IVERSEN, S. D. & CREESE, I. (1975). *Adv. Neurol.*, **9**, 81–92.
NAKAMURA, M. & FUKUSHIMA, H. (1976a). *Eur. J. Pharmac.*, **38**, 343–348.
NAKAMURA, M. & FUKUSHIMA, H. (1976b). *Psychopharmac.*, **49**, 259–261.
NAKAMURA, M. & FUKUSHIMA, H. (1977a). *Ibid.*, **53**, 121–126.
NAKAMURA, M. & FUKUSHIMA, H. (1977b). *Jap. J. Pharm., Pharmac.*, **27**, 915–918.
NAKAMURA, M., FUKUSHIMA, H. & KITAGAWA, S. (1976). *Psychopharmac.*, **48**, 101–104.
NYGREN, L., FUXE, K., JONSSON, G. & OLSON, L. (1974). *Brain Res.*, **78**, 377–394.
ROSS, S. B. & RENYI, A. L. (1967). *Life Sci.*, **6**, 1407–1415.
SILVA, M. T. A. & CALIL, H. M. (1975). *Psychopharmac.*, **42**, 163–171.
SUCHOWSKY, G. K., PEGRASSI, I., MORETTI, A. & BONSIGNORI, A. (1969). *Archs int. Pharmacodyn. Thér.*, **182**, 332–340.
UNGERSTEDT, U. (1971). In: *6-Hydroxydopamine and Catecholamine Neurons*, pp. 101–128. Editor: Malmfors, T. & Thoenen, H. Amsterdam: North-Holand.
WEIL-MALHERBE, H. (1971). In: *Methods of Biochemical Analysis*, Suppl. pp. 119–152. Editor: Glick, D. New York: Intersciences.

Role of peripheral vascular resistance and reactivity in the interaction between clonidine and imipramine in spontaneously hypertensive rats

N. K. DADKAR*, A. N. DOHADWALLA, B. K. BHATTACHARYA, *Department of Pharmacology, Research Centre, Hoechst Pharmaceuticals Ltd, Mulund, Bombay 400 080, India*

Briant, Reid & Dollery (1973) reported that the hypotensive action of clonidine in patients is antagonized by simultaneous administration of tricyclic antidepressants. Although this interaction has been demonstrated in experimental hypertensive animals (Finch, Buckingham & others, 1975; Kaul & Grewal, 1975; Aroskar, Bhattacharya & others, 1976), the exact mechanism of this interaction is not clear. Van Zwieten (1975) has shown that tricyclic antidepressants administered via the vertebral artery reduces the hypotensive action of clonidine and proposed that the antagonism occurs at the level of α-receptor in the brain. However, a peripheral mechanism of action cannot be excluded completely since tricyclic antidepressants administered into the vertebral artery might have overflowed into the systemic circulation leading to a peripheral interaction with clonidine. According to Aström (1970) noradrenaline-induced hypertension is potentiated by tricyclic antidepressants indicating that these agents may have peripheral effects at postganglionic levels. In view of these findings, studies were carried out to investigate the action of imipramine on the peripheral vascular bed by perfusing the vascularly isolated but neurologically intact hindquarter and mesenteric artery preparations in spontaneously hypertensive (SH) rats.

The male SH rats (225–250 g) used were direct descendants of the original strain developed by Okamoto & Aoki (1963). Animals were anaesthetized with a combination of sodium pentobarbitone (20 mg kg^{-1}, i.p.) and urethane (500 mg kg^{-1}, i.p.). The hindquarter was perfused at a constant flow as described by Bhattacharya, Dadkar & Dohadwalla (1977). Blood from proximal part of the abdominal aorta was forced by a peristaltic pump (Desaga) into the distal part of the aorta.

The systemic blood pressure and perfusion pressure were measured with Statham P23Db pressure transducers and recorded on a physiological recorder (Hellige). The pump speed was so adjusted that the perfusion pressure and the systemic blood pressure were almost the same. Intra-arterial (i.a.) injections were made into the tubing towards the periphery. Heparin was injected (10 mg kg^{-1}) intravenously before cannulating the aorta.

