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Effects of prazosin and two of its derivatives (UK 18.596 and UK 33.274) on α-adrenoceptors

F. KARAMAT ALI, S.P. KOSSEN, P.B.M.W.M. TIMMERMANS & P.A. VAN ZWIETEN

Department of Pharmacy, Division of Pharmacotherapy, University of Amsterdam

The antihypertensive drug prazosin exerts its blood-pressure lowering efficacy by acting as an antagonist at vascular postsynaptic α-adrenoceptors (Graham *et al.*, 1977; Cavero *et al.*, 1978). In order to further characterize the properties of prazosin-like compounds, a comparative study was carried out with prazosin and two of its new structurally related derivatives (UK 33.274 and UK 18.596). Administration of the drugs (1–100 μg/kg) either i.v. or via the vertebral artery of anaesthetized cats provoked a dose-dependent decrease in arterial pressure without affecting heart rate to a great extent. Similar to prazosin (Timmermans, Lam & Van Zwieten, 1979), UK 18.596 and UK 33.274 do not display substantial central hypotensive effects. Prazosin and its derivatives when injected i.v. proved potent hypotensive drugs in anaesthetized rats as well (1–100 μg/kg). UK 18.596 was found to be more effective than UK 33.274, but its duration of action was relatively short.

The pronounced blocking properties of the compounds at vascular postsynaptic α-adrenoceptors became evident from their antagonism towards the pressor effects of i.v. (−)-phenylephrine in pithed rats and cats. The dose-response curves of (−)-phenylephrine were shifted to the right in a parallel fashion after i.v. pretreatment (0.1 and 1 mg/kg). UK 18.596 and UK 33.274 were also studied in comparison with prazosin with respect to their effects on the clonidine-induced reduction of the elevated heart rate in pithed rats, clonidine-induced sedation in mice and at pre- and post-synaptic α-adrenoceptors in the rat vas deferens.

In low concentrations UK 18.596 and UK 33.274 inhibited [^{3}H]-prazosin binding to isolated membranes from rat cerebral cortex. Both derivatives were found 6–8 times less potent than prazosin itself in displacing [^{3}H]-prazosin from its specific binding sites in the central nervous system.

It is concluded that UK 18.596 and UK 33.274, like prazosin, display a selective antagonism for postsynaptic α-adrenoceptors in various models. Their potencies to inhibit postsynaptic α-adrenoceptors correspond with their hypotensive efficacies.

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The effect of sympathetic activity on vasomotor responses to methysergide in the femoral arterial bed of the anaesthetized dog

W. FENIUK & P.P.A. HUMPHREY

Department of Pharmacology, Glaxo Group Research Limited, Ware Division, Ware, Hertfordshire, U.K.

Saxena (1974) has shown that intravenous doses of methysergide selectively increase vascular resistance in the common carotid arterial bed of the anaesthetized dog. In similar experiments we have found that after ganglion-blockade methysergide also increases vascular resistance in the femoral arterial bed. We have therefore examined this in more detail.

Beagle dogs (7–12 kg) were anaesthetized with barbitone (300 mg/kg i.p.). Aortic blood pressure was recorded via the right femoral artery and drugs were administered via the right femoral vein. Flow was recorded in the left femoral artery using an electromagnetic flow probe. In some experiments dogs were

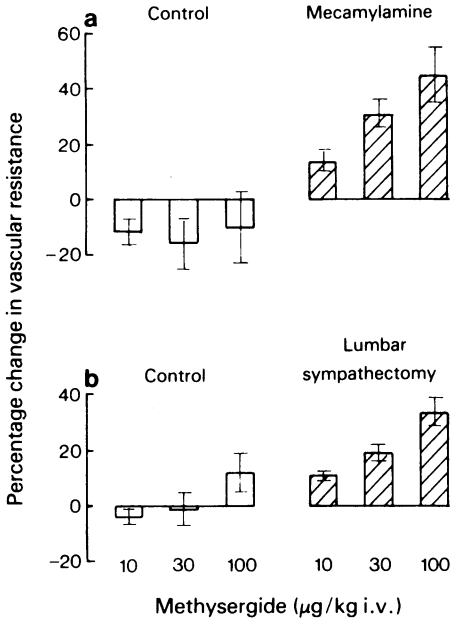

Figure 1 Left femoral arterial bed of anaesthetized dog. Effect of methysergide (10, 30, 100 μg/kg i.v.) on vascular resistance (mean aortic blood pressure ÷ mean femoral artery flow) before (control) and after (a) ganglion-blockade with mecamylamide (5 mg/kg i.v.) or (b) section of the left lumbar sympathetic chain. Values are the mean (±s.e. mean) from 6 and 5 dogs respectively. Mean control flow rate was 88 ± 9 ml/min and the mean control vascular resistance value was 1.58 ± 0.24 mm Hg. min. ml^{-1} ($n = 11$).

pretreated with atropine (0.2 mg/kg i.v.) and left femoral artery flow recorded following stimulation of the left lumbar sympathetic chain every 3 min (supramaximal voltage, 0.5 ms duration at 2 Hz for 10 s). In these experiments a muscular branch of the left femoral artery was cannulated for the local administration of noradrenaline.

Methysergide (10, 30, 100 μg/kg i.v.) produced either small increases or decreases in femoral vascular resistance. However, after mecamylamine (5 mg/kg i.v.) or section of the lumbar sympathetic chain between L_4 and L_5, methysergide produced only marked dose-dependent increases in femoral vascular resistance (Figure 1). Intravenous infusion of methysergide (10 μg kg^{-1} min^{-1}) inhibited the increases in femoral vascular resistance produced by stimulation of the lumbar sympathetic chain (70 ± 2% inhibition, mean ± s.e. mean, $n = 4$) whilst the increases in vascular resistance produced by close intra-arterially administered noradrenaline were potentiated (25 ± 15% potentiation).

Our results show that the vasomotor actions of methysergide in the dog femoral arterial bed are dependent on the degree of sympathetic activity, and suggest that the vasoconstrictor action of methysergide can be masked by a neuronal inhibitory action which may be similar to that described in the dog isolated saphenous vein (Feniuk, Humphrey & Watts, 1979).

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Are there two types of prostaglandin receptor mediating vasodilatation in the dog?

R.A. COLEMAN, P.P.A. HUMPHREY, I. KENNEDY, G.P. LEVY & P. LUMLEY

Department of Pharmacology, Glaxo Group Research Limited, Ware Division, Ware, Hertfordshire

Most prostaglandins cause vasodilatation in the anaesthetized dog (Nakano, 1972). The purpose of this study was to compare the vasodilator potencies of a range of prostaglandins in three vascular beds of the dog in an attempt to define some pharmacological characteristics of the receptors mediating this response.

Blood flow was measured, using electro magnetic flow probes, in the common carotid, femoral and superior mesenteric arteries of beagle dogs (7–11 kg) anaesthetised with barbitone sodium (300 mg/kg i.p.). Prostaglandins were administered close intra-arterially (i.a.) in random order. Up to four prostaglandins were examined in any one experiment in a maximum of two vascular beds. Prostaglandin E_1 was included in each experiment as a standard. Responses were expressed as peak percentage change in vascular resistance. All of the prostaglandins tested caused dose-dependent vasodilatation (Table 1). Prostaglandin E_1 was generally the most potent vasodilator, mean i.a. doses (95% confidence limits, number of determinations) to produce a 30% fall in vascular resistance