The cardioinhibitory and pressor actions of *NN*-diMe-6,7-diOHATN were antagonized by yohimbine in a competitive manner, although this antagonist proved more potent at presynaptic receptors. Since yohimbine had little antagonistic effect on the pressor responses to phenylephrine, and prazosin failed to antagonize the effects of *NN*-diMe-6,7-diOHATN these data lend further support to the suggestion that the prazosin-resistant postsynaptic receptor (Drew & Whiting 1979; Docherty et al 1979) resembles the α_2-adrenoceptor. These data are in close agreement with the work of Timmermans et al (1979), and Timmermans & Van Zwieten (1980) who used guanfacine or BHT 993 as the agonist and Drew (1980) who used M7 as the agonist.

The slope of the vasoconstrictor dose-response curve to phenylephrine was steeper than the corresponding slope for *NN*-diMe-6,7-diOHATN, moreover, the maximum responses elicited by phenylephrine or noradrenaline were greater. Taken in conjunction with the differential antagonistic properties of yohimbine and prazosin, these results may provide additional evidence for a sub classification of postsynaptic α-adrenoceptors in vivo.

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Involvement of central α_2-adrenoceptors in the mediation of clonidine-induced hypotension in the cat

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Clonidine-induced hypotension is due to stimulation of α-adrenoceptors in the brain stem (reviews by Van Zwieten 1975; Kobinger 1978) though the relative roles of α_1- and α_2-adrenoceptors in the mediation of this response is uncertain. In other situations in the central nervous system clonidine is known to stimulate post- and pre-synaptic adrenoceptors as demonstrated by increases in hindlimb flexor reflex activity and reductions in noradrenaline turnover respectively (Andén et al 1976). In the present study in the anaesthetized cat, we have used prazosin and yohimbine, α-adrenoceptor blocking drugs with relative selectivity for blocking α_1 and α_2 adrenoceptors respectively, to examine the nature of the central α-adrenoceptors involved in mediating the hypotension and bradycardia evoked by centrally administered clonidine.

Anaesthesia was induced in twelve female cats (1·9 to 2·4 kg) with halothane and maintained with pentobarbitone sodium, 35 mg kg^{-1} intravenously. Systemic blood pressure was recorded from a femoral artery and heart rate was monitored from the pulse in the blood pressure signal. Central administration of drugs was performed by the intracerebroventricular (i.c.v.) route using a stainless steel cannula inserted stereotaxically into the left lateral brain ventricle according to the following co-ordinates: anterior 10·5 mm, lateral 4·0 mm and horizontal between +8·25 and 9·5 mm (Snider & Niemer 1961).

The hydrochloride salts of clonidine (Boehringer), yohimbine (Sigma) and prazosin (Pfizer) were used and doses are expressed as the free base. Clonidine and yohimbine were administered in 5 and 40 μl of 0·9% w/v NaCl (saline) respectively and prazosin in 40 μl water.

In preliminary experiments clonidine, 10 μg i.c.v. caused submaximal falls in mean arterial pressure and this dose was selected for experiments involving α-adrenoceptor antagonists. Saline, 100 μl i.c.v. or yohimbine 200 μg i.c.v. had little or no effect on basal blood pressure but prazosin, 100 μg i.c.v., lowered mean arterial pressure with recovery to pre-dose levels between 20 and 40 min after administration. Clonidine was administered 20 min after saline or yohimbine and between 20 and 40 min after prazosin.

Clonidine, 10 μg, caused a gradual decrease in mean arterial pressure and heart rate over the 1 h after dosing (Fig. 1). Yohimbine, 200 μg, abolished, but prazosin,

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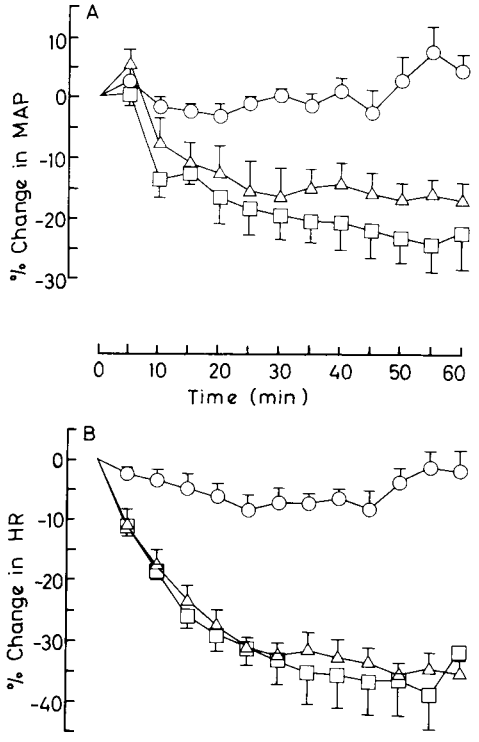

FIG. 1. Percentage changes in mean arterial pressure (MAP) (A) and heart rate (HR) (B) with time in 3 groups of anaesthetized cats receiving clonidine (10 μg i.c.v.) after the i.c.v. administration of 100 μl saline (□–□), 200 μg yohimbine (○–○) or 100 μg prazosin (△–△). Four cats were used per group and the vertical bars show the s.e. mean. Absolute values (mean ± s.e. mean) for MAP and heart rate, respectively, before clonidine administration were 113 ± 8 mm Hg and 160 ± 7 beats min^{-1} for the saline group, 109 ± 6 mm Hg and 139 ± 18 beats min^{-1} for the yohimbine group, and 101 ± 2 mm Hg and 140 ± 17 beats min^{-1} for the prazosin group.

100 μg, did not significantly alter, clonidine-induced hypotension and bradycardia in the cat (Fig. 1).

As an antagonist at post-synaptic α_1-adrenoceptors in rat isolated anococcygeus muscle prazosin is approximately 60 times more potent than yohimbine but it is 30 times less potent than yohimbine as an antagonist at pre-synaptic α_2-adrenoceptors in rat isolated vas deferens (Doxey et al 1977). Therefore, since prazosin had no effect on clonidine-induced hypotension and bradycardia when used at only half the inhibitory dose of yohimbine, it is unlikely that clonidine exerted its cardiovascular actions by stimulation of central α_1-adrenoceptors.

Our results therefore implicate α_2 (yohimbine-sensitive) rather than α_1 (prazosin-sensitive) adrenoceptors in the mediation of the hypotension and bradycardia induced by centrally administered clonidine in the anaesthetized cat. Others have reported that other α-adrenoceptor blocking drugs with relative selectivity for α_2-adrenoceptors, such as phentolamine, tolazoline and piperoxan, reduce the hypotensive action of clonidine in the cat (Schmitt & Schmitt 1970; Schmitt et al 1973; Finch 1974).

In contrast to our findings, Timmermans et al (1979) found that, in the anaesthetized cat, prazosin (3 μg kg^{-1}) infused into the vertebral artery diminished the hypotensive effect, but not the bradycardia, of a subsequent dose of clonidine (1 μg kg^{-1}). The discrepancy between our results and those of Timmermans et al (1979) may reflect differences in the distribution of prazosin in the brain dependent on route of administration. In the rat, both yohimbine and prazosin antagonize the hypotension and bradycardia to clonidine (Cavero & Roach 1978; Hamilton & Longman 1980) implicating both α_1- and α_2-adrenoceptors in the mediation of these responses in this species.

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