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Characterization of histamine receptors in tracheal smooth muscle of *Mastomys natalensis*[1]

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ABSTRACT The tracheal smooth muscle of *Mastomys natalensis* contracted with carbachol administration while histamine (H) caused concentration-dependent relaxation. The Specific H_2-receptor agonists 4-methyl histamine, dimaprit, impromidine and a high concentration of 2-methyl histamine (H_1-agonist) caused relaxation similar to H which was selectively blocked by cimetidine. Low concentrations (10^{-5}-10^{-4} mol/L) of 2-methyl histamine and of H (10^{-8}-10^{-7} mol/L) occasionally produced small contractions. Mepyramine (pyrilamine) blocked the contraction but did not modify the relaxant effect of H and its agonists. The results suggest a preponderance of histamine H_2-inhibitory receptors in the trachea of this animal.

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KEY WORDS histamine receptors; carbachol; 2-methyl histamine; 4-methyl histamine; cimetidine; pyrilamine (mepyramine); dimaprit; *Mastomys natalensis*; trachea

Significant qualitative and quantitative regional differences in the reactivity of mammalian airway smooth muscles to histamine (H) and other bronchoactive agents have been demonstrated[1-6]. In general, there is a preponderance of histamine H_1-receptors in airway smooth muscles of most mammalian species[1,3,6]. Recently histamine H_2-receptors have also been identified in the trachea of cat, horse and rhesus monkey as well as in the bronchii of man, sheep and guinea pig[7-9]. *Mastomys natalensis* is a multimammate rat found

in deserts which has been recently introduced as a laboratory animal due to its low immunological profile. No information is available in the literature about the type of histamine receptors present in the tracheal smooth muscle of this animal species. A preliminary report of part of this work has appeared[10] as a short abstract.

Materials and methods

The preparation of tracheal spiral strips and the recording of responses to agonists and their interactions with antagonists were similar to those described for other species[3]. Sixty adult *Mastomys natalensis* of either sex, weighing 60–90 g, were bled after stunning. The trachea was dissected out. Spiral strips were prepared and mounted 'in pairs' in different isolated tissue baths containing Krebs–Henseleit solution at 37℃ gassed with a mixture of 5% CO_2 + 95% O_2. The tissues were allowed to equilibrate for 2 h under a resting tension of 0.75 g. Drug responses were recorded isometrically with Grass FT 03 Force–displacement tranducers on a Grass model 7 polygraph. Relaxation was recorded on strips partially (50 ± 10% max) contracted by carbachol. After establishing cumulative concentration–response curves to agonists, a predetermined concentration of the antagonist was added to one tissue of each pair. Sixty minutes later, the concentration–response curve was re–established. The second tissue in the pair served as control to monitor any effects of time on the sensitivity of the tissue to agonists.

Carbamyl choline chloride (carbachol) was obtained from Nutritional Biochemical Corporation, while cimetidine hydrochloride, dimaprit dihydrochloride, histamine dihydrochloride, impromidine trihydrochloride, 2–methyl histamine dihydrochloride and 4-methyl histamine dihydrochloride were provided by Smith Kline and French Lab. Mepyramine maleate was purchased from May & Baker. All drug concentrations are expressed as the final molar bath concentration of the base.

The $\bar{x} \pm SE$ response to various concentrations of each agonist was determined in most cases from a minimum of 8 experiments in order to calculate the percent change which was plotted against − log mol/L concentration. Antagonism was statistically analysed by *t* test comparing the agonist response in the absence and presence of the antagonist.

Results

Effect of carbachol Carbachol caused concentration–dependent ($10^{-9} - 10^{-3}$mol/L) contractions of the tracheal strips (Fig 1).

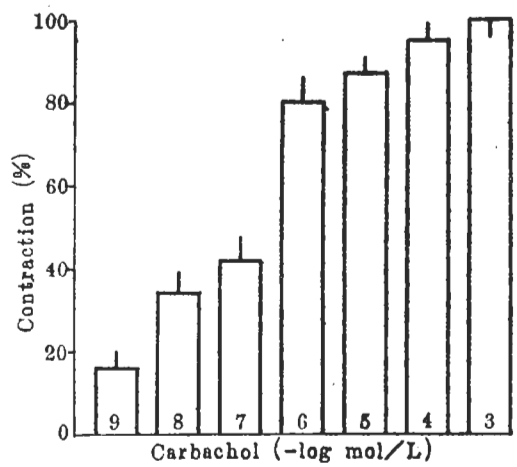

Fig 1. Concentration–dependent contraction by carbachol (10^{-9} – 10^{-3} mol/L) of tracheal smooth muscles of *Mastomys natalensis* (n = 22).

