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THE VASODILATOR PROPERTIES OF NORADRENALINE IN THE HUMAN FOREARM

BY

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The stimulant effects of noradrenaline on the heart are readily blocked by sympathetic β-receptor antagonists (Moran & Perkins, 1958; McInerny, Gilmour & Blinks, 1965; Brick, Hutchison & Roddie, 1966a). This indicates that noradrenaline can stimulate β-receptors. The powerful vasodilator effect of isoprenaline in the human forearm is also blocked by β-receptor antagonists (Glover, Greenfield & Shanks, 1962). This indicates that β-receptors occur in the smooth muscle in forearm blood vessels. It is, therefore, to be expected that noradrenaline would have some vasodilator properties in the forearm. Glover & Hutchison (1965) found evidence that this is the case. They showed that the β-receptor antagonist, propranolol, increased the vasoconstrictor response in the human forearm to intravenous infusions of noradrenaline.

When given intra-arterially in the forearm, noradrenaline causes intense vasoconstriction, so it is clear that any vasodilatation due to stimulation of β-receptors is normally masked by the more powerful stimulation of α-receptors. However, if the vasoconstrictor effects of noradrenaline were blocked with an α-receptor antagonist, noradrenaline would be expected to cause vasodilatation in the forearm. It is, therefore, surprising that Allwood & Ginsburg (1961) found that the vasoconstrictor response to noradrenaline in the forearm was not reversed after pharmacological blockade of α-receptors with phenoxybenzamine. This inconsistency led to the present experiments, which show that the vasoconstrictor response to noradrenaline is readily reversed if suitable doses of noradrenaline and α-receptor antagonist are used. Phentolamine was used to block α-receptors since its high solubility and relatively short-lived action permitted high concentrations of the drug to be used. A preliminary account of some of these findings has already been published (Brick, Hutchison & Roddie, 1966b).

METHODS

The experiments were carried out on healthy male subjects who lay supine on a couch in a laboratory maintained at a temperature between 20 and 22° C. Blood flow to both forearms was measured simultaneously by venous occlusion plethysmography. A catheter (No. 19 intracath, Bardic) was inserted into the left brachial artery and through this a continuous infusion of saline containing 0.003% ascorbic acid was infused at a rate of 4 ml./min. Drugs were diluted in the ascorbic acid-saline so that the dose for 1 min was contained in 4 ml. In some of the experiments arterial blood pressure was recorded intermittently by connecting the arterial catheter by means of a four-way tap to a capacitance manometer for 5 sec in every 30 sec.

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Noradrenaline was given as noradrenaline bitartrate (Bayer), phentolamine as phentolamine methane sulphonate (Ciba) and propranolol as the hydrochloride (I.C.I.). Doses of noradrenaline are expressed as the base and of phentolamine and propranolol as the salts.

RESULTS

Figure 1 shows venous occlusion plethysmograms of forearm blood flow before, during, and after infusions of noradrenaline into the brachial artery. In the top record noradrenaline infused by itself in a dose of 0.25 μg/min caused a large reduction in forearm

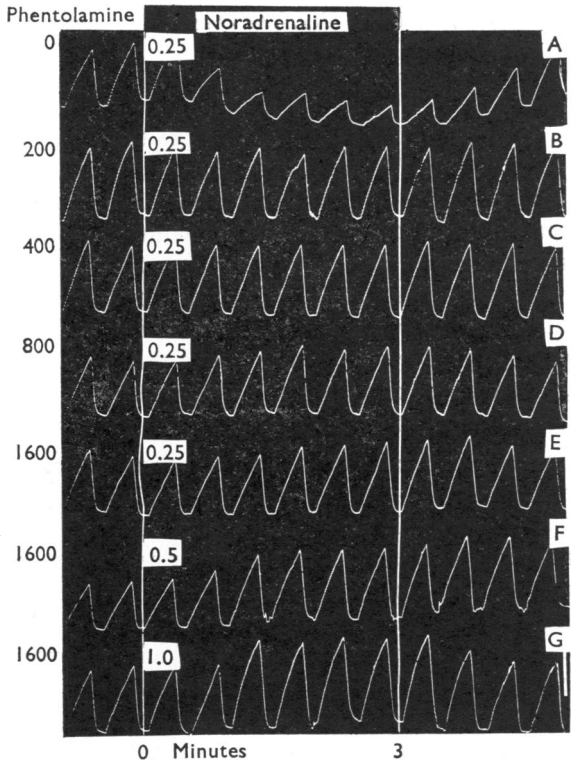

Fig. 1. Venous occlusion plethysmograms from the left forearm during an experiment in which noradrenaline and phentolamine were infused into the left brachial artery. Noradrenaline was infused for the periods marked by the pair of vertical lines at a rate of 0.25 μg/min in A, B, C, D and E, at a rate of 0.5 μg/min in F and 1 μg/min in G. These noradrenaline infusions were carried out against a background of phentolamine 200 μg/min in B, 400 μg/min in C, 800 μg/min in D and 1,600 μg/min in E, F and G. |: 10 ml. calibration.