The general technique for perfusing the mesenteric artery preparation was similar to that described for the hindquarter preparation. Blood from the carotid artery was forced by a peristaltic pump into the superior mesenteric artery.

Imipramine (0·05–0·3 mg, i.a.) adminstered into the hindquarter elicited a dose-related rise in perfusion pressure. With 0·3 mg it produced a sustained rise in

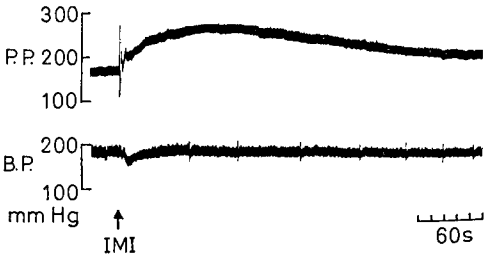

FIG. 1. Effect of intra-arterially administered imipramine (IMI 0·3 mg, i.a.) on blood pressure (B.P.) and perfusion pressure (P.P.) in perfused hindquarter preparation.

* Correspondence.

perfusion pressure which lasted for 20–35 min without any appreciable effect on the systemic blood pressure. The sustained rise in perfusion pressure reached its plateau within 6–10 min. The magnitude of the rise ranged from 45–60 mm Hg (Fig. 1). Tachyphylaxis was not observed in these experiments after repeated injections of imipramine. From these results it would appear that the direct action of imipramine may be responsible for its vasoconstrictor effects and this could be one of the reasons for inhibiting the hypotensive action of clonidine. In addition, the rise in perfusion pressure by imipramine was not altered by phenoxybenzamine (500 μg, i.a.) and propranolol (200 μg, i.a.). The doses of the antagonists used were higher than those required for inhibiting the responses of the agonists injected intra-arterially. This suggests that the action of imipramine is not mediated through α- and β-receptors of the blood vessels.

In the perfused mesenteric artery preparation, imipramine (0·3 mg, i.a.) did not produce any pressor response in the perfusion pressure. On the contrary, small transient falls in the perfusion and systemic blood pressure were observed after imipramine administration (Fig. 2).

These two different actions of imipramine may be due to major structural differences in the two preparations. The mesenteric artery preparation consists of arteries and arterioles while the hindquarter preparation comprises precapillary resistance vessels as well as intact blood vessels. Similar findings were also reported for tyramine (Dadkar, Dohadwalla & Bhattacharya, 1977).

The effect of imipramine on the hypotensive action of clonidine was studied in SH rats. Systolic blood pressures were determined in conscious rats by the tail cuff method using a piezo-electric detector. Clonidine (0·2 mg kg^{-1}, orally) and imipramine (2·0 mg kg^{-1}, orally) were administered separately or in combination, daily for 5 days. Pretreatment with imipramine (60 min before clonidine) antagonized the hypotensive action of clonidine. The fall in blood pressure in imipramine + clonidine treated rats was significantly less than that of clonidine treated rats (Table 1).

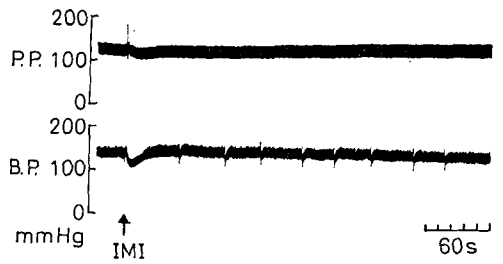

FIG. 2. Effect of intra-arterially administered imipramine (IMI, 0·3 mg, i.a.) on blood pressure (B.P.) and perfusion pressure (P.P.) in perfused mesenteric artery preparation.

Table 1. *Effect of pretreatment with imipramine and iprindole on the hypotensive action of clonidine in SH rats.* The values in parentheses represent the number of animals. The results were compared statistically using Student's *t*-test.