Effect of histamine H usually produced concentration–dependent ($10^{-7} - 10^{-2}$ mol/L) relaxation of the tracheal strip. In some experiments it caused a small contraction at low concentrations ($10^{-9} - 10^{-8}$ mol/L) (Fig 2).

Effect of H_2–receptor agonists and antagonist Three agonists were used in the

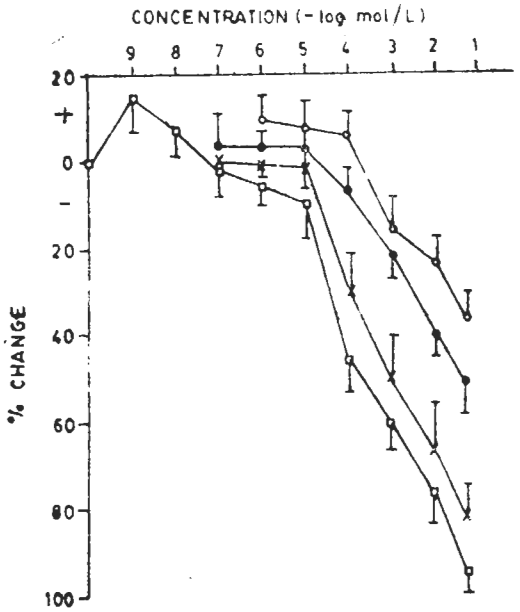

Fig 2. Relaxant effect of histamine on tracheal smooth muscles is shown by (□) (n = 16). (×) and (●) depict the H effect after mepyramine (n = 8) (10^{-5} mol/L) and cimetidine (n = 8) (10^{-6} mol/L), respectively. H response after pretreatment with a combination of mepyramine and cimetidine has been represented by (○, n = 4).

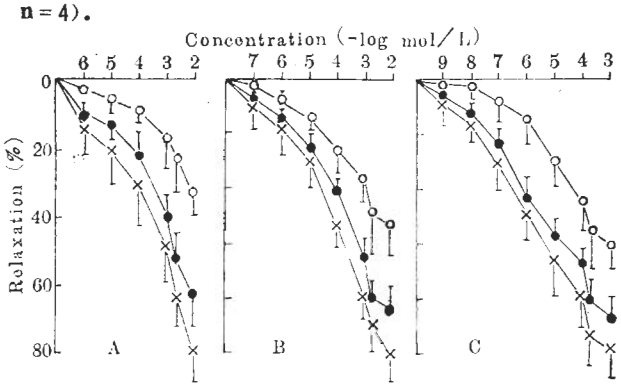

Fig 3. Effects of 4-methyl histamine (n = 7) (A), dimaprit (n = 6) (B) and impromidine (n = 11) (C) *per se* and after mepyramine (n = 6) (10^{-5} mol/L) or cimetidine (n = 5) (10^{-6} mol/L) has been shown by (×), (●) and (○), respectively.

concentration range of 10^{-9} to 10^{-3} mol/L. All produced concentration-dependent relaxation of the tracheal strips, similar to that produced by H (Fig 3). The order of potency was impromidine, dimaprit, histamine and 4-methyl histamine.

Cimetidine, a speciffic H_2-receptor antagonist, was used at a concentration of 10^{-6} mol/L. It selectively and significantly blocked the relaxation induced by H or H_2-receptor agonists ($P<0.05$, Fig 2 and 3). It also inhibited the contraction as well as relaxation induced by 2-methyl histamine (Fig 4).

