The histamine releasing activity of MCDP has been studied on rat peritoneal cells, rat leucocytes and human leucocytes. The cells were incubated with the peptide for five min at 37° C, the percentage of the total histamine released by MCDP being determined by bio-assay. Each sample contained approximately 10^7 cells in a final volume of 2 ml.

The peptide readily released histamine from rat peritoneal cells, was nearly one hundred times less active on rat leucocytes, and even less active on human leucocytes (Figure 1).

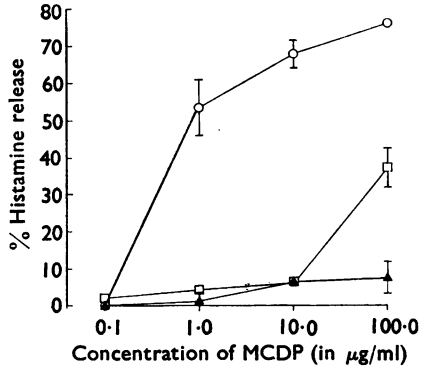

Fig. 1. Comparison of histamine release by MCDP from rat peritoneal cells (o—o), rat leucocytes (□—□). and human leucocytes (▲—▲). Mean values for spontaneous release have been subtracted.

The release of histamine from rat peritoneal cells by MCDP appears to have little dependence on the presence of calcium, shows some dependence on temperature and can be inhibited by disodium cromoglycate and other inhibitors of the anaphylactic mechanism.

MCDP may thus prove to be useful in the study of mediator release, its inhibition by drugs, and possible differences in the triggering sites for this mechanism in different tissues and species.

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Potentiation by angiotensin II of noradrenaline-induced contractions of a rabbit isolated thoracic aorta

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We have observed that angiotensin II in concentrations at, and less than, 10^{-9} g/ml, which themselves did not cause contractions of the rabbit isolated thoracic aortic strip, increased the contractile effect of noradrenaline (10^{-8} g/ml) by up to 100%. A similar action of angiotensin II has been reported on other isolated smooth muscle preparations and three major hypotheses have been postulated to explain the effect:

(i) Angiotensin II inhibits neuronal uptake of noradrenaline (Palaic & Khairallah, 1967).

(ii) A synergism exists between the contractile effects of angiotensin II and noradrenaline (Pals & Fulton, 1968).

(iii) Angiotensin II increases the amount of free intracellular calcium in the vicinity of the contractile elements in smooth muscle by releasing or 'loosening' of membrane-bound calcium (Baudouin, Meyer, Fermandjain & Morgat, 1972).

We have further investigated each of these possibilities using the rabbit isolated thoracic aortic strip.

(i) *Inhibition or noradrenaline uptake*

In the presence of cocaine ($4{\cdot}5\times10^{-6}$ g/ml), there is a maximal effect on neuronal uptake of noradrenaline in this preparation (Nedergaard & Bevan, 1971), angiotensin II caused a further enhancement of the noradrenaline contractions. In addition, the contractile action of isoprenaline, an amine which is not taken up by sympathetic neurons (Callingham & Burgen, 1966), was also increased by angiotensin II. The results of a study using ^{14}C-labelled noradrenaline show that angiotensin (10^{-6}–10^{-12} g/ml) had no significant effect on uptake into aortic strips. Thus it is suggested that inhibition of neuronal uptake of noradrenaline is not the mechanism whereby angiotensin II potentiates noradrenaline on this tissue.

(ii) *Synergism between angiotensin II and noradrenaline at α-adrenoceptors*

Angiotensin II (10^{-9} g/ml) was shown to potentiate the contractile responses to noradrenaline, acetylcholine, 5-hydroxytryptamine, histamine and potassium chloride to similar extents suggesting a general, rather than a specific sensitization.

(iii) *Mobilization of calcium stores*

Baudouin *et al.* (1972) found that angiotensin II at a concentration of 10^{-7} g/ml caused a significant release of membrane-bound Ca^{2+}, whilst a concentration of 10^{-9} g/ml or less was without significant effect. However, Angles d'Auriac, Baudouin & Meyer (1972) have shown that angiotensin II (10^{-9} g/ml) caused a 10% inhibition of calcium-binding to the membrane. However, this inhibition of calcium-binding reaches a maximum of 35% at 10^{-7} g/ml of angiotensin, whereas the potentiating effect of angiotensin on NA reaches a maximum at 10^{-9} g/ml; thus an effect on membrane-bound calcium would not appear to explain the effect of angiotensin on noradrenaline responses.

It has been found that angiotensin II had a biphasic effect on the sodium pump in smooth muscle from rat colon. They found that a concentration of 10^{-12} g/ml angiotensin II stimulated the sodium pump whilst at 10^{-9} g/ml the pump was inhibited. Gulati & Jones (1971) found that ouabain in a concentration of $7{\cdot}28\times10^{-7}$ g/ml produced a maximal inhibition of the sodium pump in dog isolated carotid artery. In our experiments this concentration of ouabain enhanced the contractile effect of noradrenaline and prevented the enhancement by subsequently administered angiotensin II. In other experiments the sodium pump was inhibited by suspending the tissue in potassium-free Kreb's solution. In these experiments too, angiotensin II did not enhance the responses to noradrenaline.

Our results suggest that the enhancement of noradrenaline contractile responses by angiotensin II in vascular smooth muscle may be a consequence of inhibition of the sodium pump rather than by an action on neuronal uptake of noradrenaline or on mobilization of membrane-bound calcium.

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