Where paralysis was due to procaine alone (0.7 to 0.8 mM) e.p.p.s were readily recordable and these were qualitatively similar to those recorded from preparations paralysed by tubocurarine. A slower decay of potential was again observed.

On the basis of these findings it is suggested that in the rat diaphragm, the neuromuscular blocking action of procaine arises from a post-junctional action. Explanations of the slowed rate of decay of the end-plate potential will be discussed.

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Inhibition by cinnarizine and chlorpromazine of the contraction induced by calcium and adrenaline in vascular smooth muscle

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Recent studies have shown that cinnarizine (1-benzhydryl-4-cinnamylpiperazine dihydrochloride) and chlorpromazine reduce the contractile response induced by depolarization of isolated arteries with potassium (Godfraind, Kaba & Polster, 1968; Godfraind & Polster, 1969). The present experiments were designed to determine whether such inhibition is due to antagonism of the function of calcium in the contractile process of vascular smooth muscle.

Strips 4 cm long were prepared by spiral section of rabbit mesenteric arteries (outside diameter 0.4–0.8 mm). They were bathed either in a polarizing solution (NaCl 112, KCl 5, $NaHCO_3$ 25, KH_2PO_4 1, $MgSO_4$ 1.2, $CaCl_2$ 1.25, and glucose 11.5 mM) or a depolarizing solution (similar but containing 100 mM KCl instead of NaCl and with $CaCl_2$ added according to the concentration required).

Mesentery arterial strips contracted in a depolarizing solution in the presence of calcium. These contractions were proportional to the calcium concentration and were reversible. When muscles had been immersed in a calcium-free medium until no contraction was evoked by the depolarizing solution, they still responded to adrenaline (10^{-4}M) but developed only one-third of the contractile tension caused by adrenaline in polarizing solution. Cinnarizine and chlorpromazine (10^{-5}–10^{-4}M) inhibited the contractile response to calcium, and relaxed depolarized muscles previously contracted by calcium. A 50% reduction in the contraction effected by 20 mM $CaCl_2$ was obtained with cinnarizine (10^{-7}M) and chlorpromazine (4×10^{-7}M).

Chlorpromazine inhibited the response to adrenaline in both polarizing and calcium-free depolarizing solution, whereas cinnarizine inhibited the response in polarizing solution but not that in calcium-free depolarizing solution.

These results suggest that cinnarizine acts by selectively inhibiting the calcium influx into the depolarized cell, and that chlorpromazine has a similar effect but may also reduce the mobilization of sequestered calcium.

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Enhancement by angiotensin of pressor responses to endogenous noradrenaline in the pithed rat

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In the anaesthetized dog angiotensin increases the cardiovascular responses to noradrenaline released from intra-neuronal storage sites without increasing the responses to injected noradrenaline (McCubbin & Page, 1963a, b). This effect seems to be dependent on an intact sympathetic innervation of the cardiovascular system because it is abolished by drugs which impair sympathetic function. Bickerton and his co-workers (Bickerton & Buckley, 1961 ; Severs, Daniels & Buckley, 1967) have produced evidence which suggests that the effect may be at least partly of central origin. The purpose of the present experiments was to re-examine this action of angiotensin in the pithed rat prepared for electrical stimulation of the entire sympathetic outflow (Gillespie & Muir, 1967) because this enables the effects of sympathetic stimulation to be observed on the intact cardiovascular system free from possible effects on the central nervous system.

Neuronal noradrenaline was released by each of three methods: first by injection of tyramine, second by injection of tetramethylammonium (TMA) and third by electrical stimulation of the sympathetic outflow. Pressor responses to all three procedures were markedly potentiated during the intravenous infusion of angiotensin in doses (20 to 200 ng/kg per min) which caused a sustained increase in blood pressure. The responses to injections of noradrenaline were usually unaffected by angiotensin but were occasionally marginally increased or decreased. The enhancement of responses to endogenously released noradrenaline often persisted for several hours after discontinuing the angiotensin infusion. In adrenalectomized rats the responses to sympathetic stimulation and to TMA were slightly reduced in height and that to TMA markedly reduced in duration when compared with control responses. The responses to both procedures were increased by angiotensin infusions, however, as in control animals.

The effects of angiotensin infusions on the responses to endogenously released noradrenaline were compared with the effects of three drugs, tyramine, noradrenaline and desmethylimipramine (DMI), each of which is known to cause release or to increase the effects of noradrenaline released from its intra-neuronal storage sites. There were clear differences in the mechanism of action of each of these substances and of angiotensin.