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Action of indoramin on pre- and postsynaptic α-adrenoceptors in pithed rats

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Clonidine has been reported to antagonize the cardiac acceleration evoked by low frequency electrical stimulation of sympathetic nerve fibres to the heart of the pithed rat (Armstrong & Boura, 1973). The drug's inhibitory action probably results from an agonist action on presynaptic α-receptors leading to decreased noradrenaline release during nerve stimulation (Werner, Starke & Schümann, 1972; Langer, 1974; Pacha, Salzmann & Scholtysik, 1975). The α-adrenoceptor antagonist phentolamine increases cardiac acceleration produced by nerve stimulation and inhibits the action of clonidine (Drew, 1976; Doxey, 1977). In this preliminary communication we describe experiments made to determine whether the competitive α-adrenoceptor antagonist indoramin (Alps, Hill & others, 1972) inhibits the action of clonidine at presynaptic receptors.

Female Charles River rats (200–290 g) were anaesthetized with 5% halothane in oxygen and pithed. Respiration was maintained artificially (60 strokes min^{-1}, 1 ml/100 g) and the rectal temperature kept at 38° by means of a thermal blanket. The right jugular vein was cannulated for drug administration. Arterial pressure was measured by means of a transducer (Statham P 23) connected to the left common carotid artery and integrated heart rate was derived using the pressure wave to trigger a tachograph. Both cardiovascular variables were displayed on a polygraph (Grass, Model 7).

The pithing rod was used to stimulate the spinal sympathetic outflow as described by Armstrong & Boura (1973). When the electrodes were close to the origin of the sympathetic cardiac nerves, stimulation evoked tachycardia with relatively little change in blood pressure. Stimulation parameters were 25 V, 0·5 ms, 0·25–8 Hz (Grass Model SD9. Stimulator). Frequency was increased logarithmically, stimulation at each frequency being continued until the maximum increase in heart rate had been obtained (usually within 1 min). Movement of skeletal muscle was reduced by intravenous tubocurarine (1 mg kg^{-1}).

* Correspondence.

Frequency response curves were made before and 10 min after injection of indoramin (3·2 mg kg^{-1}, i.v.), phentolamine (1·6 mg kg^{-1}, i.v.) or 0·9% NaCl vehicle (1 ml kg^{-1}) in groups of 5 rats. Clonidine (40 μg kg^{-1}) was then administered to all animals and the frequency responses repeated after a further 10 min.

The doses of indoramin and phentolamine were selected from preliminary experiments as being the highest that lacked negative chronotropic effects. The dose of clonidine was similarly selected as one which evoked a marked, but submaximal decrease in the frequency-dependent tachycardia.

The antagonist actions of the same doses of indoramin and phentolamine at postsynaptic sites were determined against pressor responses evoked by endogenous (80 V, pulse width 1·0 ms; duration 5 s) and exogenous nor-

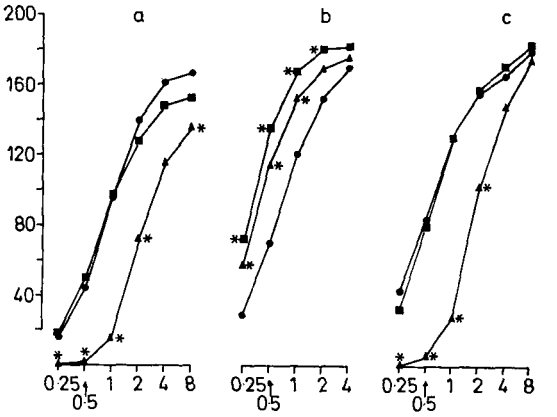

FIG. 1. Dose-response curves for the frequency-dependent tachycardia evoked by cardiac nerve stimulation. Closed circles show effects before and closed squares effects after saline or an α-antagonist. Closed triangles show effects after a subsequent dose of clonidine (40 μg kg^{-1}, i.v.) (a) saline, (1 ml kg^{-1}, i.v.) (b) phentolamine (1·6 mg kg^{-1}, i.v.) (c) indoramin (3·2 mg kg^{-1}, i.v.). The results are means of 5 experiments. Asterisks indicate significant differences from the previous response curve ($P \leq 0.05$) using paired *t*-tests. Ordinate: Increase in heart rate (beats min^{-1}). Abscissa: Frequency (Hz).

