

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.

REFERENCES

- GODFRAIND, T., KABA, A. & POLSTER, P. (1968). Differences in sensitivity of arterial smooth muscles to inhibition of their contractile response to depolarization by potassium. *Archs int. Pharmacodyn. Théor.*, **172**, 235-239.
- GODFRAIND, T. & POLSTER, P. (1969). Etude comparative de médicaments inhibant la réponse contractile de vaisseaux isolés d'origine humaine ou animale. *Thérapie*, in the Press.

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

M. D. DAY and D. A. A. OWEN*, *Pharmacological Laboratories, Department of Pharmacy, University of Aston, Birmingham 4*

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 desmethylinipramine (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.

These results show that angiotensin increases responses to endogenously released noradrenaline in the absence of both an intact central nervous system and adrenal glands. The mechanism of the effect is probably different from that of noradrenaline, tyramine or DMI.

REFERENCES

- BICKERTON, R. K. & BUCKLEY, J. P. (1961). Evidence for a central mechanism in angiotensin induced hypertension. *Proc. Soc. exp. Biol. Med.*, **106**, 834–836.
- GILLESPIE, J. S. & MUIR, T. C. (1967). A method of stimulating the complete sympathetic outflow from the spinal cord to blood vessels in the pithed rat. *Br. J. Pharmac. Chemother.*, **30**, 78–87.
- MCCUBBIN, J. W. & PAGE, I. H. (1963a). Neurogenic component of chronic renal hypertension. *Science, N.Y.*, **139**, 210–211.
- MCCUBBIN, J. W. & PAGE, I. H. (1963b). Renal pressor system and neurogenic control of arterial pressure. *Circulation Res.*, **12**, 553–559.
- SEVERS, W. B., DANIELS, A. E. & BUCKLEY, J. P. (1967). On the central hypertensive effect of angiotensin II. *Int. J. Neuropharmac.*, **6**, 199–205.

Uptake and metabolism of ^3H -noradrenaline by normal and by denervated vasa deferentia of guinea-pigs and rats

A. T. BIRMINGHAM* and L. L. IVERSEN, *Department of Pharmacology, King's College, London W.C.2, and Department of Pharmacology, University of Cambridge*

Surgical denervation of the organs innervated by the superior cervical ganglion reduces but does not abolish the uptake of catecholamines by these tissues (Hertting, Axelrod, Kopin & Whitby, 1961; Strömblad & Nickerson, 1961; Fischer, Kopin & Axelrod, 1965). Uptake of noradrenaline by the heart is also reduced after sympathetic ganglionectomy (Hertting & Schiefthaler, 1964; Hertting, 1965). We have now compared noradrenaline uptake by normally innervated and by denervated vasa deferentia.

Guinea-pigs and rats were killed 8 days after surgical denervation of one vas deferens by separating it from its mesenteric attachments (Birmingham, 1967, 1968). The uptake and metabolism of ^3H -noradrenaline by the freshly chopped tissue of normal and denervated vasa was measured by the method previously described for hearts (Iversen, 1963). After incubation for 10 min in 10 ml. Krebs–Henseleit solution containing (\pm)- ^3H -noradrenaline 137 nc/ml. the tissue was homogenized with 0.4N perchloric acid. Aliquots of the supernatant perchloric acid were used for the assay of total radioactivity and of ^3H -noradrenaline and ^3H -normetanephrine fractions obtained by ion exchange chromatography. Total endogenous noradrenaline content was assayed on the same samples by a spectrophotofluorimetric method (Euler & Lishajko, 1961); for denervated vasa it was reduced by more than 95% when compared with control values.

Normal vasa from both species showed a considerable accumulation of radioactivity after incubation with ^3H -noradrenaline (Table 1), giving a tissue : medium ratio of almost 10 : 1. Denervated vasa from the same animals also accumulated radioactivity, but only to levels between 30 and 40% of normal vasa. There was a significantly higher proportion of labelled noradrenaline metabolites in the denervated vasa than in the controls (Table 1).