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## COMMUNICATIONS

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### Pharmacological effects of histamine on the isolated cat nictitating membrane

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Histamine is a direct stimulant of the smooth muscle in several tissues. Yet, using isotonic recording Thompson (1958) reported that low concentrations of histamine in only a few preparations stimulated the smooth muscle of the cat nictitating membrane.

In the present studies, carried out with the isolated medial muscle of the cat nictitating membrane, it was found that histamine stimulated this smooth muscle and the effect was concentration-dependent (5.4 $\mu$M to 5.4 mM). The maximum development of tension in response to histamine was 13.2 ± 0.6 g in the controls ($n$ = 8). The maximum tension developed by (−)-noradrenaline under these experimental conditions was 19.2 ± 1.6 g ($n$ = 9). The effect of histamine does not seem to be mediated through the activation of alpha-adrenoceptors because the concentration-effect curve for histamine was not affected in the presence of 2.9 $\mu$M phentolamine. However, the responses to the highest concentration of histamine employed (5.4 mM) appear to be related to the release of endogenous noradrenaline because they were reduced after pretreatment with reserpine (0.3 mg/kg, 24 h before the experiment).

The responses to exogenous (−)-noradrenaline were not affected in the presence of either 5.4 or 16 $\mu$M histamine ($pD_2$ in the controls: 5.04 ± 0.04; histamine 5.4 $\mu$M: 5.08 ± 0.03 and histamine 16 $\mu$M: 5.12 ± 0.04).

In the tissues previously labelled with $^3$H-noradrenaline, exposure to 16 or 54 $\mu$M histamine produced a concentration-dependent increase in the spontaneous outflow of radioactivity: 1.65 ± 0.09-fold with 16 $\mu$M ($n$ = 8) and 3.36 ± 0.21-fold with 54 $\mu$M histamine ($n$ = 4). Under these experimental conditions the deaminated glycol, $^3$H-DOPEG (3,4-dihydroxyphenylglycol) accounted for more than 75% of the total increase in outflow of radioactivity elicited by exposure to histamine. In the presence of pirylamine 2.7 $\mu$M the releasing effect of histamine, 54 $\mu$M, was markedly reduced.

Transmitter overflow elicited by postganglionic

nerve stimulation (10 Hz, during 2 min, supramaximal voltage) was increased approximately 2-fold in the presence of 16 or 54 $\mu$M 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 ($\mu$Eq.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