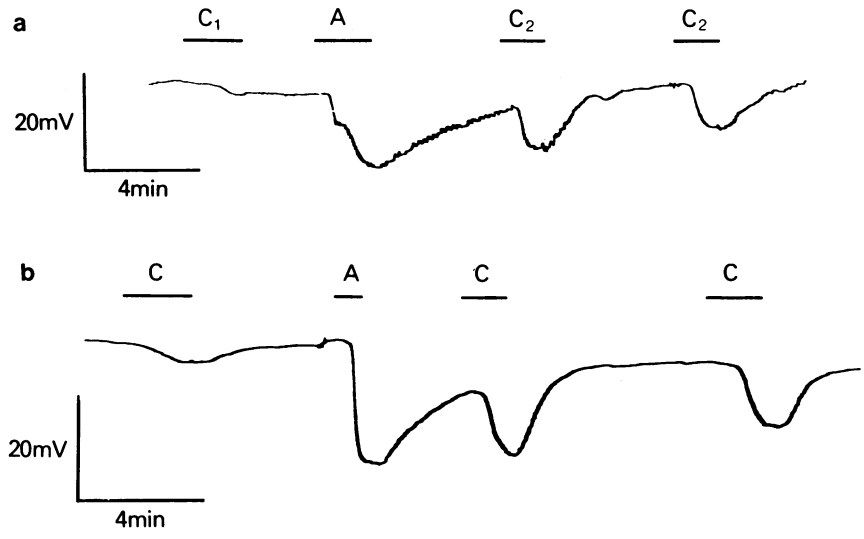

Figure 1 Figure *1a* shows responses to cyclic AMP (1 mM at 'C_1' and 0.25 mM at 'C_2') before and after an application of the α-agonist (−)amidephrine (10 μM at 'A'). Figure *1b* is from another experiment where the chloride in the bathing fluid had been replaced by isethionate, and shows that potentiation of cyclic AMP (0.5 mM at 'C') by (−)amidephrine (10 μM at 'A') is not chloride-dependent.

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Alterations to vasodilator effects of isoprenaline in the dog following intra-arterial infusions with isoprenaline, salbutamol and orciprenaline

P.S. COLLIER* & R.G. SHANKS

Department of Pharmacy and Department of Therapeutics and Pharmacology, The Queen's University of Belfast, Northern Ireland

Recently there has been much interest in the possible development of tolerance to sympathomimetic bronchodilator drugs (Conolly, Davies, Dollery & George, 1971; Minatoya & Spilker, 1975).

In the present studies the effects of infusions of three sympathomimetic drugs on the blood flow response to isoprenaline have been investigated in twenty anaesthetized dogs.

Heart rate, arterial blood pressure and blood flow in the external iliac artery were recorded. In each dog, isoprenaline (0.001, 0.002, 0.004 and 0.008 μg/kg) was injected into the external iliac artery and the increase in blood flow noted. The maximum dose of isoprenaline injected was such that changes in heart rate and arterial blood pressure were minimal.

In group 1, four successive dose response curves were constructed allowing 40 min between each. The remaining three groups received an infusion into the external iliac artery for 30 min between successive dose response curves. Group 2 was infused with isoprenaline 0.002 $\mu g\ kg^{-1}\ min^{-1}$ between dose response curves 1 and 2, 0.006 $\mu g\ kg^{-1}\ min^{-1}$ between dose response curves

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

A.G.H. BLAKELEY & R.J. SUMMERS*

Department of Pharmacology, The University, Glasgow G12 8QQ

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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