blood flow as shown by the reduction in the steepness of the plethysmograms. The second trace shows a run in which a similar infusion was made against a background of α-receptor blockade with the drug phentolamine infused at a rate of 200 μg/min. The vasoconstrictor response to noradrenaline was greatly reduced. As can be seen from the slopes of the plethysmograms, noradrenaline caused only a small decrease in flow. In the next three traces, similar infusions of noradrenaline were made against a background

of increasing doses of phentolamine. When phentolamine was infused at 400 and 800 μg/min, noradrenaline infusion was more or less without effect. However, when phentolamine 1,600 μg/min was used, there was a suggestion that noradrenaline caused an increase in flow; the plethysmograms at the end of the noradrenaline infusion were slightly steeper than those in the control period. When the dose of noradrenaline was increased to 0.5 μg/min this effect became even more marked. In the bottom trace, phentolamine was again infused in a dose of 1,600 μg/min throughout the run and the dose of noradrenaline was increased to 1 μg/min; this resulted in a large increase in forearm blood flow.

From this sort of experiment it became apparent that α-receptor blockade could reduce, abolish or reverse the vasoconstrictor response to noradrenaline in the forearm depending on the degree of the blockade and the dose of noradrenaline.

The results shown in Fig. 2 indicate that the vasodilatation produced by noradrenaline in the forearm during α-receptor blockade is due to stimulation of β-receptors. The

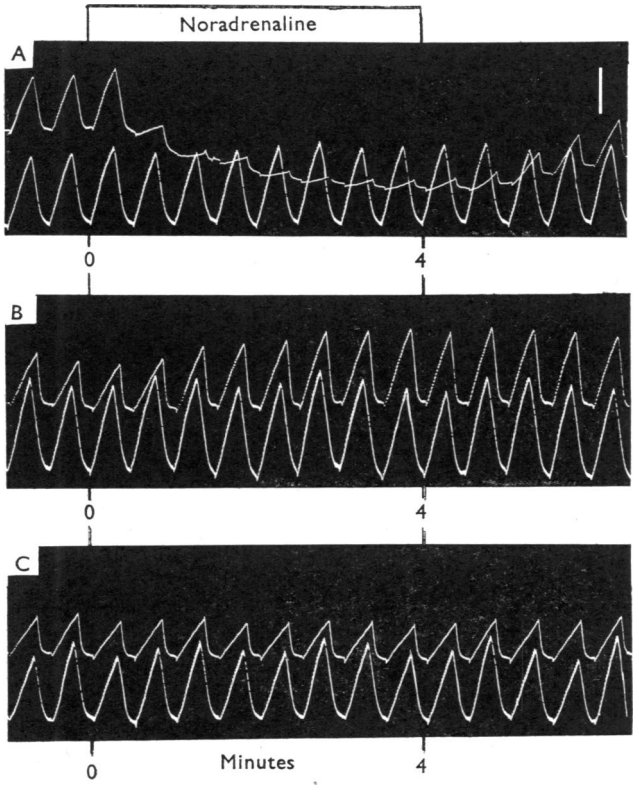

Fig. 2. Venous occlusion plethysmograms from an experiment in which noradrenaline was infused into the left brachial artery at a rate of 1 μg/min for three periods of 4 min: (a) before α-blockade, (b) during α-blockade of the left forearm using phentolamine 1,600 μg/min intra-arterially, (c) during combined α- and β-blockade of the left forearm using phentolamine, 1,600 μg/min, and propranolol, 10 μg/min intra-arterially. Upper trace—left forearm; lower trace—right forearm. Noradrenaline: period of infusion of noradrenaline. |: 10 ml. calibration.

upper panel shows plethysmograms of forearm blood flow recorded simultaneously from both forearms. At time zero noradrenaline (1 μg/min) was infused into the left brachial artery. Blood flow in the infused forearm, shown by the upper trace, rapidly fell towards zero as shown by the almost horizontal inflow curves. After the infusion blood flow slowly recovered. There was no appreciable change in flow to the opposite control arm. The middle panel shows the effect of a repeat infusion of noradrenaline made in the forearm with a background infusion of phentolamine at a rate of 1,600 μg/min. Instead of falling, blood flow to the left forearm rose from approximately 4.8 to approximately 8 ml./100 ml./min. Again there was no change in flow to the control side. The bottom panel shows that this increase in blood flow was due to stimulation of β-receptors by noradrenaline. When the noradrenaline infusion was repeated during β-blockade with propranolol in addition to α-blockade with phentolamine, noradrenaline was without effect.

