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.

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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.

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