**References**

ADLER-GRASCHINSKY, E. & LANGER, S.Z. (1975). Possible role of a ß-adrenoceptor in the regulation of noradrenaline release by nerve stimulation through a positive feed-back mechanism. *Br. J. Pharmac.*, **53**, 43–50.

CELUCH, S.M., DUBOCOVICH, M.L. & LANGER, S.Z. (1977). Stimulation of presynaptic beta-adrenoceptors enhances [$^3$H]-noradrenaline release during nerve stimulation in the perfused cat spleen. *Br. J. Pharmac.* (in press).

LANGER, S.Z. (1974). Presynaptic regulation of catecholamine release. *Biochem. Pharmac.*, **23**, 1793–1800.

LANGER, S.Z. (1977). Presynaptic receptors and their role in the regulation of transmitter release. Sixth Gaddum Memorial Lecture, *Br. J. Pharmac.*, **60**, 481–497.

O'DEA, R.F. & ZATZ, M. (1976). Catecholamine stimulated cyclic GMP accumulation in the rat pineal: Apparent presynaptic site of action. *Proc. Nat. Acad. Sci. U.S.A.*, **73**, 3398–3402.

PELAYO, F., DUBOCOVICH, M.L. & LANGER, S.Z. (1977). Regulation of noradrenaline release in the rat pineal through a negative feed-back mechanism mediated by presynaptic alpha-adrenoceptors. *Eur. J. Pharmac.* **45**, 317–318.

STARKE, K. (1977). Regulation of noradrenaline release by presynaptic receptors systems. *Rev. Physiol. Biochem. Pharmac.*, **77**, 1–124.

WELLER, M. (1977). Evidence for the presynaptic location of adenylate cyclase and the cyclic AMP stimulated protein kinase which is bound to synaptic membranes. *Biochim. Biophys. Acta*, **469**, 350–354.

## The effect of sympathetic nerve stimulation on [$^3$H]-prazosin release in rabbit pulmonary arteries

D. CAMBRIDGE, M.J. DAVEY & R. MASSINGHAM

*Department of Medicinal Biology, Biological Research Group, Pfizer Central Research, Pfizer Limited, Sandwich, Kent.*

It was initially suggested by Story (personal communication, 1976) that prazosin might be taken up into adrenergic nerve endings, displace noradrenaline from its neuronal storage sites and subsequently be released along with transmitter noradrenaline. However, in preliminary experiments employing, 2-[$^{14}$C] prazosin (4.47 μCi/mg; $10^{-4}$M) inconclusive evidence was obtained of the release of prazosin from neuronal storage sites in response to nerve stimulation (Cambridge, Davey & Massingham, 1977). Since concentrations of prazosin in excess of $10^{-6}$M cause a calcium independent, apparently intraneuronal, release of noradrenaline and its metabolites (Cambridge *et al*, 1977), it was decided to repeat these experiments with [$^3$H]-labelled prazosin of higher specific activity.

Spirally cut strips of rabbit pulmonary arteries were weighed and incubated for 1 h in Krebs bicarbonate solution at 37°C containing $10^{-8}$ or $10^{-6}$M [$^3$H]-prazosin (300 mCi/mmol). The strips were then mounted between platinum electrodes for transmural stimulation after the method of Su & Bevan (1970). The superfusate was collected in sequential 3 min fractions and counted for [$^3$H]. Strips were stimulated on 6 occasions during the superfusion, which lasted 126 min, after which they were solubilized and counted for total [$^3$H].

Initial stimulations did not evoke any contraction in the tissues incubated with prazosin ($10^{-6}$M) but contractions to nerve stimulations became progressively larger with time in those tissues pretreated with prazosin ($10^{-8}$M), presumably as the superfusion removed prazosin from the tissues.

Transmural stimulation was not accompanied by a simultaneous enhanced release of [$^3$H] above basal levels into the superfusate. Similarly when tissues were exposed to tyramine ($10^{-5}$M for 3 min) instead of electrical stimulation there was again no associated increase in the rate of [$^3$H] lost from the tissue. Cooling (incubating at 0°C) caused a small (approximately 10%) reduction in the accumulation of [$^3$H] in the tissues. However whereas it had previously been shown that desipramine reduced the accumulation of [$^{14}$C] when strips were incubated with 2[$^{14}$C]-prazosin ($10^{-4}$M) (Cambridge *et al*, 1977), in the present series of experiments the accumulation of [$^3$H] during 60 min incubation in [$^3$H]-prazosin ($10^{-6}$M) was not modified by addition of cocaine ($10^{-4}$M) or desipramine ($6 \times 10^{-6}$M) to the Krebs solution.

