Effect of Centrally Acting \(\alpha\)-Adrenergic Agonists on Sympathetic Nervous System Function in Humans

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SUMMARY Three studies were undertaken to reevaluate (1) whether there is a peripheral component in the reduction of sympathetic activity caused by centrally acting drugs; and (2) whether the antihypertensive effect of these drugs is due entirely to this reduction. Plasma growth hormone and norepinephrine concentrations were used as respective markers of central \(\alpha\)-adrenoceptor stimulation and peripheral sympathetic activity. In six normal volunteers, intravenous infusion of 0.2 mg clonidine and 2 mg guanfacine was compared. The falls in systolic blood pressure and plasma norepinephrine concentration were slightly greater after clonidine (18 mm Hg and 0.22 ng/ml) than after guanfacine (12 mm Hg and 0.13 ng/ml) administration. These falls occurred earlier than the rise in growth hormone, which rose to a maximum of 23 and 20 IU/ml respectively at 45 minutes after dosing. In six patients with essential hypertension clonidine and \(\alpha\)-methyldopa caused similar falls in blood pressure and plasma norepinephrine concentration although these changes occurred later with \(\alpha\)-methyldopa. Plasma growth hormone levels remained undetectable in most patients. In Wistar rats the effect of central and peripheral \(\alpha_2\)-blockade on clonidine-induced changes was compared. Two groups of six rats received intravenous RX 781094, 0.3 mg/kg, or vehicle 10 minutes before receiving clonidine, 5 \(\mu\)g/kg i.v. In the latter, control group, clonidine reduced mean blood pressure by 30.7 ± 1.9 mm Hg and heart rate by 46 ± 6.7 beats/min. Plasma norepinephrine fell from 0.22 ± 0.023 ng/ml to 0.116 ± 0.013 ng/ml. After pretreatment with RX 781094, blood pressure did not change and heart rate fell by 18 ± 2.7 beats/min. Plasma norepinephrine rose from 0.253 ± 0.03 ng/ml to 0.445 ± 0.062 after RX 781094 and then fell to 0.36 ± 0.045 ng/ml after clonidine. Two further groups received either RX 781094, 10 \(\mu\)g i.c.v., or vehicle 10 minutes prior to receiving clonidine, 5 \(\mu\)g/kg i.v. In the controls clonidine caused falls in blood pressure and heart rate comparable to results achieved in human volunteers. After RX 781094 administration, blood pressure and heart rate fell by 6.0 ± 2.0 mm Hg and by 31 ± 6.0 beats/min. In the controls clonidine reduced plasma norepinephrine from 0.29 ± 0.26 ng/ml to 0.19 ± 0.13 ng/ml; after RX 781094 pretreatment, clonidine reduced plasma norepinephrine from 0.31 ± 0.038 to 0.25 ± 0.04 ng/ml. These three studies indicate that the hypotensive effect of the drugs studied is due largely to their sympatholytic action, and that this action is mediated mainly at central \(\alpha\)-adrenergic receptors.

(Hypertension 6 (Suppl II):II-57-II-62, 1984)

KEY WORDS • clonidine • \(\alpha\)-methyldopa • guanfacine • RX 781094 (idazoxan) • blood pressure • plasma norepinephrine

The hypotensive effects of clonidine and \(\alpha\)-methyldopa are thought to be caused by a reduction in peripheral sympathetic nervous activity, consequent upon the stimulation of central \(\alpha\)-adrenergic receptors by the drugs.1,2 Both clonidine and \(\alpha\)-methylnorepinephrine, the active metabolite of \(\alpha\)-methyldopa, display relative selectivity for the \(\alpha_2\)-receptors; because this receptor subgroup includes the presynaptic \(\alpha\)-receptors, some of the sympatholytic activity of the drugs possibly may be mediated by these peripheral presynaptic \(\alpha_2\)-receptors.3,4 Two recent developments have permitted a reevaluation of the relative importance of central and peripheral \(\alpha\)-receptors in the action of these drugs: (1) Plasma growth hormone concentration has been shown to be a useful index of central \(\alpha\)-adrenergic receptors stimulation5 and may be used in conjunction with plasma norepinephrine concentration as an approximate index of peripheral sympathetic nervous activity. (2) RX 781094 (idazoxan), an \(\alpha_2\)-receptor antagonist more selective than yohimbine, became available and can now be administered in humans.6

