Contractions were obtained when $CaCl_2$ was added cumulatively to rat vasa deferentia suspended in a depolarising solution (Na^+ = 16.2, K^+ = 127.6, Hepes = 10.0, Glucose = 11.1, Cl^- = 130.0, Mg^{2+} = 1.2 and SO_4^{2-} = 1.2 mM). These contractions were inhibited by verapamil in much lower concentrations than those required to inhibit rhythmic contractions. The maximum of the Ca^{2+} dose-response curve was depressed by 18 ± 2%, n = 3, by verapamil 0.1 μg/ml and by 60 ± 4%, n = 3, by verapamil 1 μg/ml (Figure 1(b)).

These results show that in the rat vas deferens rhythmic contractions do not require entry of Ca^{2+} through varapamil-sensitive channels, the calcium probably being supplied from an intracellular store. Because low concentrations of verapamil block $CaCl_2$ contractions in depolarized tissues this suggests a selective inhibition of transmembrane Ca^{2+} flux, whereas the block of rhythmic contractions by higher concentrations is probably a non-specific action, such as a local anaesthetic effect (Haeusler, 1972). Nevertheless, the dependence of the rhythmic contractions on $[Ca^{2+}]o$ suggests a superficial Ca^{2+} store is essential and the possibility remains that Ca^{2+} may enter through a separate channel that is not blocked by verapamil (Golenhofen & Hermstein, 1975).

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Withdrawal of centrally acting antihypertensives in conscious dogs

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The occurrence of rebound hypertension and tachycardia on the abrupt withdrawal of clonidine therapy in man is now well established. An animal model for this syndrome has however been difficult to obtain and the results have been contradictory. Dix & Johnston (1977) and Oates, Stoker, Monaghan & Stokes (1978) demonstrated the phenomenon in rats while Cavero, Fenard, Finch, Lefevre & Roach (1977) could not. Using the Alderley Park strain of Wistar rats and SHR of the Okamoto strain we have been unable to demonstrate rebound even when following the protocols described in the papers of Dix & Johnston (1977) or Oates *et al.* (1978).

In beagle dogs a rebound effect on heart rate (HR) has been consistently observed following clonidine withdrawal after 10 days of dosing (100–200 μg/kg 2× or 3× daily). Blood pressure (BP) and HR were measured on days 1, 4 and 9 of treatment and following the withdrawal at 4 h intervals for 28 h and then daily for the next 2–3 days. Nine dogs have been studied, in four of which only HR was measured. BP was recorded from indwelling catheters and during treatment diastolic BP fell by 23 ± 3.4% (mean ± s.e. mean) ($P < 0.005$) from a control value of 87.4 ± 4.5 mmHg. The control HR was 75.4 ± 3.3 bts/min and it varied condiserably during therapy. When measured 3 h after dosing HR was depressed consistently. This reduction varied between 48.5 ± 7.1% ($P < 0.01$) on day 1 and 32.2 ± 4.6% ($P < 0.001$) on day 9. The HR was depressed 8 h after the initial doses but by day 9 HR was 37.6 ± 8.8% ($P < 0.005$) above controls at this time.

On withdrawal of clonidine the BP returned to control with no significant overshoot while HR showed a marked rebound. Eight h after the last dose HR was elevated by 38.0 ± 12.1% ($P < 0.025$). HR reached a maximum 16 h after the last dose, the elevation being 59.9 ± 18.8% ($P < 0.005$), before returning to control levels over the next 2–3 days.

Similar experiments have been performed with ICI 106270 (600 μg/kg 3× daily) a new centrally acting antihypertensive (Clough, Hatton, Pettinger, Samuels & Shaw, 1978). Ten dogs have been used in 5 of which only HR was measured. During treatment diastolic BP fell by 18 ± 3.9% ($P < 0.025$) from a control value of 113.7 mmHg. The control HR was 88.9 ± 4.1 beats/min and during therapy it did not increase significantly above control levels at any time. As with

clonidine. HR was consistently depressed 3 h after each dose. Following withdrawal of ICI 106270 both BP and HR returned to control with no significant overshoot in either during the subsequent 2–3 days.

The tachycardia on withdrawal of clonidine in dogs occurred in every animal treated and may represent a useful model for assessing the likelihood of centrally acting antihypertensives to produce rebound in man. In this model ICI 106270 did not produce rebound tachycardia.

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The effects of mianserine, amitriptyline, ciclazindol and viloxazine on presynaptic α-receptors in isolated rat atria

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Presynaptic α-receptor antagonists evoke increases in stimulus-induced noradrenaline release in cardiac tissue which possess few, if any, postsynaptic α-receptors (Starke, 1972). According to Schildkraut's (1965) hypothesis of depression, elevation of the synaptic concentration of noradrenaline (NA) leads to an antidepressant effect. Presynaptic α-receptor blockade has been proposed as a mode of action of some antidepressants (Baumann & Maitre, 1975).

Low frequency field stimulation of isolated rat atria (three trains of 4 s duration, consisting of square wave pulses, 0.5 ms pulse width, 10–25 V, not exceeding 2.5 Hz, delivered at 30 s intervals) in the presence of atropine sulphate (5 μM) evoked increases in rate which were sensitive to modulation of presynaptic α-receptors. The presynaptic α-agonist clonidine (3.2×10^{-9}–3.2×10^{-8} M) inhibited stimulus induced rate increases without affecting submaximal responses to exogenous NA.

The presynaptic α-antagonist piperoxan (3.2×10^{-6} M) did not affect the intrinsic atrial rate or the response to NA. However, the response to stimulation was enhanced and the action of clonidine was blocked. Mianserine (2.9×10^{-6} M) similarly enhanced responses to stimulation and blocked the action of clonidine, but was more potent than piperoxan. The intrinsic atrial rate and responses to NA were not affected.

Amitriptyline (1.4×10^{-6} M) and desmethylimipramine (2.9×10^{-7} M) increased the intrinsic rate (mean 10/min and 17/min respectively, $n = 6$) without modifying the response to NA. Responses to stimulation were weakly enhanced. Amitriptyline evoked a partial block of the action of clonidine. These agents induced arrhythmia which limited further studies in this system. Ciclazindol (2.7×10^{-6} M) produced a larger increase in intrinsic rate (34/min, $n = 6$), but did not affect the response to NA. There was a weak, non significant increase in responses to stimulation, and a partial block of the response to clonidine. Viloxazine (1.1×10^{-5} M) also increased the intrinsic rate (67/min, $n = 2$) precluding observation of other parameters. A lower concentration (1.1×10^{-6} M) which had a minimal effect on basal rate (15/min, $n = 7$) did not affect the response to stimulation but reduced the response to NA. The response to clonidine was not significantly affected.

The increase in intrinsic rate observed with these antidepressants could result from block of reuptake or from release of NA (Tessel, Smith, Russ & Hough, 1978), whereas antagonism of the action of clonidine probably results from presynaptic α-receptor antagonism. On this basis, mianserine and piperoxan are potent presynaptic α-receptor antagonists, the other antidepressants are less potent, particularly viloxazine which shows no activity.

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