These results provide direct evidence that prazosin at concentrations up to $10^{-6}$M does not enter the sympathetic neurones in vascular smooth muscle via Uptake-1. Furthermore they militate against the idea that prazosin is taken up in the storage granules and released exocytotically along with transmitter

noradrenaline in response to nerve stimulation. The results with tyramine suggest that there is also no evidence that prazosin is stored in the vesicles within sympathetic neurones and it seems likely therefore that the release of transmitter noradrenaline by high concentrations of prazosin is probably by disruption of the vesicular membrane. Autoradiographic studies are currently underway to confirm these findings.

**References**

CAMBRIDGE, D., DAVEY. M.J. & MASSINGHAM, R. (1977). The pharmacology of antihypertensive drugs with special reference to vasodilators, α-adrenergic blocking agents and prazosin. *Med. J. Aust., Special Supp.*, **2**, 2–6.

SU, C. & BEVAN, J.A. (1970). *J. Pharmacol. Exp. Therap.* **172**, 62–68.

## Substituted aryl-tetrahydro-pyrrolo imidazoles: a new class of centrally acting antihypertensives

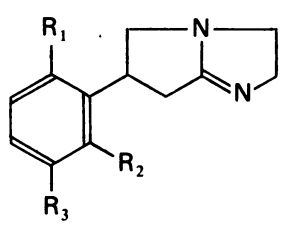
D.P. CLOUGH, R. HATTON, S.J. PETTINGER, GILLIAN M.R. SAMUELS & A. SHAW

*Departments of Biology and Chemistry, ICI Ltd Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire SK10 4TF*

In a search for new centrally acting antihypertensive agents, compounds with the general structure shown in Table 1 were synthesized. They were designed to be lipophylic α-stimulants and have been evaluated in tests used to study antihypertensive agents. Since other centrally acting antihypertensives, for example clonidine, cause sedation as a side effect in man and animals (Dollery, Davies, Draffan, Dargie, Dean, Reid, Clare & Murray, 1976; Hoefke & Kobinger, 1966) these compounds were also tested for sedative activity. This report gives the initial results with the 4 analogues in Table 1 in comparison with clonidine.

The effects on the blood pressure (BP) and heart rate (HR) of anaesthetized rats (pentobarbitone sodium, 60 mg/kg i.p.) are shown in Table 1. Also

**Table 1** The effects of the substituted 6-phenyl-2,3,6,7-tetrahydro-5H-pyrrolo-(1,2-a) imidazoles on BP and HR of anaesthetized rats (i.v.) and potencies as sedatives relative to clonidine in mice (p.o.).




| *Compound ICI No.* | $R_1$ | $R_2$ | $R_3$ | *Dose (μg/kg i.v.)* | *n* | *Change in BP 15 min after dose (mm Hg)* | *Change in HR 15 min after dose (bts/min)* | *Potency as sedative Clonidine = 1* |
|---|---|---|---|---|---|---|---|---|
| | | | | 5 | 6 | −27 | −55 | 0.1 |
| 101187 | Cl | Cl | H | 10 | 9 | −31 | −104 | |
| | | | | 30 | 3 | −58 | −77 | |
| | | | | 5 | 2 | −7 | −35 | 0.013 |
| 106270 | Cl | F | H | 10 | 10 | −30 | −66 | |
| | | | | 30 | 7 | −35 | −76 | |
| | | | | 10 | 4 | −17 | −44 | 0.16 |
| 109683 | Cl | Br | H | 30 | 4 | −30 | −47 | |
| | | | | 10 | 3 | −13 | −35 | |
| 110802 | Cl | Cl | $CH_3$ | 30 | 3 | −33 | −42 | 0.23 |
| | | | | 100 | 3 | −37 | −25 | |
| | | | | 5 | 4 | −41 | −69 | 1 |
| Clonidine | | | | 10 | 10 | −46 | −113 | |
| | | | | 30 | 3 | −45 | −97 | |