This paper describes three studies — one in normal volunteers, one in hypertensive patients, and one in animals—in which these developments were imple-
mented. The first study compared changes in blood pressure and plasma norepinephrine and growth hormone concentrations after administration of clonidine and guanfacine. Guanfacine is a more selective α2-receptor agonist than clonidine,7 and its delayed onset of antihypertensive action suggested that the finding of an early fall in plasma norepinephrine concentration would be evidence of a peripheral action.8 Using the same parameters, the second study compared clonidine and α-methyldopa administration in hypertensive patients. In a previous study in which α-methyldopa 250 mg was administered as a single dose to 14 hypertensive patients, we found no fall in plasma norepinephrine concentration and no detectable α-methylnorepinephrine in plasma of most patients. We therefore wished to investigate, with the use of a higher dose of α-methyldopa, whether there was a difference between this drug and clonidine in their effects on central α-receptors and peripheral sympathetic activity, as reflected in plasma growth hormone and norepinephrine concentrations.

The third, animal, study was the most direct attempt to assess separately the central and peripheral actions of clonidine: RX 781094 (idazoxan) was given in different experiments either centrally or peripherally before the administration of intravenous clonidine.

Methods

Study 1

The subjects were six healthy male volunteers. Each was studied on two occasions not less than 1 week apart. Two forearm venous cannulae were inserted and heart rate and blood pressure were measured by ECG monitoring and Roche Arteriosonde (Roche Diagnostics, Div. Hoffman-La Roche, Inc., N. J.) respectively. After baseline measurements, either 0.2 mg clonidine or 2 mg guanfacine was infused over 15 minutes. The administration of the drugs was randomized and double blind. Measurements of heart rate, blood pressure, plasma norepinephrine and growth hormone were made for 2½ hours after dosing (including early readings during the infusion of the drug).

Study 2

Six patients with essential hypertension were studied. They were either untreated or received a thiazide alone. None had evidence of target organ damage from hypertension. Each patient attended the clinical laboratory on two occasions, at least 1 week apart, and received in a double-blind crossover fashion either clonidine, 0.2 mg, or α-methyldopa, 750 mg orally. The same measurements as in Study 1 were performed for 8 hours after dosing.

Study 3

In the third study each experiment was conducted in groups of six male Wistar rats. All animals had indwelling carotid arterial and jugular venous cannulae and were studied after administration of the anesthetic Inactin (gift of Dr. Pittman, BYK Ltd., W. Germany). Measurements taken were the same as in the clinical studies, namely heart rate, blood pressure, and plasma norepinephrine and growth hormone concentrations. For peripheral administration of RX 781094, 0.3 mg/kg was given as a 5-minute infusion. Five minutes later clonidine, 5 μg/kg, was injected intravenously. Measurements were made prior to each drug administration and for 60 minutes after the injection of clonidine. Control rats received a vehicle infusion (5% D/W) instead of the RX 781094. For central α-receptor blockade, RX 781094 was given at dosages of 10 and 50 μg i.c.v. in separate groups of animals. Control rats received a vehicle injection i.c.v. The time course of the experiment was as with peripheral administration: clonidine, 5 μg/kg, was injected intravenously 5 minutes after the end of RX 781094 administration.

Analytical Methods

Plasma norepinephrine was measured by a double-isotope enzymatic technique.9 Plasma growth hormone was measured by radioimmunoassay.10 Plasma α-methylnorepinephrine was measured by high-performance liquid chromatography (HPLC) with electrochemical detection.11

Results

Study 1

Both drugs caused a similar fall in blood pressure and plasma norepinephrine concentration and a rise in plasma growth hormone (Fig. 1). The fall in blood pressure and plasma norepinephrine occurred earlier than the rise in growth hormone.

Study 2

Clonidine and α-methyldopa reduced blood pressure and plasma norepinephrine concentration, although the falls after α-methyldopa administration were slightly smaller and occurred later than those after clonidine administration (Fig. 2). Plasma growth hormone levels remained undetectable in most patients throughout the study; nor was plasma α-methylnorepinephrine detected in most patients after α-methyldopa administration.