Treatment and dose (mg kg^{-1}, orally)	Fall in systolic blood pressure mm Hg after daily administration				
	1	2	3	4	5
Imipramine 2·0 (n = 10)	6·0 ± 6·1	4·3 ± 5·4	5·0 ± 5·0	5·0 ± 4·8	4·7 ± 3·9
Iprindole 4·0 (n = 6)	5·7 ± 6·1	4 ± 6·6	3 ± 5·0	3·3 ± 9·5	2·0 ± 5·4
Clonidine 0·2 (n = 10)	48·3 ± 6·9	58·0 ± 4·9	58·3 ± 3·5	60·0 ± 4·0	66·6 ± 5·3
Imipramine + clonidine 2·0 + 0·2 (n = 10)	12·5* ± 6·9	21·0* ± 3·0	24·0* ± 5·7	28·0* ± 6·3	37·5* ± 4·0
Iprindole + clonidine 4·0 + 2·0 (n = 6)	41 ± 6·2	46·6 ± 6·9	50·6 ± 5·6	54·3 ± 6·1	58·3 ± 6·2

The results are mean ± s.e.m.
* Significantly different from clonidine treated group $P < 0·001$.
Imipramine and iprindole were administered 60 min before clonidine.
Systolic blood pressure was recorded in SH rats 120 min after clonidine administration.

Iprindole, though clinically similar to other tricyclic antidepressants, does not block reuptake, nor alter noradrenaline turnover when given chronically at comparable doses (Rosloff & Davis, 1974; Leonard & Kafoe, 1976). It was also observed in our laboratories that iprindole at a dose of 4·0 mg kg^{-1}, orally, did not alter the hypotensive action of clonidine (Table 1).

On the other hand, trazodine, a non-tricyclic compound with antidepressant properties and noradrenaline uptake-inhibiting properties has been shown to diminish the hypotensive action of clonidine (Masotti, Scotti de Carolis & Longo, 1976; Van Zwieten, 1977).

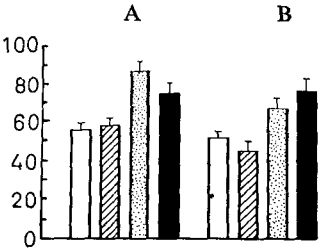

FIG. 3. Histogram representing the mean increase in perfusion pressure mm Hg after intra-arterial administration of a—noradrenaline (0·5 μg) and b—angiotension II (0·5 μg) in perfused hindquarter preparations of spontaneously hypertensive rats, pretreated with imipramine (2 mg kg^{-1}, orally) and clonidine (0·2 mg kg^{-1}, orally) daily for eight days. Vertical bars show s.e. m. (n = 10 animals per group). Open columns: control; hatched columns: clonidine; stippled columns: imipramine; solid columns: clonidine and imipramine.

These findings suggest that imipramine may impair the hypotensive action of clonidine by increasing the responsiveness of noradrenaline at the neuroeffector cells of the cardiovascular system. Since arterial hypertension is associated with hyper-reactivity of blood vessels to vasoconstrictor agents (Somlyo & Somlyo, 1970; Haeusler & Finch, 1972), and imipramine potentiates the peripheral action of catecholamines (Osborne & Sigg, 1960), the effect of noradrenaline and angiotensin II on vascular reactivity in the perfused hindquarter preparation was studied for this reason in control and SH rats treated for 8 days.

Noradrenaline (0·5 μg, i.a.) and angiotensin II (0·5 μg, i.a.) elicited the pressor responses in perfusion pressure. However, the same doses of these agents failed to show any appreciable effect in systemic blood pressure. Pretreatment with clonidine (0·2 mg kg^{-1}, orally for 8 days) did not alter the responses to noradrenaline and angiotensin II, whereas imipramine (2·0 mg kg^{-1}, orally for 8 days) significantly potentiated ($P < 0.01$) the responses to these agents. Imipramine + clonidine pretreatment showed increased ($P < 0.01$) vasoconstrictor responses to noradrenaline and angiotensin II compared with that of control and clonidine-treated groups (Fig. 3).

From these studies it appears that pretreatment with imipramine would build up a high concentration of catecholamines at the peripheral cells by inhibition of the neuronal uptake. This action of imipramine may counteract the decrease in peripheral sympathetic activity induced by clonidine thereby antagonizing its hypotensive action.

