rat (Gillespie & McGrath, 1973; Docherty & McGrath, 1979). The longitudinal isometric tension of isolated transversely bisected portions of vas deferens was monitored in Krebs' bicarbonate solution at 37°C (McGrath, 1978). Pre-junctional effects were assessed as percent inhibition of (a) the cardio-accelerator response to a single supramaximal stimulus (0.05 ms) to the sympathetic outflow at T1 (Gillespie, MacLaren & Pollock, 1970) or (b) the contractile response of the prostatic portion of vas deferens to a single field stimulus (0.5 ms) (McGrath, 1978). Post-junctional effects were assessed as (c) the increase in diastolic pressure (d) the contraction of anococcygeus and (e) the potentiation of the contractile response to a single field stimulus (0.5 ms) of the epididymal portion of the vas deferens.

(a) and (b) The order of potency for pre-junctional effects was similar in the heart and vas deferens. Dose/response curves were parallel; oxymetazoline, guanabenz and clonidine were approximately equipotent and xylazine was × 10 less potent. Phenylephrine had no detectable inhibitory effect.

(c) The order of potency for the pressor effect was different from that in (a) and (b). Xylazine was 10× less potent than guanabenz but the curves for clonidine and oxymetazoline lay to the left of that of guanabenz. Phenylephrine lay between xylazine and guanabenz. After prazosin (1 mg/kg) the effect of phenylephrine was abolished, guanabenz, oxymetazoline and clonidine became equipotent and xylazine was unaffected, i.e. the pattern in (a) and (b) was repeated. After yohimbine (1 mg/kg) the dose/response curve for each drug was moved to the right but the effect was greatest for guanabenz and xylazine.

(d) For contraction of anococcygeus oxymetazoline, clonidine and phenylephrine were approximately equipotent and prazosin sensitive, while guanabenz and xylazine were prazosin resistant and 100–1000× less potent.

(e) For potentiation of responses in vas deferens clonidine and oxymetazoline were equipotent, phenylephrine 10× less potent (all prazosin sensitive) and neither guanabenz nor xylazine produced any detected potentiation.

These results suggest that (1) phenylephrine acts on α_1, guanabenz and xylazine on α_2 and clonidine and oxymetazoline on both α_1 and α_2-adrenoceptors (2) the post-junctional effects in the vas deferens were α_1, in anococcygeus mainly α_1 with a small α_2 component and in blood vessels had a significant component from both α_1 and α_2-adrenoceptors.

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The effect of amitriptyline on presynaptic receptors in the dog saphenous vein

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According to the catecholamine hypothesis of affective disorders, antidepressant drugs should increase the concentration of noradrenaline in the synaptic cleft (Schildkraut, 1965). This could be achieved by the blockade of neuronal uptake, however, the potency of antidepressant drugs to inhibit uptake and their clinical effectiveness correlate poorly (Ghose & Coppen, 1977). Since the release of noradrenaline from the adrenergic nerves is modulated by a number of inhibitory presynaptic receptors (Langer, 1977), blockade of these receptors could also be an important mode of action for antidepressant drugs.

We have examined the effects of amitriptyline on presynaptic receptors in the dog isolated saphenous vein. Spiral strips of vein were mounted in organ baths for isometric tension recording. Other strips were incubated with [^{3}H]-noradrenaline and mounted for superfusion, isometric tension recording and the measurement of radioactivity and of [^{3}H]-noradrenaline in the superfusate (McGrath, 1977).

In the presence of cocaine (3×10^{-5} M), amitripty-

line (10^{-7} to 10^{-5} M) inhibited contractions evoked by electrical stimulation (0.3 to 4 Hz) of the post-ganglionic adrenergic nerves ($n = 5$) and by exogenous noradrenaline (5×10^{-9} to 5×10^{-6} M, $n = 5$). Amitriptyline (10^{-6} and 10^{-5} M) depressed contractions evoked by noradrenaline (5×10^{-8} M) to a significantly greater extent ($P < 0.05$) than contractions of equivalent amplitude evoked by electrical stimulation (0.6 Hz). In superfusion experiments, amitriptyline (5×10^{-6} M) increased the overflow of radioactivity and of [^{3}H]-noradrenaline from electrically stimulated (1 Hz) strips of vein both in the absence ($n = 5$) and presence ($n = 6$) of cocaine. Thus amitriptyline has a presynaptic effect, unrelated to uptake blockade, which increases the release of noradrenaline from the adrenergic nerve ending. This increase in the stimulated overflow of [^{3}H]-noradrenaline was abolished by phentolamine (10^{-5} M, $n = 6$), indicating that it was due to blockade of presynaptic α receptors by amitriptyline.

Exogenous acetylcholine (2.7×10^{-7} M) depressed the increase in tension and in the overflow of radioactivity and of [^{3}H]-noradrenaline from electrically stimulated (2 Hz) strips of vein ($n = 6$). This presynaptic inhibitory action of acetylcholine was significantly reduced ($P < 0.001$) by amitriptyline (10^{-6} M, $n = 6$). Exogenous histamine (10^{-5} M) also depressed the increase in the overflow of radioactivity from electrically stimulated (2 Hz) veins. This effect was not attenuated by amitriptyline (5×10^{-6} M, $n = 5$).

These results demonstrate that amitriptyline in the above concentrations is an antagonist of presynaptic α and muscarinic receptors. Blockade of these receptors could be important both in the central actions of the drug and in the genesis of the tachycardia and cardiac arrythmias often caused by amitriptyline (Moir, *et al.*, 1972).

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Preliminary characterisation of the presynaptic receptor for 5-hydroxytryptamine in dog isolated saphenous vein

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We have shown that 5-hydroxytryptamine (5-HT) inhibits contractile responses induced by electrical stimulation in dog saphenous vein and have suggested that this effect is mediated via a specific pre-synaptic 5-HT receptor (Feniuk, Humphrey & Watts, 1978). This receptor like the 5-HT receptor situated post-synaptically in this preparation, is only weakly blocked by the 5-HT antagonist methysergide (Feniuk, Humphrey & Watts, 1979). Indeed methysergide appears to be a partial agonist at the postsynaptic receptor (Apperley, Humphrey & Levy, 1977) and we have therefore investigated whether methysergide has agonistic activity on the presynaptic receptor.

Saphenous veins were removed from barbitone anaesthetised dogs and cut spirally into strips. These were stimulated electrically *in vitro* as described previously (Feniuk, *et al.*, 1978, 1979) and the inhibitory effects of 5-HT and methysergide examined. In other experiments we studied electrically stimulated tritium release following incubation with 1-[7-^{3}H]-noradrenaline (10 m Ci/0.67 $\times 10^{-6}$ mol/l) at 37°C for 2 h in a modified Krebs solution (Apperley, Humphrey & Levy, 1976) containing ascorbic acid (1.1×10^{-4} mol/l) and disodium EDTA (4.0×10^{-6} mol/l). Each strip was then transferred to a bath and washed to remove extracellular tritium using Krebs solution containing ascorbic acid, disodium EDTA, cocaine (3.0×10^{-5} mol/l), indomethacin (2.8×10^{-6} mol/l) and corticosterone (4.0×10^{-5} mol/l). Subsequently the bath was drained and refilled every 2 min and the amount of radioactivity in the Krebs measured by liquid scintillation counting. Each strip was stimulated electrically for 2 min at 2 Hz every 20 minutes. In some experiments [^{3}H]-noradrenaline was separated from the other tritiated metabolites using paper chromatography (Levin, 1973).

5-HT and methysergide inhibited contractions induced by electrical stimulation producing 50% inhi-