2 and 3 and 0.018 $\mu g\ kg^{-1}\ min^{-1}$ between dose response curves 3 and 4. Groups 3 and 4 were infused in a similar manner to group 2 with salbutamol 0.002, 0.006 and 0.018 $\mu g\ kg^{-1}\ min^{-1}$ and orciprenaline 0.02, 0.06 and 0.18 $\mu g\ kg^{-1}\ min^{-1}$ respectively.

A decrease in the blood flow response was seen with similar doses of isoprenaline in successive dose response curves of each group. This was significant only in group 2 ($P < 0.01$) and group 3 ($P < 0.001$). Isoprenaline and orciprenaline infusions at the dose levels used produced equivalent increases in blood flow but the decrease in responsiveness to isoprenaline was not as great in group 4 as in group 2. Salbutamol infusions produced the smallest increase in blood flow but caused the greatest decrease in blood flow response to isoprenaline.

Thus the decrease in responsiveness to isoprenaline that followed the infusions with isoprenaline and salbutamol did not relate to the increase in flow caused by the infusions, nor could it be explained in terms of duration of action, as all infusions were for 30 min and the resting flow rate was regained within 10 min following the infusions.

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The effects of AH 5158 on the overflow of transmitter and the uptake of [^{3}H]-(−)-noradrenaline in the cat spleen

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AH 5158, an adrenoreceptor blocking drug, produces competitive blockade of both α and β adrenoceptors (Farmer, Kennedy, Levy & Marshall, 1972; Kennedy & Levy, 1975). The effects of this drug on the overflow of transmitter following nerve stimulation with 200 stimuli at 10 and 30 Hz have been examined in the isolated blood perfused cat spleen. At 30 Hz, concentrations up to 10^{-4} M of the drug produced a dose-dependent elevation of transmitter overflow and a potentiation of the vascular response of the spleen. Higher concentrations ($1\text{-}4.2 \times 10^{-4}$ M) decreased transmitter overflow and depressed the vascular response. At 10 Hz, 5-(1-hydroxy-2-((1-methyl-3-phenylpropyl)amino)ethyl)salicylamide (AH 5158) (3.3×10^{-5} M) elevated transmitter overflow from 264 ± 56 pg/stim to 556 ± 109 pg/stim ($P < 0.05$; $n = 8$).

Two explanations for the elevation of overflow produced by the lower concentrations are inhibition of transmitter uptake and the α-receptor mediated feedback controlling transmitter liberation (Langer, 1974).

AH 5158 (1.5×10^{-4} M) inhibited noradrenaline uptake increasing the recovery of [^{3}H] in the venous blood during close arterial infusion of [^{3}H]-(−)-noradrenaline (370 ng/min; blood flow 8 ml/min) from 51 ± 2% to 77 ± 4% ($P < 0.01$; $n = 4$). Uptake inhibition alone could account for the effects on overflow and response.

In isolated strips of splenic capsule both AH 5158 (3.8×10^{-5} M) and the competitive α-adrenolytic 2-piperidinomethyl-1,4-benzodioxan hydrochloride (933F) (7.4×10^{-6} M) produced similar 10-fold parallel shifts to the right of the dose-response curve to (−)-noradrenaline. In the perfused spleen 933F (5.7×10^{-6} M) increased the overflow of transmitter following nerve stimulation at 10 Hz to 1506 ± 78 pg/stim ($n = 14$) by a mechanism involving only presynaptic α-adrenoceptor inhibition.

The local anaesthetic action of AH 5158 (Farmer *et al.*, 1972) could account for the depressant effect of high drug concentrations on transmitter overflow but is not important at 3.3×10^{-5} M since subsequent addition of 933F (8×10^{-6} M) increased the overflow at 10 Hz to 1306 ± 237 pg/stim ($n = 6$).

These experiments support the hypothesis that there are in the spleen presynaptic and postsynaptic α-adrenoceptors with different sensitivities to antagonist drugs. In the spleen AH 5158 is an inhibitor of noradrenaline uptake and an antagonist of postsynaptic α-adrenoceptors.

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The sympathetic nervous system and renovascular hypertension in the rat

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The integrity of central noradrenergic neurones is essential for the development and maintenance of DOCA salt hypertension in the rat (Haeusler, Finch & Thoenen, 1972; Dargie, Dollery & Lewis, 1975) and perinephritis hypertension in the rabbit (Chalmers, Dollery, Lewis & Reid, 1974). Plasma noradrenaline levels are increased in the DOCA salt model and the rise in both blood pressure and plasma noradrenaline can be prevented by pretreatment with intracisternal (i.c.) 6-hydroxydopamine (6-OHDA) (Dargie, Lewis, Reid & Zivin, 1975).

We have measured plasma noradrenaline (NA) as an index of peripheral sympathetic activity in a renovascular model of experimental hypertension in the rat and have assessed the relationship between central and peripheral sympathetic activity in the development of hypertension in this model.

Male Wistar rats (weighing 200 g) had a silver clip 0.007 in. wide placed over the left renal artery followed by contralateral nephrectomy. Control rats underwent a sham procedure involving placement of a broad non-constricting clip over the renal artery and contralateral nephrectomy. Blood pressure was measured by tail plethymography at 24 h, 7, 14 and 28 days respectively. The animals were killed by decapitation and the first 1 ml of arterial blood from the trunk was collected in iced heparin tubes for estimation of NA by the method of Henry, Starman, Johnson & Williams (1975).

Two groups of rats were pre-treated 14 days before with intracisternal 6-OHDA or ascorbate saline vehicle. Renal arterial clip or sham operations were carried out on each group. Blood pressure was measured after 7 days, the animals were decapitated and blood collected.

In the first series of experiments blood pressure was significantly elevated ($P < 0.01$) in the rats with renal arterial clips at 24 h, 7, 14 and 28 days. Mean systolic blood pressure (± s.e. mean) ranged from 144 ± 5 mmHg at 24 h to a maximum of 177 ± 9 at 14 days. Blood pressures (in corresponding 'sham-operated' rats) were 109 ± 4 and 115 ± 4 mmHg. Plasma NA in the clip groups was higher than sham operated rats at each time examined. These differences were significant at 7, 14 and 28 days. At 14 days plasma NA was 1.91 ± 0.32 μg/ml in clip groups and 0.93 ± 0.24 ng/ml in sham operated controls ($P < 0.05$).

Blood pressure and plasma noradrenaline were elevated in the group of rats given i.c. vehicle and renal arterial clip. However, in the group pretreated with i.c. 6-OHDA blood pressure and plasma noradrenaline levels did not rise and were not significantly different from their controls.

It is concluded that peripheral sympathetic activity is increased in the one kidney Goldblatt model of experimental hypertension and that this increase in sympathetic activity is mediated by catecholamine mechanisms in the central nervous system.

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