Figure 3 shows the average results of four experiments of a similar type to that shown in Fig. 2 in which noradrenaline (0.75 μg/min) was infused for 10 min periods. Blood

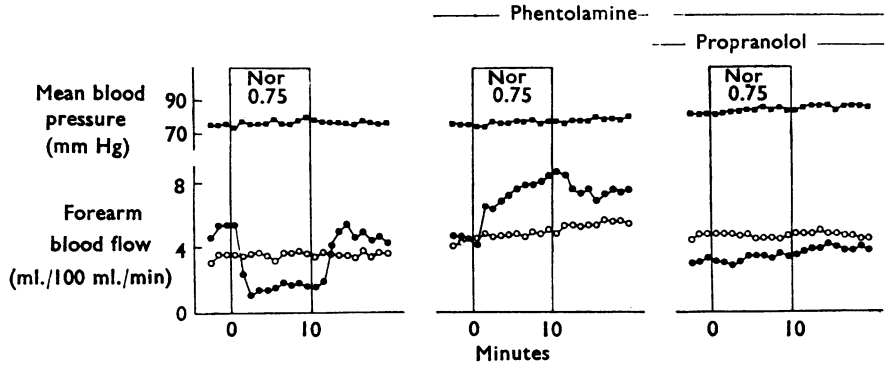

Fig. 3. The average response of forearm blood flow, in four experiments, to the infusion of noradrenaline, 0.75 μg/min, into the left brachial artery: (a) before α-blockade, (b) during α-blockade using phentolamine, 1,600 μg/min intra-arterially, (c) during combined α- and β-blockade using phentolamine, 1,600 μg/ml, and propranolol, 10.0 μg/min, intra-arterially. NOR 0.075: noradrenaline infusions, ——Phentolamine——: phentolamine infusion; ——Propranolol——: propranolol infusion; ●: blood flow in left or experimental forearm; ○: blood flow in right or control forearm; ■: mean arterial blood pressure.

flow in the experimental forearm is represented by closed circles and in the control forearm by open circles. Arterial blood pressure was measured directly and is plotted as mean blood pressure. Before α-blockade noradrenaline caused vasoconstriction. During α-blockade with phentolamine (1,600 μg/min), noradrenaline caused vasodilatation. Finally, during β-blockade with propranolol (10 μg/min) as well as α-blockade with phentolamine (1,600 μg/min), noradrenaline had little effect on blood flow.

Figure 4 shows how the response to intra-arterial noradrenaline varies in an α-blocked forearm when the dose of noradrenaline is gradually increased. In this experiment phentolamine (1,600 μg/min) was infused for 6 min before and during each run in order to produce α-blockade. Five doses of noradrenaline ranging from 0.075 to 75.0 μg/min were infused intra-arterially to the left forearm against this background. Noradrenaline

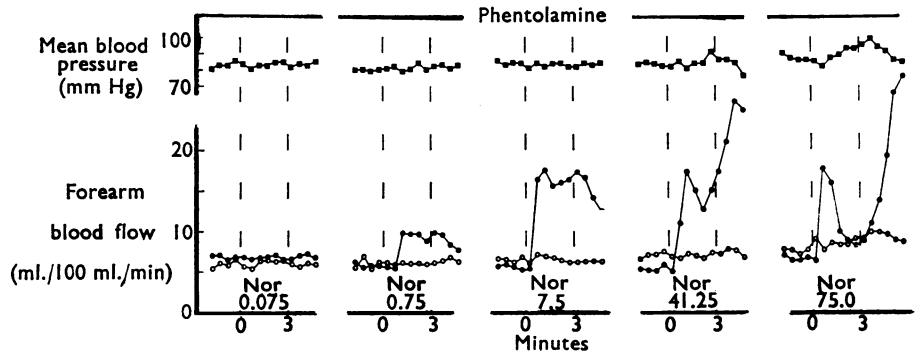

Fig. 4. The response of forearm blood flow, in one experiment, to various doses of noradrenaline intra-arterially in a forearm treated with phentolamine, 1,600 μg/min intra-arterially. Nor: infusions of noradrenaline; the numbers refer to the dose of noradrenaline in μg/min. ——Phentolamine——: infusion of phentolamine; ●: blood flow to left forearm; ○: blood flow to right forearm; ■: mean arterial pressure.

