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

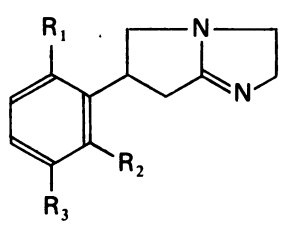
D.P. CLOUGH, R. HATTON, S.J. PETTINGER, GILLIAN M.R. SAMUELS & A. SHAW

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	

shown are the potencies of these compounds as sedatives relative to clonidine as assessed by oral dosing in mice (rota-rod test, locomotor activity, fall in body temperature). It is apparent that in this series of compounds there is a separation between the sedative and hypotensive activity in some of the analogues. For instance ICI 101187 was as potent as clonidine in lowering BP while it was only 1/10 as active as a sedative, whereas ICI 109683 and ICI 110802 were less active than ICI 101187 in lowering BP but were about twice as potent as sedatives, although still less sedative than clonidine. ICI 106270 was slightly less potent than clonidine in lowering BP, but was only about 1/80 as potent as a sedative.

When given intravenously to conscious renal hypertensive dogs at a dose of clonidine (10 μg/kg) ICI 101187 and ICI 106270 produced initial BP increases then prolonged falls in BP of $-29 \pm 3/-26 \pm 2$ mmHg ($n = 6$) with clonidine, $-26 \pm 3/-26 \pm 3$ mmHg ($n = 7$) with ICI 101187, and with ICI 106270 the fall in BP was $-23 \pm 4/-13 \pm 3$ mmHg ($n = 7$). Given orally at a dose of 250 μg/kg to conscious renal hypertensive dogs clonidine, ICI 101187, and ICI 106270 produced falls in BP of $-23 \pm 6/-26 \pm 6$ mmHg ($n = 5$), $-19 \pm 5/-23 \pm 2$ mmHg ($n = 5$) and $-18 \pm 6/-13 \pm 6$ mmHg ($n = 3$) respectively. These falls in BP were of about 5h duration. Dogs were prepared with a cannula in a lateral ventricle to allow administration of compounds directly into the CSF of conscious animals and doses of as low as 1 μg/kg of clonidine, ICI 101187 and ICI 106270 produced falls in BP of 20 mmHg.

In chloralose anaesthetized cats sympathetic efferent activity is reduced by all three compounds whether they were administered centrally or intravenously. Further CNS testing of both ICI 101187 and ICI 106270 has confirmed that the sedative potential of these compounds is much lower than that of clonidine.

References

DOLLERY, C.T., DAVIES, D.S., DRAFFAN, G.H., DARGIE, H.J., DEAN, C.R., REID, J.L., CLARE, R.A., MURRAY, S. (1976) Clinical pharmacology and pharmacokinetics of clonidine. *Clin. Pharmacol. Therap.*, **19**, 11–17.

HOEFKE, W. & KOBINGER, W. (1966) Pharmakologische Wirkungen des 2-(2,6-Dichlorophenylamino)-2-imidazoline hydrochlorid, einer neuen antihypertensiven Substanz. *Arzneimittel-Forsch.*, **16**, 1038–1050.

Changes in tyrosine hydroxylase and phenylethanolamine N-methyl transferase activity in individual brain nuclei during the development of renovascular hypertension in the rat

M.A. PETTY & J.L. REID

Department of Clinical Pharmacology, Royal Postgraduate Medical School, London

In the early stages of renovascular hypertension, as blood pressure rises, there is a transient reduction in noradrenaline concentration of certain brain nuclei (Petty & Reid, 1977). To determine whether this initial fall in tissue noradrenaline reflects increased or decreased neuronal activity, we have measured the activity of the rate-limiting enzyme tyrosine hydroxylase (TH) by a modification of the method of Shiman, Akino & Kaufman (1971) in the same brain nuclei. Phenylethanolamine-N-methyl transferase (PNMT) activity has also been measured in these areas, since Saavedra, Grobecker & Axelrod (1976) reported that PNMT was increased in some regions of brainstem in spontaneous and mineralocorticoid hypertension.

Hypertension was produced in male Wistar rats by applying a silver clip to the left renal artery, and contralateral nephrectomy (the one kidney Goldblatt model). Animals were decapitated after 3, 7 and 28 days, and brain nuclei removed by the microdissection technique of Palkovits (1973). At 3 days after operation, TH activity was higher in the nucleus of the solitary tract, and the parahypoglossal nucleus, when compared to sham operated litter mates, whereas in the hypothalamus there was a significant reduction in the periventricular ($P < 0.05$), paraventricular ($P < 0.01$) and posterior hypothalamic ($P < 0.05$) nuclei. There were no changes in PNMT activity at this time. Seven days after operation, there was no difference between the levels of TH in clipped and sham operated animals. PNMT activity was now significantly increased in the nucleus of the solitary tract (14.6 ± 2.2, 7.4 ± 1.2 nmol/mg protein/h in hypertensive and control groups, $P < 0.05$). There was no difference in TH levels 28 days after operation but PNMT activity was higher in the brainstem regions of hypertensive animals (nucleus of the solitary tract ($P < 0.01$), parahypoglossal nucleus ($P < 0.05$), locus coeruleus ($P < 0.05$), cerebellar cortex ($P < 0.02$)). At no time was a change in PNMT observed in the hypothalamic nuclei.

The decrease in noradrenaline 3 days after opera-