Differential antihypertensive effects of clonidine in different models of experimental hypertension in rats

N. K. DADKAR, V. A. AROSKAR, A. N. DOHADWALLA*, *Department of Pharmacology, Research Centre, Hoechst Pharmaceuticals Limited, Mulund, Bombay 400 080 India*

While investigating the blood pressure lowering activity of different antihypertensive agents, it was found that the extent of hypotensive effect of clonidine was dissimilar in different models of experimental hypertension (Dohadwalla et al 1978). Furthermore, it has been reported that small initial doses of clonidine lowered blood pressure. As the dose was increased, the blood pressure became refractory to the action of drug (Conolly et al 1972). These findings prompted us to investigate the possible factors responsible for the differential hypotensive activity of clonidine in male spontaneously hypertensive (SH), renal hypertensive (RH) and deoxycorticosterone acetate (DOCA) hypertensive rats. SH rats were direct descendants of the original strain developed by Okamoto & Aoki (1963). For renal hypertension, rats were made hypertensive by clamping the left renal artery with silver clip (aperture 0·2 mm), leaving contralateral kidney intact (Goldblatt et al 1934). Mineralocorticoid hypertension was induced by implantation of 4 pellets (25 mg each) of DOCA, subcutaneously after removing the left kidney and substituting 1·0% sodium chloride solution for drinking water (Peterfalvi & Jequier 1960). Systolic blood pressures were determined in conscious rats by the tail-cuff method using a piezo-electric detector. Animals with systolic blood pressure of 160 mm Hg and above were considered hypertensive. Clonidine was administered daily for 5 days.

Clonidine (0·1 mg kg^{-1}, orally) caused a marked fall in systolic blood pressure in SH rats, less of a fall in RH rats and least in DOCA rats. Even though there was no significant difference in the extent of hypotensive activity in all three models of hypertension on day one, the subsequent fall in blood pressure in SH rats was significantly greater ($P < 0.001$) than that seen in RH and DOCA rats (Fig. 1).

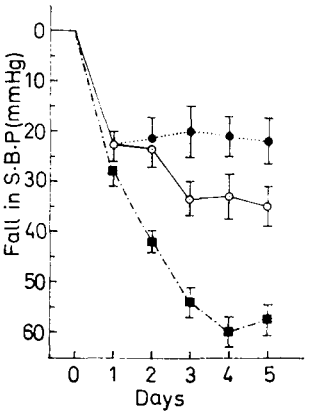

FIG. 1. The effect of clonidine (0·1 mg kg^{-1}, orally) given daily for 5 days, on systolic blood pressure of spontaneously hypertensive (■, n = 36), renal hypertensive (○, n = 18) and DOCA hypertensive (●, n = 18) rats. Each point represents the mean ± s.e.m. Data from different groups were examined using an analysis of variance (i.e. area under the curves). Ordinate: fall in systolic blood pressure (S.B.P.) mm Hg; Abscissa: time in days.

This differential hypotensive activity seen in RH and DOCA rats may be attributed to the hyperreactivity of blood vessels to peripheral α-receptor agonistic activity of clonidine. This view is further supported by the recent observations that high doses of clonidine exhibited resistance to its own hypotensive activity, because of it increasing peripheral vasoconstriction (Wing et al 1977). In view of these findings, we have investigated the action of clonidine on the peripheral vascular bed by perfusing the vascularly-isolated, but neurologically intact, mesenteric artery preparation in hypertensive rats.

Animals were anaesthetized with a combination of sodium pentobarbitone (20 mg kg^{-1}, i.p.) and urethane (500 mg kg^{-1}, i.p.). The mesenteric artery was perfused at a constant flow as described by Bhattacharya et al (1977). Intra-arterial (i.a.) injections were made into the rubber tubing leading towards the periphery. Five animals were used in each group. Results were expressed as change in perfusion pressure in mm Hg for each rat. Statistical significance between groups was assessed by Student's *t*-test.

Clonidine (3 μg) administered into the mesenteric artery elicited a rise in perfusion pressure which lasted for 2–3 min without any appreciable effect on the systemic blood pressure. The rise in perfusion pressure in DOCA (76 ± 7·0 mm Hg) and RH (65 ± 5·7 mm Hg) rats was greater ($P < 0.01$) compared with that seen in SH (40 ± 4·2 mm Hg) rats. From these results, it appears that the increased vasoconstrictor effect of clonidine could be one of the reasons for the diminished hypotensive activity in DOCA and RH rats.