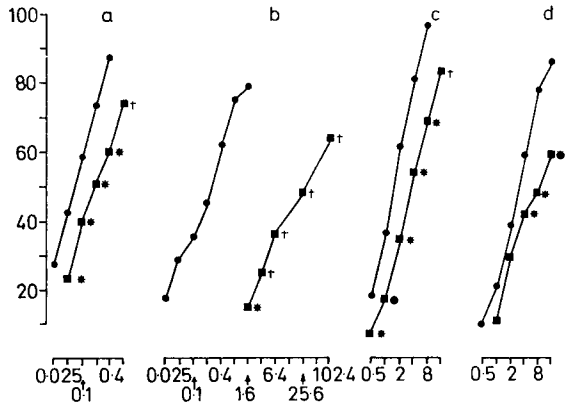

FIG. 2. Effects of 3·2 mg kg^{-1}, intravenous indoramin (a and c) and 1·6 mg kg^{-1}, intravenous phentolamine (b and d) on pressor responses evoked by exogenous noradrenaline and sympathetic nerve stimulation in pithed rats. Closed circles show effects before and closed squares effects after the drug. The results are means of at least 6 experiments. Asterisks indicate significant differences from control response curves ($P \leq 0.05$) using paired *t*-tests. † Unpaired data. Ordinate: Increase in diastolic blood pressure (mmHg). Abscissa a,b: Noradrenaline (μg); c,d: Frequency (Hz).

adrenaline in the pithed rat preparation of Gillespie & Muir (1967).

Saline produced no significant change in the tachycardia evoked by sympathetic nerve stimulation (Fig. 1a). A subsequent dose of clonidine evoked a pressor response and a significant ($P \leqslant 0.05$) reduction in the frequency dependent tachycardia (Fig. 1a) although there was little effect on basal heart rate.

Phentolamine produced a significant ($P \leqslant 0.05$) increase in the cardiac acceleration evoked by sympathetic nerve stimulation and prevented the cardiac inhibitory effect of clonidine (Fig. 1b).

Indoramin had no significant effects on the electrically evoked tachycardia and failed to prevent the cardiac inhibitory action of clonidine (Fig. 1c).

The same doses of phentolamine and indoramin significantly ($P \leqslant 0.01$) inhibited the pressor responses evoked by exogenous noradrenaline (Fig. 2a, b) and sympathetic nerve stimulation (Fig. 2c, d).

The results from this study substantiate those of other workers (Armstrong & Boura, 1973; Drew, 1976; Doxey, 1977). The inhibitory effect of clonidine on the responses to cardiac nerve stimulation and its reversal by phentolamine is consistent with the hypothesis that sympathetic nerve endings contain α-receptors that control the release of noradrenaline (Langer, 1974). Phentolamine does not appear to show selectivity for either the pre- or postsynaptic sites.

Indoramin neither potentiated the frequency-dependent tachycardia nor reversed the inhibitory effect of clonidine at a dose which blocked the action of noradrenaline at postsynaptic sites. Previous experiments have shown that indoramin competitively antagonizes the action of noradrenaline on guinea-pig and rat aortae and perfused mesenteric vasculature (Alps & others, 1972; Collis & Alps, 1973). The present studies indicate that its action is selective at peripheral postsynaptic sites.

Postsynaptic selectivity may confer a therapeutic advantage for indoramin over the earlier non-selective α-adrenoceptor antagonists such as phentolamine since blockade of presynaptic receptors could result in reversal of competitive postsynaptic antagonism by increasing noradrenaline release. Lack of postsynaptic selectivity could account for the ineffectiveness of the earlier α-adrenoceptor antagonists in the treatment of hypertension (Rand, McCulloch & Story, 1975).

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