the hypotensive activity of both R 28935 and R 29814 by the α-sympatholytic drug prazosin. Following the administration of prazosin (3 μg/kg) via the vertebral artery (v.a.) of the chloralose-anaesthetized cat, the depressor effect of 3 μg/kg of R 28935 (41.9 ± 4.3%; $n = 6$) subsequently applied via this artery was reduced to 13.2 ± 0.6% ($P < 0.001$). Similarly, the central hypotensive action of R 29814 (30 μg/kg) was abolished by prazosin (3 μg/kg; v.a.). I.v. pretreatment with prazosin (3 μg/kg) did not diminish the centrally initiated hypotensive responses to R 28935 and R 29814. The quantitative aspects of this antagonism at a central level resulted from a parallel shift to the right of the dose-response curve for the central hypotensive effect of R 28935, induced by prazosin (3 μg/kg) applied previously to the v.a.

I.p. treatment of pentobarbitone-anaesthetized normotensive rats with prazosin (100 μg/kg) caused parallel shifts of the dose-response characteristics of the hypotensive effects of i.v. R 28935 and R 29814 in anaesthetized animals (1 h later). R 28935 and R 29814 showed no increase in arterial pressure in pithed rats, indicating the absence of α-sympathomimetic properties. As compared with prazosin both compounds were only moderately effective in antagonizing the pressor responses of i.v. L-phenylephrine. Finally, at low concentrations R 28935 and R 29814 displaced [^{3}H]-prazosin from its specific binding sites in membranes from rat cerebral cortex. The results suggest that the interaction between prazosin and benzodioxan antihypertensives occurs within the central nervous system. In contrast to earlier reports α-adrenoceptors seem to play a part. In view of the predominant blocking activity of prazosin at postsynaptically located (α_1) adrenoceptors, the receptive sites involved in this mutual interference may be characterized accordingly. It remains uncertain, however, whether R 28935 as well as R 29814 have to be considered either as agonists or antagonists.

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Effects of α-adrenoceptor agonists and antagonists on adrenergic neurotransmitter overflow from dog isolated saphenous veins

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Recent reports suggest that the presynaptic α-adrenoceptors in different tissues may have different characteristics (Doxey & Everitt, 1977; Dubocovich, 1979). Presynaptic α-adrenoceptors have been identified, but not subclassified, in dog saphenous vein (McGrath, 1977); we have therefore examined their sensitivity to α-adrenoceptor agonists and antagonists in an attempt to subclassify them.

The neuronal noradrenaline stores in spirally cut pieces of saphenous vein (10–15 mm long) were labelled with (−)-[^{3}H]-noradrenaline as previously described (Drew, Levy & Sullivan, 1979). After loosely bound noradrenaline had been washed from the tissues, each strip was mounted between platinum electrodes in a 1.5 ml organ bath and superfused with Krebs solution at 37°C, gassed with 95% O_2 and 5% CO_2 and containing cocaine (3×10^{-5} M), corticosterone (4×10^{-5} M), propranolol (10^{-6} M) and indomethacin (3×10^{-6} M). Adrenergic nerves were stimulated at 2 Hz (supramaximal voltage, 0.5 ms pulse duration) for periods of 3 min at intervals of 18 min; as many as six periods of stimulation were applied during an experiment. The tritium overflowing into the superfusate before, during and after nerve stimulation was measured by liquid scintillation counting.

The overflow of radioactivity caused by nerve stimulation was enhanced 2–4 fold by yohimbine (10^{-8}–10^{-6} M), phentolamine (10^{-7}–10^{-5} M) or prazosin (10^{-6} M); phentolamine and prazosin were respectively about 10 and 100 times less potent than yohimbine at doubling the overflow, which suggests that adrenergic neurotransmission in the dog saphenous vein is regulated by presynaptic α_2-adrenoceptors. This view is supported by the finding that tritium overflow was reduced 20–80% by (−)-adrenaline (10^{-7} and 10^{-6} M), (−)-α-methylnoradrenaline

(3×10^{-8} and 10^{-7} M) and (−)-noradrenaline (10^{-7} to 10^{-6} and 10^{-5}M) but that (±)-methoxamine (3×10^{-5} M) was only weakly active and (−)-phenylephrine (10^{-5} M) was ineffective. Surprisingly, clonidine (10^{-8}–10^{-6} M) did not inhibit the overflow of radioactivity in four out of five experiments. However, clonidine (10^{-7} and 10^{-6} M) reduced tritium overflow by 40–60% if cocaine and corticosterone were omitted from the Krebs solution.

Our results are consistent with the suggestion (Medgett, McCulloch & Rand, 1978) that clonidine is a partial agonist at presynaptic α_2-adrenoceptors. Thus, when the local concentration of endogenous noradrenaline in the vicinity of the presynaptic α-adrenoceptors is low clonidine behaves as an agonist and this effect is additive with that of the noradrenaline. However, when the local concentration is increased, as would occur after inhibition of its uptake (Dubocovich & Langer, 1974), then clonidine competes with noradrenaline for access to the presynaptic receptors, and because of its lower efficacy reduces the feedback inhibition. The net effect is no change or an increase in transmitter overflow. This proposal is supported by the finding that clonidine (10^{-6}M) antagonised the effects of exogenous noradrenaline on tritium overflow in the presence of the uptake inhibitors.

These findings show that the effect of clonidine at presynaptic α-adrenoceptors depends upon the experimental conditions, and they may explain the apparent lack of agonist activity of clonidine at presynaptic α-adrenoceptors in the guinea-pig vas deferens and portal and caval veins (Stjärne, 1975) and the cat spleen (Dubocovich, 1979).

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A comparison of the relaxant and autonomic effects of pancuronium and its monoquaternary derivative Organon NC 45 in the pithed rat

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Pancuronium produces tachycardia in some patients, part of which has been attributed to blockade of cardiac parasympathetic transmission (Saxena & Bonta, 1970; Hughes & Chapple, 1976). In the pithed rat, however, pancuronium can potentiate the cardioacceleration to sympathetic stimulation or to noradrenaline by inhibiting the neuronal uptake of noradrenaline (Docherty & McGrath, 1978). In the anaesthetized cat, the monoquaternary derivative of pancuronium, Organon NC 45, retains much of the relaxant activity but has a relatively greater loss of parasympathetic blockade (Durant, 1978).

We have now compared, in the pithed rat, the effects of pancuronium with those of NC 45 (0.001–10 mg/kg) on neurotransmission at three sites, (1) the somatic neuromuscular junction, (2) the cardiac sympathetic and (3) the cardiac parasympathetic.

Rats were pithed by the method of Gillespie, MacLaren & Pollock (1970) and respired with 100% O_2 (Clanachan & McGrath, 1976). Neuroeffector responses were obtained: (a) single supramaximal pulses (0.05 ms) applied to the spinal outflows (C6-T1) via the pithing rod: this elicited, simultaneously, a sympathetic cardioaccelerator response and contraction of forelimb skeletal muscle (isometric tension); (b) 50 supramaximal pulses (5 Hz) applied to the peripheral portion of the divided, right, cervical vagus: leading to a parasympathetically-mediated fall in heart rate.

(1) 'Relaxant' effect: 50% inhibition of forelimb 'twitch'; pancuronium (0.18 mg/kg), NC 45 (0.38 mg/kg). NC 45 was faster in onset and shorter in duration than pancuronium.

(2) Cardiac sympathetic: both compounds pro-