in renal hypertension in rabbits. *J. Physiol. Lond.*, **238**, 403–411.

GARCIA-SEVILLA, J.A., DUBOCOVICH, M.L. & LANGER, S.Z. (1979). Angiotensin II facilitates the potassium-evoked release of ^{3}H-noradrenaline from the rabbit hypothalamus. *Eur. J. Pharmac.* (in press).

LEVER, A.F. & ROBERTSON, J.I.S. (1964). Renin in the plasma of normal and hypertensive rabbits. *J. Physiol. Lond.*, **170**, 212–218.

STARKE, K. (1971). Action of angiotensin on uptake, release and metabolism of ^{14}C-noradrenaline by isolated rabbit hearts. *Eur. J. Pharmac.*, **14**, 112–123.

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.

References

CAVERO, I., FÉNARD, S., GOMENI, R., LEFÈVRE, F. & ROACH, A.G. (1978). Studies on the mechanism of the vasodilator effects of prazosin in dogs and rabbits. *Eur. J. Pharmac.*, **49**, 259–270.

GRAHAM, R.M., OATES, H.F., STOKER, L.M. & STOKES, G.S. (1977). Alpha blocking action of the antihypertensive agent prazosin. *J. Pharmac. exp. Ther.*, **201**, 747–752.

TIMMERMANS, P.B.M.W.M., LAM, E. & VAN ZWIETEN, P.A. (1979). The interaction between prazosin and clonidine at α-adrenoceptors in rats and cats. *Eur. J. Pharmac.*, **55**, 57–66.

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