nerve stimulation (10 Hz, during 2 min, supramaximal voltage) was increased approximately 2-fold in the presence of 16 or 54 μM histamine. The fraction of the tritiated noradrenaline released by nerve stimulation which was collected as ^{3}H-DOPEG was increased significantly in the presence of histamine. Simultaneously, there was a marked reduction in the formation of ^{3}H-normetanephrine from ^{3}H-noradrenaline released by nerve stimulation.

The effects of histamine on adrenergic nerve endings are considered of interest because of the known effects of this amine on the cell body of the postganglionic adrenergic neurone. In the superior cervical ganglion, histamine has a facilitatory effect on neurotransmission which is mediated by H_1 receptors, and an inhibitory effect which is mediated by H_2 receptors (Brimble & Wallis, 1973). Consequently, the effects of histamine on adrenergic neurotransmission and on the smooth muscle of the nictitating membrane were studied in the presence of agents which block either H_1-receptors (pirylamine) or H_2-receptors (burimamide).

It is concluded that histamine has a prejunctional effect which resembles the effects of reserpine-like agents (Adler-Graschinsky, Langer & Rubio, 1972; Graefe, Stefano & Langer, 1973). In addition, histamine enhances ^{3}H-noradrenaline overflow elicited by nerve stimulation and it stimulates the smooth muscle of the cat nictitating membrane.

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Dose response relationship and comparison of the secretory potency of methyl histamine and histamine on the isolated guinea pig stomach

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The side-chain-methylated derivatives Nα-methyl histamine (NαMeH) and Nα, Nα-dimethyl histamine ($N\alpha Me_2H$) are more active than histamine in stimulating gastric secretion (Code, Maslinski & Mossine, 1971). Code (1973) has therefore suggested that these Nα-methyl histamines may be physiological stimulators of parietal cells. In the guinea pig NαMeH and $N\alpha Me_2H$ were less potent than histamine in stimulating H_1-receptors to produce broncho-constriction, increased permeability of skin vessels and contraction of the isolated ileum (Bertaccini & Vitali, 1964). 5-methyl histamine (5MeH) is a gastric secretagogue of approximately equal potency with histamine in various species but has relatively little activity on H_1 receptors (Bertaccini & Impicciatore, 1974; Black, Duncan, Durant, Ganellin & Parsons, 1972). We have now compared the potency of these three histamine derivatives with histamine on the H_2-receptors of the guinea pig stomach.

Male guinea pigs (300-500 g) were given a low residue diet with water freely available for 48 h before the experiment. The guinea pig was killed by a blow on the head followed by bleeding. Half-stomach preparations were set up as described previously (Spencer, 1973). 4 or 5 dose levels, differing by a factor of two, of the four test substances were randomized between 168 preparations. After a base-line secretory plateau to theophylline hydrate (0.2 mg/ml) had been obtained, the test substance was administered to the serosal side for 60-90 min and then removed by washing the preparation twice. The base-line secretion level was regained before applying another dose. Usually three or four tests could be completed on each preparation. The rate of acid secretion (μEq.cm^{-1} h^{-1}) stimulated by each dose was calculated as the difference between the mean of 3 consecutive periods of test stimulation 30 min after administration of the test and the mean of 3 consecutive periods of theophylline-induced secretion immediately before administration of the drug.

The highest dose of each drug gave a smaller mean response than the second highest dose

indicating that the maximum response had been obtained. Omitting the highest dose tested, the mean response for each drug was linearly related to the log dose. The common regression coefficient

$$(b) = \frac{\text{response}}{\log_{10} \text{dose}},$$

was obtained by the method of Snedecor & Cochrane (1969). b = 2.06, (fiducial limits 1.20, 2.92 at $P = 0.05$). None of the regression coefficients for the four drugs differed significantly from the common regression coefficient. The molar potency ratios with reference to histamine were NαMeH 2.3 ± 0.22 s.e. mean $N\alpha Me_2H$, 0.85 ± 0.26 s.e. mean, 5MeH 0.43 ± 0.27 s.e. mean.

We have therefore confirmed that NαMeH is a more potent stimulus for gastric acid secretion than histamine but the potency ratio in the guinea pig is less than that observed in cats and dogs.

We have also shown that in the guinea pig $N\alpha Me_2H$ is an approximately equipotent and 5MeH is a less potent H_2-receptor agonist than histamine.

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Effects of atropine on gastric secretion and mucosal blood flow in conscious dogs.

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Atropine is known to decrease gastric acid secretion in the dog (Gregory & Tracy, 1961) rat (Johansson, Lundell & Svensson, 1971) and cat (Svensson & Emas, 1974), and is still used clinically as an anti-secretory and spasmolytic drug. For therapeutic use an anti-secretory drug is likely to be more beneficial if it does not greatly reduce the ratio of gastric mucosal blood flow (MBF) to secretory rate.

We have examined the effects of atropine on MBF and acid secretion in six dogs with Heidenhain pouches. Food was withheld but water allowed for 18 h before experiments. Submaximal gastric acid secretion was induced by pentagastrin (1-4 $\mu g\ kg^{-1}\ h^{-1}$) or bethanechol (60 $\mu g\ kg^{-1}\ h^{-1}$). Atropine was given during the secretory plateau. Secretion was collected over 15 min periods and acid output measured by titration. MBF was estimated by radioactive aniline clearance (Curwain & Holton, 1973). Effects on acid secretion and MBF were calculated as follows: Measurements for the three 15 min periods preceding the dose of atropine were compared with the mean of the three values from 15-60 min after atropine. Results are expressed as percentage changes ± s.e. mean.

In four experiments in four dogs atropine sulphate (100 μg/kg i.v.) decreased pentagastrin-stimulated acid secretory rate (62.8 ± 12.4) and MBF (44.5 ± 18). The concentration of acid secreted decreased by 14.8 ± 3.7 and 23.5 ± 7.5 respectively 45 and 60 min after atropine, but the pH of the secretion was less than 3.0. The ratio of MBF to secretion rose (39.3 ± 12.8) during secretory inhibition.

Atropine sulphate (100 μg/kg i.v.) also decreased acid secretion stimulated by bethanechol. In three experiments in three dogs secretion decreased by a mean of 83.0 ± 11.0. In one of these experiments the pH of the secretion remained less than 3.0 and the ratio of MBF to secretion rose by 56% during secretory inhibition. In the other two experiments acid concentration fell so much that the pH was above 3.0. Under these conditions aniline clearance does not measure MBF.

In twelve further experiments smaller doses of atropine (1-25 μg/kg i.v. or s.c.) inhibited secretion in response to both stimuli but were more