Furthermore, it has been suggested that elevated blood pressure may induce adaptive structural changes in the vessel walls which might be responsible for increased vascular reactivity to vasoconstrictor stimuli (Folkow et al 1958; Lais & Brody 1978).

In addition we have found that imipramine, by

* Correspondence.

increasing the vascular responsiveness to noradrenaline at the neuro-effector cells of the cardiovascular system, antagonized the hypotensive action of clonidine (Dadkar et al 1978). A similar mechanism might also be responsible for the diminished hypotensive effect of clonidine in RH and DOCA rats. This possibility of increased noradrenaline sensitivity was investigated by studying the vascular reactivity to this agent in the perfused mesenteric artery preparation in different models of hypertension. Noradrenaline produced a dose-dependent rise in the perfusion pressure of the preparation. The dose response curve of noradrenaline exhibited significantly steeper slope and higher maxima in DOCA and RH rats (Fig. 2),

The maximum pressor responses to noradrenaline in DOCA rats (257·8 ± 2·8 mm Hg) and RH rats (232·0 ± 8·9 mm Hg) were found to be significantly greater ($P < 0.001$) compared with the effect seen in SH rats (188·3 ± 3·2 mm Hg). Taking the maximum response as 100%, we have calculated the 50% of maximum response (M 50) for all the groups. The M 50 for noradrenaline in DOCA rats (0·13 ± 0·015) and RH rats (0·17 ± 0·02) was also found to be significantly lower ($P < 0.005$) than those observed in SH rats (0·24 ± 0·001). These findings are compatible with the hypothesis that the vascular reactivity to noradrenaline was significantly increased in DOCA and RH rats as compared to SH rats.

From these studies, two possibilities may be outlined for the differential effect of clonidine in different hypertensive rat models. Firstly, an enhanced peripheral α-receptor agonistic activity of clonidine results in vasoconstriction and offers resistance to its hypotensive activity. Secondly, the difference in the pathogenesis of hypertension in RH and DOCA rats compared with SH rats may cause supersensitivity to noradrenaline which counteracts the decrease in peripheral sympathetic outflow induced by clonidine, thereby antagonizing its hypotensive action.

September 26, 1978

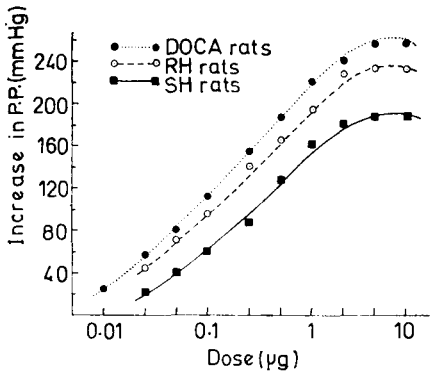

FIG. 2. The dose response curves for the increase in perfusion pressure produced by noradrenaline in perfused mesenteric artery preparation from spontaneously hypertensive (■) renal hypertensive (○) and DOCA hypertensive (●) rats. Each point represents the mean of 10 experiments. Ordinate: increase in perfusion pressure (P.P.) mm Hg. Abscissa: doses of noradrenaline in μg.

REFERENCES

Bhattacharya, B. K., Dadkar, N. K., Dohadwalla, A. N. (1977) Br. J. Pharmacol. 59: 243–246

Conolly, M. E., Briant, R. H., George, C. F., Dollery, C. T. (1972) Eur. J. Clin. Pharmacol. 4: 222–227

Dadkar, N. K., Dohadwalla, A. N., Bhattacharya, B. K. (1978) J. Pharm. Pharmacol. 30: 58–60

Dohadwalla, A. N., Dadkar, N. K., Bhattacharya, B. K. (1978) Abstt. 7th Int. Congress of Pharmacology, Paris, France, 540

Folkow, B., Grimby, G., Thulesius, O. (1958) Acta Physiol. Scand. 44: 255–272

Goldblatt, H., Lynch, J., Hanzel, R. F., Summerville, W. W. (1934) J. Exp. Med. 59: 347–379

Lais, L. T., Brody, M. J. (1978) Eur. J. Pharmacol. 47: 177–189

Okamoto, K., Aoki, K. (1963) Jpn. Circ. J. 27: 282–293

Peterfalvi, M., Jequier, R. (1960) Arch. Int. Pharmacodyn. Ther. 124: 237–254

Wing, L. M. H., Reid, J. L., Davies, D. S., Dargie, H. J., Dollery, C. T. (1977) Br. Med. J. 1: 136–138