In animals treated in this way however, mepyramine plus meclofenamate significantly inhibited the reaction over the first minute following antigen challenge, the period of the reaction identified by Collier & James (1967) as being mediated by kinins. Similar results were obtained for flufenamic acid (5 mg/kg).

In actively sensitized guinea-pigs, similar results were obtained, although there were quantitative differences. Thus, mepyramine was less effective in blocking bronchoconstriction following challenge with antigen (0.6 mg/kg of ovalbumen) in active than passively sensitized animals. Moreover, whereas in passively sensitized guinea-pigs mepyramine inhibited over the whole of the 10 min period for which the reaction was followed, in actively sensitized animals mepyramine inhibited the reaction only over the initial 4–5 minutes. Sodium meclofenamate had no effect when given alone but potentiated the reaction in mepyramine treated animals; again, however, the initial period of bronchoconstriction was inhibited in animals given mepyramine plus meclofenamate.

These results confirm the potentiation of mediator release by non-steroidal anti-inflammatory agents and have shown its importance in an *in vivo* situation. From the results obtained, it appears that sodium meclofenamate potentiated the SRS-A mediated portion of anaphylactic bronchoconstriction, probably through an effect upon the synthesis of prostaglandins thought to play a modulatory role in the control of mediator release (Walker, 1972). Differences were observed between the relative importance of the mediators in anaphylactic bronchoconstriction in actively and passively sensitized animals, and it appears that histamine is less important in actively sensitized animals.

References

COLLIER, H.O.J. & JAMES, G.W.L. (1967). Humoral factors affecting pulmonary inflation during acute anaphylaxis in the guinea-pig *in vivo*. *Br. J. Pharmac.*, **30**, 283–301.

DAVIES, G.E. & JOHNSTON, T.P. (1971). Quantitative studies on anaphylaxis in guinea-pigs passively sensitized with homologous antibody. *Int. Archs. Allergy appl. Immunol.*, **41**, 648–654.

ENGINEER, D.M., PIPER, P.J. & SIROIS, P. (1976). Interaction between the release of SRS-A and of prostaglandins. *Br. J. Pharmac.*, **57**, 460–461P.

WALKER, J.L. (1972). The regulatory function of prostaglandins in the release of histamine and SRS-A from passively sensitized human lung tissue. In *Advances in the Biosciences*, ed. Bergström, S. & Bernhard, S., pp. 235–240. Braunschweig: Pergamon Press Vieweg.

Effects of activation of H_1- and H_2-receptors on central cardiovascular structures in cats and on behaviour in chickens

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Intracerebroventricular administration of histamine increased blood pressure, heart rate and amplified sympathetic discharges. Intracerebroventricular administrations of mepyramine but not of metiamide have been reported to reduce this effect which was therefore suggested to be mediated by activation of H_1-receptors (Finch & Hicks, 1976).

In chloralose-anaesthetized cats, histamine, 4-methylhistamine, 2-(2-aminoethyl) pyridine and betahistine were administered into the lateral ventricle of the brain. Histamine (2–10 μg/kg) induced a rise in blood pressure which was reduced by mepyramine indicating the involvement of H_1-receptors. 2-(2 aminoethyl) pyridine, and betahistine, two stimulants of H_1-receptors, induced hypertension and tachycardia. The pressor effect reached 35 mmHg after 100 μg/kg of 2-(2 aminoethyl) pyridine and 15 mmHg after 200 μg/kg of betahistine.

These effects were suppressed by an intraventricular administration of mepyramine (100 μg/kg) but not of metiamide (50 μg/kg). High doses of 4-methylhistamine (100 μg/kg), a stimulant of H_2-receptors, injected into the lateral ventricle of the brain, induced a brief increase in blood pressure (15–20 mmHg). At higher doses, this effect was followed by a hypotension, possibly due to leakage into the systemic circulation. The rise in blood pressure was abolished by an intracerebroventricular injection of metiamide (100 μg/kg) and of mepyramine (50 μg/kg).

Histamine in newborn chickens induced sleep characterized by a loss of the righting reflex. The duration of sleep was 12 min after 50 mg/kg, i.m. of the drug. 4-Methylhistamine (50 mg/kg, i.m.) induced sleep for 6 min, but 2-(2 aminoethyl) pyridine and betahistine (100 mg/kg, i.m.) failed to abolish the righting reflex.

These experiments show the predominant role of the activation of H_1-receptors for the stimulation of central cardiovascular structures, but activation of H_2-receptors induced also an effect possibly by increasing the level of 3'5'-cyclic AMP which has been shown to increase blood pressure when introduced into the lateral ventricle of the brain (Delbarre, Senon & Schmitt, 1975). In contrast, H_2- but not H_1-receptors seem to play a role in inducing sleep in chickens.

