(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-

duced (i) a small tachycardia, independent of nerve stimulation (see Docherty & McGrath, 1978), (ii) a dose-dependent potentiation of nerve-induced responses with equivalent effects from pancuronium (0.3 mg/kg) and NC 45 (10 mg/kg). A similar effect was found on the adrenergically-mediated contraction of the vas deferens in the pithed rat (see McGrath, 1978) which was potentiated to a greater extent by pancuronium than by NC 45.

(3) Cardiac parasympathetic: 50% inhibition of nerve-induced fall in heart rate; pancuronium (0.008 mg/kg), NC 45 (4.3 mg/kg).

NC 45 was, therefore, less potent than pancuronium as a relaxant by $\times 2.1$, as a potentiator of cardiac sympathetic transmission by approximately $\times 33$ and as a blocker of parasympathetic transmission by $\times 538$, when compared at doses producing equivalent effects. The dose/response curves were, however, much steeper for blockade of somatic than of parasympathetic transmission; consequently 'ID 50' values should be used with caution in comparing effects at these two sites.

The blockade of neuronal re-uptake of noradrenaline, by raising the concentration of noradrenaline outside the varicosity, not only potentiates the post-junctional effect but increases the degree of pre-junctional, α-adrenoceptor mediated inhibition (Docherty & McGrath, 1979). Hence, in the presence of pancuronium (1 mg/kg) the α-adrenoceptor antagonists, yohimbine and phentolamine, potentiated the tachycardia produced by low frequency cardioaccelerator stimulation by blocking the inhibitory, pre-junctional effect of transmitter noradrenaline. Pancuronium and pre-junctional α-adrenoceptor antagonists in combination may, therefore, produce tachycardia.

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Three types of muscarinic receptors?

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Although receptors are often classified by the relative activity of agonists it is probably preferable to classify then by comparing the affinities of antagonists. In such a comparison Barlow, Franks & Pearson (1972) found that the muscarine-sensitive acetylcholine receptors of the guinea-pig ileum, bronchial muscle and iris were indistinguishable. Barlow, Berry, Glenton, Nikolaou & Soh (1976), however, subsequently found compounds with lower affinity for muscarine-sensitive acetylcholine receptors in guinea-pig atrial pacemaker cells than for the receptors in the ileum. Muscarine-sensitive acetylcholine receptors can therefore be classified into m_1, in the ileum and m_2 in the atria.

Marshall & Ojewole (1979) have reported that certain neuromuscular blocking agents have greater affinity for receptors associated with the inotropic effects of acetylcholine on the electrically driven atria from reserpinized guinea-pigs than for receptors in the ileum. We have therefore measured the affinity of pancuronium as an antagonist of carbachol and calculated the dose-ratio from the change in the size of the contraction as well as from the change in the rate with guinea-pig atria in Ringer-Locke solution at 30°C. We also made similar experiments with 4-diphenylacetoxy-*N*-methylpiperidine methiodide, the most selective of the compounds previously studied by Barlow *et al.* (1976).