centrations vary seven-fold in different patients given the same oral dose (Shand, Nuckolls & Oats, 1970). This observation, together with an analysis of areas under the time concentration curves after I.V. and oral dosing, led to the suggestion that propranolol was extensively extracted or metabolized at the first pass through the liver (Gibaldi, Boyes & Feldman, 1971). We have therefore studied hepatic extraction, hepatic clearance, and whole body clearance of propranolol under (a) steady state conditions and (b) during logarithmically declining infusion into the hepatic portal vein.

In 4 anaesthetized dogs a constant I.V. infusion of (+)-propranolol was given after a loading dose of 0·3 mg/kg. Hepatic extraction was determined from the difference between the arterial and hepatic venous concentrations. Liver blood flow was estimated by the Fick principle using $^{198}$Au colloidal gold and hepatic clearance of propranolol was calculated by multiplying liver blood flow by the extraction ratio. Whole body clearance of propranolol was obtained by dividing the infusion rate by the blood level at steady state. The results of these studies and four similar experiments in which (−)-propranolol was given are shown in the Table 1.

TABLE 1. *Kinetics of propranolol under steady state conditions*

| Isomer | Vd (a) l/kg | Hepatic extraction % | Hepatic clearance (ml/kg)/min | Whole body clearance (ml/kg)/min | Hepatic clearance (%) whole body |
|---|---|---|---|---|---|
| Dextro | | | | | |
| Mean ± S.E. n=4 | 2·07 ± 03·5 | 87·8 ± 1·5 | 18·2 ± 1·7 | 24·0 ± 1·7 | 75·6 ± 2·3 |
| Laevo | | | | | |
| Mean ± S.E. n=4 | 2·62 ± 0·60 | 80·0 ± 4·6 | 17·8 ± 4·1 | 20·0 ± 3·8 | 86·3 ± 8·0 |

Hepatic extraction of propranolol varied from 69 to 92% and hepatic clearance accounted for 65–103% of the whole body clearance. Since the major site of clearance of propranolol is in the liver and extraction by this organ so high, the half-life of propranolol will be largely dependent on liver blood flow.

After oral (or portal venous) dosing the amount of propranolol reaching the systemic circulation will depend upon variations in the efficiency of extraction by the liver. However, it appears that the process of extraction by the liver can be saturated and stored propranolol may then be released into the circulation.

REFERENCES

GIBALDI, M., BOYES, R. W. & FELDMAN, S. (1971). Influence of first-pass effect on availability of drugs on oral administration. *J. Pharmaceut. Sci.*, **60**, 1338–40.

PATERSON, J. W., CONOLLY, M. E., DOLLERY, C. T., HAYES, A. & COOPER, R. G. (1970). The pharmacodynamics and metabolism of propranolol in man. *Europ. J. Clin. Pharm.*, **2**, 127–133.

SHAND, D. G., NUCKOLLS, E. M. & OATES, J. A. (1970). Plasma propranolol levels in adults with observations in four children. *Clin. Pharmacol. Therap.*, **11**, 112–120.

## Histamine release by MCDP (401), a peptide from the venom of the honey bee

E. S. K. ASSEM and G. ATKINSON*

*Department of Pharmacology, University College London, and Medical Unit, University College Hospital Medical School, London*

Mast cell degranulating peptide (MCDP), first isolated from bee venom (Breithaupt & Haberman, 1968), is made up of twenty-two amino acids and has two disulphide bridges (Hanson & Vernon, 1969). It contains a relatively high proportion of the more basic amino acids, a property generally associated with histamine releasing activity.

The present work has been initiated by tests on the isolated blood leucocytes of research workers handling the peptide, some of whom developed symptoms suggestive of rhinitis and bronchospasm. No significant release of histamine was obtained from these patients' leucocytes. This led to the conclusion that these patients were not allergic to the peptide; their symptoms possibly being due to direct release of histamine from tissue mast cells.

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).

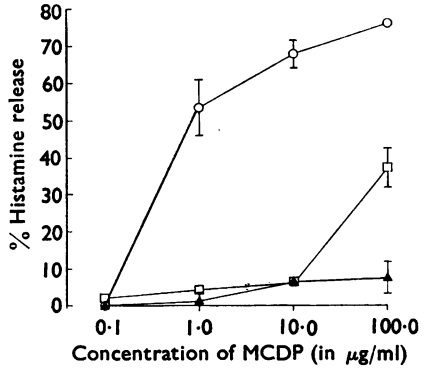


Fig. 1. Comparison of histamine release by MCDP from rat peritoneal cells (o—o), rat leucocytes (□—□). and human leucocytes (▲—▲). Mean values for spontaneous release have been subtracted.

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.

Supported by The Wellcome Trust and the Medical Research Council.

REFERENCES

BRITHAUPT, H. & HABERMAN, E. (1968). Mastzelldegranulierendes Peptid (MCD-Peptid) aus Bienengift: Isolierung, biochemische und pharmakologische Eigenschaften. *Naunyn-Schmiedebergs Arch. Pharmak. u. exp. Path.*, **261**, 252–270.

HANSON, J. M. & VERNON, C. A. (1969). Peptides. *British Pat. No.* 20906/69.

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

M. D. DAY and A. F. MOORE*

*Department of Pharmacy, University of Aston in Birmingham, B4 7ET*

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).