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REFERENCES

AROSKAR, V. A., BHATTACHARYA, B. K., DADKAR, N. K. & DOHADWALLA, A. N. (1976). *Ind. J. Pharmac.*, **8**, 50.
ASTRÖM, A. (1970). *Acta physiol. scand.*, **80**, 510–518.
BHATTACHARYA, B. K., DADKAR, N. K. & DOHADWALLA, A. N. (1977). *Br. J. Pharmac.*, **59**, 243–246.
BRIANT, R. H., REID, J. L. & DOLLERY, C. T. (1973). *Br. med. J.*, **1**, 522–523.
DADKAR, N. K., DOHADWALLA, A. N. & BHATTACHARYA, B. K. (1977). *J. Pharm. Pharmac.*, **29**, 48–49.
FINCH, L., BUCKINGHAM, R. E., MOORE, R. A. & BUCHER, T. J. (1975). *Ibid.*, **27**, 181–186.
HAEUSLER, G. & FINCH, L. (1972). *Naunyn-Schmiedebergs Arch. Pharmac.*, **272**, 101–116.
KAUL, C. L. & GREWAL, R. S. (1975). *Ind. J. exp. Biol.*, **13**, 289–290.
LEONARD, B. E. & KAFOE, W. F. (1976). *Biochem. Pharmac.*, **25**, 1939–1942.
MASOTTI, M., SCOTTI DE CAROLIS, A. & LONGO, V. G. (1976). *Curr. Ther. Res.*, **19**, 133–139.
OKAMOTO, K. & AOKI, K. (1963). *Jap. Circulation J.*, **27**, 282–293.
OSBORNE, M. & SIGG, E. B. (1960). *Archs int. Pharmacodyn. Thér.*, **129**, 273–289.
ROSLOFF, B. N. & DAVIS, J. M. (1974). *Psycopharmacologia (Berlin)*, **10**, 53–64.
SOMLYO, A. P. & SOMLYO, A. V. (1970). *Pharmac. Rev.*, **22**, 249–353.
VAN ZWIETEN, P. A. (1975). *Archs int. Pharmacodyn. Thér.*, **214**, 12–30.
VAN ZWIETEN, P. A. (1977). *Pharmacology*, **15**, 331–336.

Effects of neutral amino acids on the antihypertensive action of methyldopa in spontaneously hypertensive rats

F. G. ZAVISCA, R. J. WURTMAN*, *Laboratory of Neuroendocrine Regulation, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, U.S.A.*

The mechanism by which methyldopa (α-methyl-3,4-dihydroxyphenylalanine) lowers blood pressure probably involves its uptake into the central nervous system (cns) and its decarboxylation to form an amine (Henning & Van Zweiten, 1968; Chalmers & Wurtman, 1971; Heise & Kroneberg, 1973; Van Zweiten, 1973; Maitre, Hedwall & Waldmeier, 1974; Chalmers, 1975; Scriabine, Clineschmidt & Sweet, 1976a; Scriabine, Ludden & others, 1976b). Inhibition of the enzyme aromatic amino acid decarboxylase (AAAD) within the cns thus abolishes methyldopa's antihypertensive effect, while inhibition of AAAD only in peripheral organs not only fails to block the fall in blood pressure, but actually potentiates it (Henning & Van Zwieten, 1968; Scriabine & others, 1976b). That a cns locus mediates methyldopa's antihypertensive action is also suggested by the observation that application of the methyldopa metabolite α-methylnoradrenaline to various brainstem and hypothalamic loci also lowers blood pressure (DeJong, Nijkamp & Bohus, 1975; Struyker-Boudier, Smeets & others, 1975; DeJong & Nijkamp, 1976).

Since methyldopa is a large neutral amino acid (LNAA) similar in structure to the naturally occurring amino acids phenylalanine and tyrosine, one might expect that its transport from the blood to the brain would be mediated by the same specific uptake system as that transporting the LNAAs normally present in

* Correspondence.