Reference

DELBARRE, B., SENON, DANIELLE & SCHMITT, H. (1975). Study on the cardiovascular action of dibutyryl-3, 5-cyclic AMP (DB.AMP) following the intraventricular administration to cats. Abstracts Sixth International Congress of Pharmacology, Helsinki, 1975, No. 516, p. 227.

FINCH, L. & HICKS, P.E. (1976). Central hypertensive action of histamine in conscious normotensive cats. *Eur. J. Pharmacol.*, **36**, 263–266.

Histamine receptors in the cranial circulation of the monkey

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Histamine has been implicated in the pathogenesis of cluster headache and migraine, but histamine H_1-receptor antagonists such as mepyramine have been of little therapeutic benefit in these disorders (Anthony & Lance, 1971). This may well be due to the nature of the cranial vascular histamine receptors. To investigate the nature of these receptors, we have compared the effects of the H_2-receptor antagonists, metiamide (Black, Duncan, Emmett, Ganellin, Hesselbo, Parsons & Wyllie, 1973) and cimetidine (Brimblecombe, Duncan, Durant, Ganellin, Parsons & Black, 1975), with those of mepyramine, on cranial and systemic vasodilator responses to histamine in *Macaca nemestrinas* monkeys, anaesthetized with i.v. pentobarbitone sodium.

Common and external carotid blood flows on one side were measured simultaneously using an electromagnetic flowmetering technique. Blood pressure was monitored at the carotid bifurcation. Internal and external carotid vascular resistances were calculated from these measurements. Systemic blood pressure was measured in the aortic arch. Cumulative dose-response curves for the decreases in internal and external carotid vascular resistance produced by intracarotid histamine infusions, and dose-response curves for the systemic vasodepressor effects of i.v. histamine doses, were established. Antagonism was assessed in terms of shifts of dose-response curves, expressed as dose ratios (means and 95% confidence limits).

Metiamide was administered to seven monkeys, in progressively increasing doses of 0.25, 1 and 5 mg/kg at 90 min intervals. External carotid dose-response curves were shifted to the right following the 1 and 5 mg/kg doses, the dose ratios being 1.7(1.1–2.6) and 4.1(2.4–6.9) respectively. The internal carotid dose ratios at these dose levels were 1.3(0.7–2.3) and 4.7(1.0–21.0) respectively. In four monkeys treated similarly with cimetidine, the external carotid dose ratios following the 1 and 5 mg/kg doses were 2.0(1.6–2.5) and 7.2(2.1–24.1) respectively, while the internal carotid dose ratios were 1.0(0.4–2.6) and 2.7(0.7–10.7) respectively. These doses of metiamide and cimetidine had no effect on vasodepressor responses. When mepyramine (2 mg/kg) was subsequently administered to these H_2-receptor antagonist-treated monkeys, vasodepressor responses were abolished and internal carotid dose-response curves were shifted further to the right. However, there was no appreciable increase in external carotid blockade.

In four monkeys, mepyramine was administered initially. Progressively increasing doses of 0.5, 2 and 10 mg/kg produced dose-dependent shifts to the right of vasodepressor dose-response curves, the dose ratios being 3.0(0.5–16.7), 6.3(1.1–37.3) and 8.3 range (6.7–10.4). After the 10 mg/kg dose, the internal carotid dose ratio was 2.0(0.1–37.6), and the external carotid dose ratio was only 1.8(0.4–8.2). Subsequent administration of metiamide or cimetidine (1 mg/kg) did not alter mepyramine-induced reduction of vasopressor responses, but increased the effect in both cranial circulations.

These results suggest that the cranial vasodilator effects of histamine are mediated predominantly by H_2-receceptors in the external carotid circulation, and by both H_1- and H_2-receptors in the internal carotid vasculature.

References

ANTHONY, M. & LANCE, J.W. (1971). Histamine and serotonin in cluster headache. *Archs. Neurol.*, **25**, 225–231.

BLACK, J.W., DUNCAN, W.A.M., EMMETT, J.C., GANELLIN, C.R., HESSELBO, T., PARSONS, M.E. & WYLLIE, J.H. (1973). Metiamide – an orally active histamine H_2-receptor antagonist. *Agents and Actions*, **3**, 133–137.

BRIMBLECOMBE, R.W., DUNCAN, W.A.M., DURANT, G.J., GANELLIN, C.R., PARSONS, M.E. & BLACK, J.W. (1975). The pharmacology of cimetidine, a new histamine H_2-receptor antagonist. *Br. J. Pharmac.*, **53**, 435P–436P.