Experimental renal hypertension and [^{3}H]-noradrenaline release from the rabbit hypothalamus: enhanced K^+-evoked overflow of tritium and lack of facilitation through presynaptic angiotensin II receptors

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Several reports suggest the participation of a central noradrenergic mechanism in the development of renal hypertension (Chalmers, Dollery, Lewis & Reid, 1974) and a possible role of angiotensin II (ANG II) in its pathophysiology (Lever & Robertson, 1964). Since ANG II can facilitate the release of noradrenaline (NA) in the peripheral (Starke, 1971) and central (Garcia-Sevilla, Dubocovich & Langer, 1979) nervous system, through the activation of presynaptic facilitatory angiotensin receptors, the possible involvement of these release modulating receptors in the genesis of the renovascular hypertension cannot be ruled out. This investigation was undertaken to compare the presynaptic facilitatory effect of ANG II on NA release in the central and peripheral nervous system from normal and renal hypertensive rabbits.

The one-kidney Page model of renovascular hypertension was used. Hypertension was induced by wrapping the left kidney in cellophane together with contralateral nephrectomy. Five weeks after the operation the systolic blood pressure had increased from a basal value of 104 ± 3 mm Hg to 138 ± 4 mm Hg ($n = 13$; $P < 0.001$; paried t-test). The experiments were performed in hypothalamic slices and isolated right atria prelabelled with [^{3}H]-NA (specific activity 10.43 Ci/mmole; New England Nuclear, Boston, Massachusetts). The release of [^{3}H]-NA was induced either by exposure to 20 mM K^+ (hypothalamus) or by field stimulation at 2 Hz for 90 s (atrium). The tissues were superfused with Krebs solution containing 10 μM cocaine (hypothalamic slices) or 0.3 μM atropine (atria).

In control hypothalamic slices, the fraction of the total tissue radioactivity released by the first (S_1) exposure to K^+ was 9.86 ± 0.66 ($\times 10^{-3}$) ($n = 54$) and the ratio obtained between two consecutive stimulation periods (S_2/S_1) was 0.72 ± 0.06 ($n = 13$). In hypothalamic slices from renal hypertensive rabbits, the fraction of total tissue radioactivity released by S_1 was significantly increased: 24.08 ± 3.31 ($\times 10^{-3}$) ($n = 36$; pooled data from 13 rabbits) ($P < 0.001$), and the ratio S_2/S_1 was: 1.04 ± 0.04 ($n = 6$). In sham-operated rabbits (right nephrectomy) the K^+-evoked release of [^{3}H]-NA from hypothalamic slices did not differ from control rabbits. In control hypothalamic slices, exposure to ANG II before S_2 increased, in a concentration-dependent manner (0.01–0.1 μM), the release of [^{3}H]-NA induced by K^+. The maximum effect was reached with 0.1 μM ANG II ($S_2/S_1 = 1.56 \pm 0.17$; $P < 0.001$). In hypothalamic slices from hypertensive rabbits, however, ANG II (0.1 μM) failed to increase the release of [^{3}H]-NA induced by K^+, S_2/S_1 being 1.05 ± 0.11 ($n = 13$; pooled data from 6 rabbits).

In control atria the fraction of total tissue radioactivity released by the first period of nerve stimulation (S_1) was 4.12 ± 0.32 ($\times 10^{-3}$) ($n = 27$) and the ratio obtained between two consecutive periods of nerve stimulation (S_2/S_1) was 1.27 ± 0.47 ($n = 4$). In atria from hypertensive rabbits the fraction of total tissue radioactivity released by S_1 was 5.63 ± 0.80 ($\times 10^{-3}$) ($n = 12$) and it did not differ from the controls. In sham-operated rabbits the amount of tritium released by S_1 was of the same magnitude: 6.01 ± 1.97 ($\times 10^{-3}$) ($n = 3$). In control atria, exposure to 10 nM ANG II produced a nearly 4-fold increase in the stimulation-evoked overflow of the [^{3}H]-transmitter ($S_2/S_1 = 3.90 \pm 0.56$; $n = 10$; $P < 0.01$). This facilitatory effect of ANG II (10 nM) on [^{3}H]-NA release from atria remained unchanged in both hypertensive ($S_2/S_1 = 3.17 \pm 0.30$; $n = 12$; $P < 0.01$) and sham-operated ($S_2/S_1 = 3.01 \pm 0.57$; $n = 3$) groups of rabbits.

The present results further support the importance of central noradrenergic mechanisms in the pathophysiology of renal hypertension. In fact, the enhancement of [^{3}H]-NA released from the hypothalamus of renal hypertensive rabbits may reflect changes in the presynaptic regulatory mechanisms of transmitter release that may prove relevant to the pathological state. Whether or not presynaptic inhibitory α-adrenoceptors and/or other regulatory mechanisms for NA release are involved in this phenomenon remains to be elucidated. The failure of ANG II to increase [^{3}H]-NA release in the hypothalamus of renal hypertensive rabbits could be due to subsensitivity of presynaptic ANG receptors or simply the consequence of the increased release of NA in S_1, which, by acting on the presynaptic inhibitory α-adrenoceptors, could mask the facilitatory effect of ANG II (Garcia-Sevilla, *et al.*, 1979). In atria from renal hypertensive rabbits both the stimulation-evoked release of [^{3}H]-NA and the effect of ANG II were unchanged, suggesting that noradrenergic neurotransmission in the central nervous system rather than in the periphery is affected in this experimental model of hypertension.

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

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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

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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