Study 3

Intravenous injection of RX 781094 followed by intravenous clonidine caused almost 90% blockade of the initial hypotension and prevented any significant reduction in plasma norepinephrine concentration (Fig. 3). When 10 μg RX 781094 was injected i.c.v., a similar blockade of hypotension occurred, but there was still a significant fall in plasma norepinephrine concentration (p < 0.05, paired t-test) (Fig. 4). When 50 μg RX 781094 was injected i.c.v., there was no fall in plasma norepinephrine concentration after clonidine administration; this dose also caused partial inhibition of the early pressor effect of clonidine. Because the animals were anesthetized, all levels of plasma growth hormone were elevated and there was no change after clonidine administration. The levels of growth hor-
that guanfacine is slower than clonidine to penetrate the brain was not confirmed. Possibly, the greater α₂ selectivity of guanfacine requires that a higher proportion of the drug must enter the brain to counteract the pressor effect of peripheral extrasynaptic α₂-receptor stimulation. Because of the relatively short delay before the rise in growth hormone and the small number of subjects studied, it is not possible to be certain if the early fall in plasma norepinephrine concentration confirms the hypothesis that these drugs can reduce norepinephrine release independently of their stimulation of central α-receptors.

The experiments with centrally administered RX 781094 in rats also imply a limited role for peripheral presynaptic receptor stimulation in the reduction in plasma norepinephrine concentration, but probably no role in the hypotension. Even the lower dose of centrally administered RX 781094 almost completely antagonized the hypotension within 5 minutes after clonidine administration. There was no further antagonism of the hypotension when the higher dose of RX 781094 was used — perhaps because clonidine is not a pure α₂-agonist. At the lower dose of RX 781094, the fall in plasma norepinephrine concentration was only partially inhibited, and it is possible that the remaining fall is
Figure 2B. Effect of oral clonidine (0.2 mg) and α-methyldopa (750 mg) on plasma norepinephrine concentration in six patients with essential hypertension. Values are mean ± SD. * = p < 0.05; ** = p < 0.01; *** = p < 0.001; comparison by paired t-test with baseline value. Baseline blood pressure and heart rate were 146 ± 21.0/99 ± 10.8 mm Hg and 69.2 ± 11.7 beats/min for α-methyldopa, and 134.7 ± 22.3/92.6 ± 8.3 and 78.8 ± 11.7 for clonidine.

Figure 3. The changes in blood pressure (A) and plasma norepinephrine concentrations (B) after clonidine (CLON), 5 μg/kg i.v., was administered in two groups of six anesthetized rats. These rats had received earlier a 5-minute i.v. infusion of either RX 781094, 0.3 mg/kg, or vehicle (RX). Values are mean ± SD. The preclonidine mean arterial pressures were 109 ± 6 and 107 ± 2 mm Hg for RX 781094- and vehicle-treated rats respectively.
due to the peripheral action of clonidine. Unfortunately, the use of anesthesia prevented the growth hormone results from providing an indication of whether the lower dose of RX 781094 had achieved complete central α-receptor blockade. Although the higher dose of RX 781094 did completely antagonize the fall in plasma norepinephrine, this higher dose itself caused a rise in plasma norepinephrine before the clonidine was injected (Fig. 4). The effect of centrally administered RX 781094 itself should be studied to determine if a further rise in plasma norepinephrine concentration would have been observed during the hour after RX 781094 administration if no clonidine had been injected. Alternatively, the 50-μg dose may have had some peripheral action, because it was almost as large as the intravenous dose of RX 781094 and did partially inhibit the early pressor action of clonidine in some rats.

The comparison of α-methyldopa and clonidine in hypertensive patients has not confirmed the earlier evidence that α-methyldopa reduces blood pressure without a fall in plasma norepinephrine concentration. Indeed, there appears to be a good correlation between the time course of the falls in blood pressure and plasma norepinephrine concentration after administration of the two drugs (these correlations will be calculated when more patients have been studied). Again we found little or no circulating α-methylnorepinephrine in patients after acute α-methyldopa administration; this contrasts with the predominance of this metabolite over endogenous norepinephrine that has been demonstrated to occur in brain nuclei within a few hours of α-methyldopa administration. Perhaps the most interesting observation in this study has been the failure of either drug to stimulate a rise in plasma growth hor-
mone concentration. This contrasts with the large rises in the volunteer study and seems to confirm an earlier observation that clonidine fails to elevate plasma growth hormone concentration in hypertensive subjects. The subjects in these two studies are not, of course, directly comparable, and appropriately matched controls would need to be studied before concluding that there is a defect of central α-receptors in hypertension.

Acknowledgments
RX 781094 was a generous gift of Dr. J. Doxey, Reckitt & Colman.

References
Effect of centrally acting alpha-adrenergic agonists on sympathetic nervous system function in humans.
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Hypertension. 1984;6:II57
doi: 10.1161/01.HYP.6.5_Pt_2.II57

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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