(0.075 μg/min) caused no change in forearm blood flow. 0.75 μg/min caused a small increase in blood flow and 7.5 μg/min caused a greater increase. 41.25 μg/min caused a large initial increase in flow but this was not sustained and when 75.0 μg/min was infused the initial increase in flow was followed by a return almost to the control level. There was a large increase in blood flow after the end of the infusion in the last two runs; this dilatation lasted for over 10 min after the end of the infusion of noradrenaline (75.0 μg/min). In order to compare the magnitude of the dilator response to noradrenaline during the infusion of these doses, excess blood flow during each infusion was calculated by measuring the area under each curve. The results are shown in Fig. 5. With increasing doses of noradrenaline the vasodilator response initially increased, but

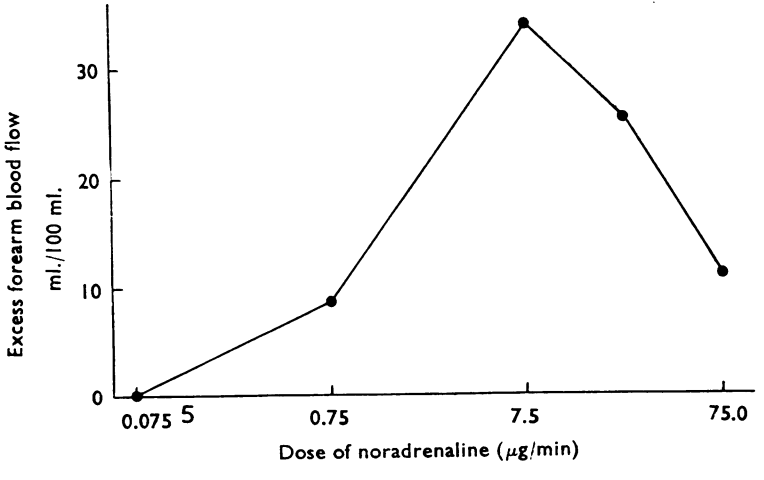

Fig. 5. Summary of the dilator responses, in one experiment, to various doses of intra-arterial noradrenaline in a forearm treated with phentolamine, 1,600 μg/min intra-arterially. ● : excess blood flow to left forearm during the noradrenaline infusion.

when the dose was increased further the dilator response was reduced. A possible explanation of the reduction in the dilator response with high doses is that the α-receptor constrictor effect of noradrenaline had broken through the blockade and so reduced the dilator effect.

DISCUSSION

These experiments show that the constrictor effect of noradrenaline on forearm blood vessels can be reduced, abolished or reversed by blockade of α-receptors with phentolamine, the response being dependent on the dose of noradrenaline and the degree of α-blockade. When reversal occurs it is due to stimulation of β-receptors in the forearm blood vessels as it is abolished by β-blockade using propranolol. A similar reversal of the vasoconstrictor response to noradrenaline has been demonstrated in a skeletal muscle vascular bed in a perfused dog's leg (Lanier, Green, Hardaway, Johnson & Donald, 1953; Green, Denison, Williams, Garvey & Tabor, 1954; Youmans, Green & Denison, 1955). In the experiments of Allwood & Ginsburg (1961) it would appear that the dose of phenoxybenzamine used to produce α-blockade did not cause a sufficient degree of blockade to unmask a vasodilator component to the action of noradrenaline in the forearm.

Although it is usually masked by the more potent vasoconstrictor action, the vasodilator activity of noradrenaline is considerable. Thus after phentolamine the intra-arterial infusion of noradrenaline (0.75 μg/min) caused a doubling of forearm blood flow; a similar increase in flow is usually caused by intra-arterial infusions of histamine (0.25 μg/min), acetylcholine (1.0 μg/min) and adenosine triphosphate (16.0 μg/min) (Duff, Patterson & Shepherd, 1954). The vasodilator properties of noradrenaline are therefore comparable to those of acetylcholine on a weight for weight basis.

It is concluded that the action of noradrenaline on forearm blood vessels is normally the summation of a predominant vasoconstrictor or α-receptor action and a weaker vasodilator or β-receptor action. This is similar to the mechanism of the action of adrenaline on forearm blood vessels which was first shown to be a summation of a vasoconstrictor and a vasodilator action by Lande & Whelan (1959) and later confirmed by Glover *et al.* (1962) and Lowe & Robinson (1964).

SUMMARY

1. The blood flow response to intra-arterial noradrenaline in the human forearm was studied before and after blockade of sympathetic α-receptors with phentolamine.

2. The usual vasoconstrictor response to noradrenaline was converted to a vasodilator response when high doses of intra-arterial phentolamine (1,600 μg/min) were used for blockade.

3. The vasodilatation in response to noradrenaline was due to stimulation of β-receptors as it was abolished by treating the forearm with the β-receptor antagonist propranolol (10 μg/min).

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