Interaction between histamine H_2-receptor antagonists and the hypotensive effects of clonidine in rats

L. FINCH, C.A. HARVEY, P.E. HICKS & D.A.A. OWEN

Department of Pharmacology, University of Bradford, Bradford and Department of Pharmacology, Smith Kline & French Laboratories Ltd., Welwyn Garden City, Hertfordshire

Clonidine is a potent centrally acting antihypertensive agent, the major action of which has been considered to be due to central α-adrenoceptor stimulation (Schmitt, Schmitt & Fenard, 1973). Recently, however, hypotension elicited by peripheral administration of clonidine to rats has been reported to be antagonized by central administration of the histamine H_2-receptor antagonist, metiamide, (Karppannen, Paakkari, Huotari & Orma, 1976; Paakkari, Paakkari & Karppannen, 1976) thus suggesting a possible central involvement of histamine receptors with the hypotensive effects of clonidine. Furthermore, clonidine appears to stimulate histamine H_2-receptors in the heart *in vitro* (Csongrady & Kobinger, 1974) and to stimulate cAMP accumulation in rat brain slices by interaction with histamine H_2-receptors (Audigier, Virion & Schwartz, 1976). In conscious cats however, metiamide failed to antagonize hypotension after central administration of clonidine (Finch & Hicks, 1976). The present study reports further findings on the interaction between clonidine and the histamine H_2-receptor antagonists metiamide and cimetidine.

Rats were anaesthetized with urethane (1.25 g/kg i.p.). The trachea was cannulated and arterial blood pressure measured. Drugs were injected into lateral brain ventricles (i.c.v.) or via an intravenous catheter.

Intravenous administration of clonidine (30 μg/kg) caused a fall in mean blood pressure. In one group, clonidine lowered blood pressure by 46.3 ± 6.9 mm Hg (mean $\pm$ s.e. mean, $n=8$) in rats pretreated with saline i.c.v. but only 14.8 ± 4.5 mm Hg in rats pretreated with metamide (400 μg i.c.v.); metiamide (800 μg) abolished the responses to clonidine. Metiamide reduced but did not abolish the bradycardia due to clonidine. Cimetidine, although less effective than metiamide, also antagonized the hypotensive response to clonidine.

Treatment with either H_2-receptor antagonist i.c.v. 15–30 min after clonidine (30 μg/kg) produced a rapid reversal of the hypotensive response to clonidine although this was not well sustained. The smallest effective dose of metiamide was 50 μg and total reversal was achieved by all doses of either antagonist in excess of 100 μg ($n=6$ per group). In contrast, metiamide (400 μg) given intravenously did not reverse clonidine hypotension.

Administration of either metiamide or cimetidine, (400 and 800 μg i.c.v.) alone caused dose-dependent increases in blood pressure with variable effects on heart rate. Although the antagonists alone increase blood pressure when given in large doses i.c.v. this is unlikely to account for their ability to prevent clonidine-induced hypotension when administered as pretreatments or to reverse the response when administered in lower doses after clonidine.

These results confirm an interaction between clonidine and centrally administered histamine H_2-receptor antagonists. However, centrally mediated hypotensive responses to histamine have yet to be demonstrated (Finch & Hicks, 1976) suggesting that it may be premature to implicate histamine H_2-receptors in the hypotensive response to clonidine. An interaction between clonidine and cimetidine is not of clinical significance, since autoradiography has indicated that cimetidine does not penetrate the blood brain barrier (Cross, 1976) and no interaction has been observed between clonidine and the histamine H_2-receptor antagonists when these are given systematically.

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