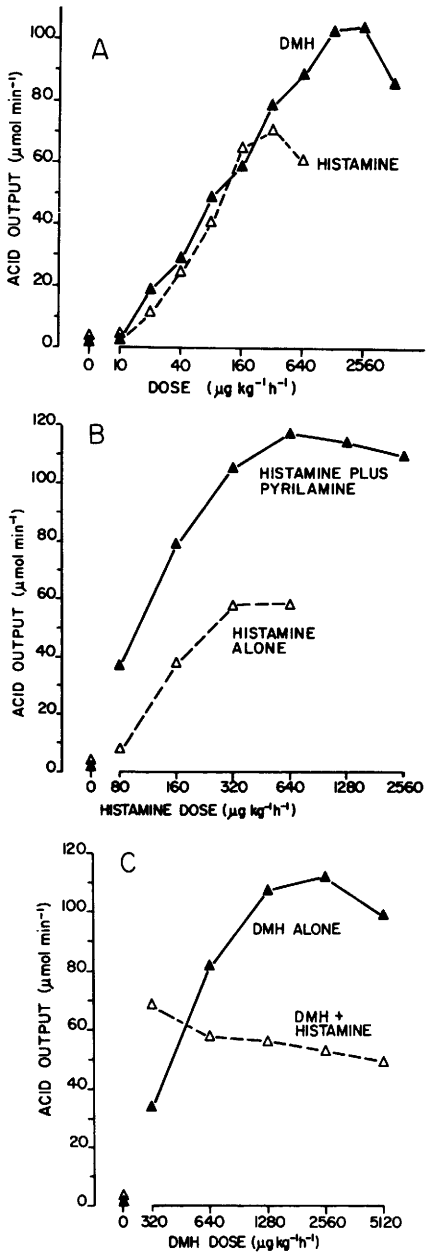


FIG. 1. Gastric acid secretion in cats with gastric fistulas in response to *N*-methyl, 5-methyl histamine dihydrochloride (dimethyl histamine, DMH) or to histamine dihydrochloride, alone or with a background of another drug. The abscissa gives the dose of stimulant on a logarithmic scale; the ordinate, output of acid per minute during the last 15 min of each dose period. (A) Comparison of DMH and histamine. Means of one test in each of six cats. (B) Comparison of histamine alone with histamine on a background of pyrilamine (loading dose of 4 mg $kg^{-1}$ followed by infusion of 2 mg $kg^{-1}$ $hr^{-1}$ throughout the test). Means of one test in each of five cats. (C) Comparison of DMH alone with DMH on a background of continuous infusion of 640 μg $kg^{-1}$ $hr^{-1}$ of histamine. Means of one test in each of four cats.

histamine or by using an analog with little H1 action, the full stimulatory action of H2 agonism was revealed.

Since the inhibitory effect of histamine was not surmountable by increasing the dose of DMH (Fig. 1C), the inhibition can be classified as showing noncompetitive kinetics.

Previous studies (6) of the effect of histamine H1 receptor antagonists on histamine-stimulated gastric acid secretion have not shown the higher maximal response to this combination that we found in the present study. This failure may have been due to inadequate doses of histamine or antihistaminic, to species differences, or to unidentified factors. Lin (7) showed that a histamine H1 receptor antagonist increased the acid secretion in response to histamine in an anesthetized cat but he did not establish that the maximal response was increased.

Previous studies (2, 3) on the monomethyl histamines with selective activity on histamine H2 receptors failed to show maximal responses higher than those to histamine. A possible explanation for this is that the degree of selectivity for H2 receptors is greater for the dimethyl derivative than for the monomethyl ones.

Histamine H2 receptor antagonists inhibit not only histamine but also all other stimulants of gastric acid secretion that have been tested (8), thus supporting the hypothesis that histamine is involved in all modes of gastric acid stimulation. The present study indicates that histamine is an inhibitor as well as a stimulator of gastric acid secretion. The locus of the H1 receptor for inhibition of acid secretion cannot be deduced from the present study. It need not be on the parietal cell or even in the stomach. The possible physiological importance of inhibition of acid secretion by histamine remains to be determined.

*Summary.* In cats with gastric fistulas, the histamine H2 receptor agonist *N*-methyl, 5-methyl histamine gave a higher maximal rate of acid secretion than histamine. Histamine plus a histamine H1 recep-

tor antagonist also gave a higher maximal rate of acid secretion than histamine alone. These findings are compatible with the hypothesis that histamine acts on H1 receptors to inhibit acid secretion.

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