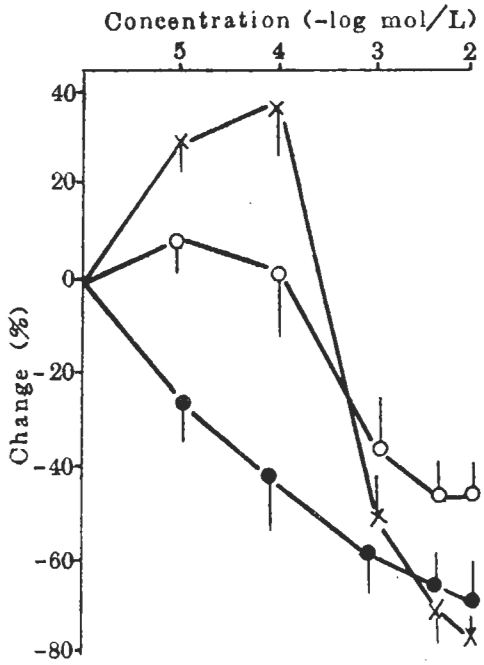

Fig 4. (×) represent *per se* effect of 2-methyl histamine (n = 8). (●) and (○) indicate the effect after mepyramine (n = 4) (10^{-5} mol/L) or cimetidine (n = 4) (10^{-6} mol/L), respectively.

Effect of an H_1-receptor agonist and an antagonist The H_1-receptor agonist used was 2-methyl histamine. Like H, it caused slight contractions at low concentrations (10^{-5} -10^{-3} mol/L) and relaxation was obtained with higher concentrations (10^{-3}-10^{-2} mol/L) (Fig 4). Mepyramine (10^{-5} mol/L) was able to block the contractions induced by H as well as 2-methyl histamine. However, it did not significantly modify the relaxant effect of any agonist (Fig 2-4).

Discussion

The tracheal smooth muscle of *Mastomys natalensis* appears to possess marked qualitative and quantitative differences from other mammals with respect to responsiveness to histamine. The overall effect of H on tracheal smooth muscle depends on its stimulatory or inhibitory action on a mixed population of H_1- and H_2-receptors which may act in opposite or similar directions. The relative ratio of H_1- and H_2-receptors differs not only amongst species, organs and tissues, but it may even vary from one segment to another in the same species[1,2,4-6].

Histamine, in general, relaxed the tracheal smooth muscle of *Mastomys natalensis* although in a few experiments relaxation was preceded by slight contraction. The relaxant effect was selectively blocked by cimetidine, an H_2-receptor antagonist[11]. Furthermore, the H_2-receptor agonists 4-methyl histamine[12], dimaprit[13] and impromidine[14] also relaxed the tracheal strip which was again blocked by cimetidine. Mepyramine, a specific H_1-receptor antagonist[15], did not alter the relaxant effect of H or H_2-receptor agonists. The relaxation observed with higher concentrations of 2-methyl histamine seems to be due to the action of this agent on H_2-receptors since the effect is significantly blocked by cimetidine. These observations suggest a preponderance of histamine H_2-inhibitory receptors in tracheal smooth muscle of *Mastomys natalensis*, a distribution similar to that reported for cat and rhesus monkey[2,3]. As reported above, low concentrations (10^{-8} mol/L) of H occasionally produced a mild potentiation of carbachol induced contraction. The effect was more marked with 2-methyl histamine, an H_1-receptor agonist[12]. Such an effect was never obtained with H_2-receptor agonists. These observations coupled with antagonism of the response with mepyramine at a concentration which has no effect on the relaxant effect (Fig 3-4) suggest mediation of the response via H_1-receptors. Blockade of the response by cimetidine, at the concentration required to block the relaxant effect, was unexpected and cannot be satisfactorily explained on the basis of currently available data. It appears reasonable to suggest, however, that H_1-receptors are also present in tracheal smooth muscles of *Mastomys natalensis* and that they exert a weak antagonistic effect on H_2-receptor stimulation.

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非洲软毛鼠气管平滑肌中组胺受体的性质

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提要　卡巴胆碱使非洲软毛鼠(大鼠，学名为 *Mastomys natalensis*) 的气管平滑肌收缩，但组胺可引起松弛，并有量-效相关性。H_2 受体的专一性激动剂 4-甲基组胺，dimaprit，impromidine 和高浓度的 2-甲基组胺 (H_1-激动剂)引起的松弛与组胺相似，可被西咪替丁选择性地阻断。

低浓度的 2-甲基组胺 (10^{-5}-10^{-4} mol/L) 和组胺 (10^{-8}-10^{-7} mol/L) 有时可引起弱的收缩。美吡拉敏 (mepyramine，pyrilamine)可阻断此收缩，但是不改变组胺及其激动剂的松弛效应。

以上结果提示：在此非洲软毛大鼠的气管中以 H_2 抑制受体占优势。

关键词　组胺受体；卡巴胆碱；2-甲基组胺；4-甲基组胺；西咪替丁；美吡拉敏；dimaprit；非洲软毛鼠；气管

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