0.0125 mg/kg. In contrast, prazosin had little or no effect on the pressor responses to low doses of noradrenaline (30–300 ng/kg) but reduced those to higher doses (>1 μg/kg). Pretreatment with propranolol or cocaine did not markedly alter the interaction between prazosin and noradrenaline.

The α-adrenoceptor blocking actions of phentolamine and prazosin were also examined in chloralose anaesthetized cats, from which the right adrenal gland had been removed. In these experiments, matched submaximal pressor responses to single doses of phenylephrine and noradrenaline and to right splanchnic nerve stimulation were obtained before and after administration of the antagonist. Phentolamine caused a dose-related reduction in the response to each stimulus; the mean doses of phentolamine which reduced by 50% (ED_{50}) the responses to phenylephrine, noradrenaline and nerve stimulation were 0.20, 0.38 and 1.22 mg/kg respectively. The corresponding ED_{50} values for prazosin were 0.04, 2.69 and >10 mg/kg respectively. Thus prazosin was about 5 times more potent than phentolamine against phenylephrine, but was much less potent against noradrenaline and nerve stimulation.

The results of these experiments suggest that there maybe two types of postsynaptic α-adrenoceptors. Phenylephrine stimulates only one type and prazosin blocks only this type. Low doses of noradrenaline stimulate the prazosin-insensitive type and high doses stimulate both types. Phenotolamine blocks both types of α-adrenoceptor. The general distribution of these two types of receptors is not known but those innervated by the right splanchnic nerve in the cat seem to be predominantly of the prazosin-insensitive type. The prazosin-insensitive receptors may resemble the presynaptic α-adrenoceptors located on the terminals of the adrenergic nerves supplying the rabbit pulmonary artery (Cambridge, Davey & Massingham, 1977) and rat heart (Cavero, Lefèvre & Roach, 1977) at which prazosin is a weak antagonist and phenylephrine is a weak agonist.

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Calcium, cyclic amp and the response of rat descending colon to angiotensin, to prostaglandin E_2 and to potassium chloride

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The increased intracellular calcium for muscle contraction may arise from intracellular or extracellular sources (Van Bremmen, Farinas, Casteels, Gerba, Wuytack & Deth, 1973) perhaps associated with altered cyclic AMP levels (Marshall & Kroeger, 1973). Smooth muscle responses to angiotensin (Khairallah, Vadaparampil & Page, 1965) and prostaglandins (Coceani & Wolfe, 1966) are sensitive to changes in extracellular calcium. The role of calcium and cyclic AMP in the response of rat descending colon to angiotensin, Prostaglandin E_2 and potassium has now been investigated.

Isotonic contractions were recorded of muscle preparations from male Wistar rats suspended in aerated Tyrode solution. Preparations were exposed to a calcium-free Tyrode containing EDTA (0.025 mmol). Half-maximal responses to angiotensin were reduced to $7.8 \pm 1.3\%$ ($n=6$) after 15 min whereas half-maximal responses to prostaglandin E_2 and potassium were reduced to $50.8 \pm 4.9\%$ ($n=6$) and $39.2 \pm 5.6\%$ ($n=6$) respectively. The reduction of angiotensin responses was significantly greater than those of prostaglandin E_2 or potassium ($P<0.001$). SKF525A inhibits calcium influx associated with depolarization (Kalsner, Nickerson & Boyd, 1970). Preparations were exposed to calcium free Tyrode containing 2.6×10^{-5} mol SKF525A for 60 minutes. On reintroduction of calcium the tonic responses to angiotensin and prostaglandin E_2 were reduced and potassium was inactive. Subsequent removal of SKF525A allowed recovery of

responses, rapidly for angiotensin and prostaglandin E_2 but slowly for potassium.

Tyrode containing 2,4-dinitrophenol (0.05 mmol) caused little reduction of the phasic responses to angiotensin and prostaglandin E_2 but a progressive reduction of tonic responses to $4.0 \pm 1.9\%$ ($n=6$) and $3.6 \pm 2.5\%$ ($n=6$) respectively after 65 minutes. The corresponding potassium response was reduced to $42.0 \pm 6.7\%$ ($n=6$) ($P<0.01$).

Angiotensin, prostaglandin E_2 and potassium responses were recorded following a 30 min exposure to Tyrode solution containing imidazole (0.05 mol) or theophylline (0.3 mmol) and plotted as a percentage of the maximum response against log concentration. Imidazole caused a non-specific potentiation of all responses. Theophylline caused a reduction of responses to all agonists but the ED_{50} log concentration shift was significantly greater for angiotensin (0.45 ± 0.05, $n=6$) and prostaglandin E_2 (0.64 ± 0.16, $n=6$) than for potassium (0.14 ± 0.03, $n=6$) ($P<0.001$). Isoprenaline (5×10^{-9}–1.6×10^{-7} mol) added 30 s before the agonists caused a dose dependent decrease in the responses, the reduction of the potassium responses was significantly less than those of angiotensin or prostaglandin E_2 ($P<0.001$).

These findings support suggestions that potassium causes depolarization of smooth muscle (Goodman & Weiss, 1971) associated with calcium influx and subsequent intracellular release (Cheng, 1976). Responses to angiotensin and prostaglandin E_2 may consist of two phases, an initial transient associated with depolarization and a sustained tonic response independent of depolarization but dependent upon metabolic energy. This supports other reports of the energy dependence of prostaglandin (Coceani & Wolfe, 1966) and angiotensin (Crocker & Wilson, 1975) responses. This tonic phase of the angiotensin response is more dependent upon extracellular calcium than that of prostaglandin E_2. Increases in cyclic AMP induced by isoprenaline or theophylline had little effect upon potassium responses but markedly reduced angiotensin or prostaglandin E_2 sustained responses which may be related to an effect upon calcium distribution.

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Substrate selective inhibition of monoamine oxidase by mexiletine

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Mexiletine (1-methyl-2-(2,6-xylyloxy)-ethylamine hydrochloride, Kö 1173) is an effective antiarrythmic agent in man and other animals, with a local anaesthetic potency comparable with that of lignocaine, to which it shows a structural similarity (Singh & Vaughan Williams, 1972). However, mexiletine is also an α-substituted monoamine, which suggested that it could inhibit monoamine oxidase (MAO), since many compounds with this structure are known to possess this property (Blaschko, Richter & Schlossmann, 1937; Pugh & Quastel, 1937; Mantle, Tipton & Garrett, 1976).

The hearts, livers and brains of male Wistar rats of 300–350 g body weight, were homogenized in 1 mM potassium phosphate buffer, pH 7.4. The homogenates were centrifuged at low speed to remove unbroken cells and nuclei, and the supernatant fractions used for all experiments. MAO activity was assayed radiochemically with [^{3}H]-tyramine, [^{3}H]-5-HT, [^{14}C]-β-phenylethylamine and [^{14}C]-benzylamine as substrates.

The effects of mexiletine were measured *in vitro* by addition to aliquots of the tissue homogenates either 20 min before or at the same time as the addition of substrate. All incubations were carried out in an atmosphere of oxygen at 37°C, and repeated at least 5 times.