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PERIPHERAL VASCULAR EFFECTS OF MIXTURES OF ISOPRENALINE AND NORADRENALINE IN MAN

BY

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Mixtures of isoprenaline (0.05 μg/min) and noradrenaline (0.05, 0.1 and 0.25 μg/min) were infused into the brachial artery of subjects. The response, an initial transient increase in forearm blood flow followed by a decrease to or below the resting level, resembled the response to an intra-arterial infusion of adrenaline (0.05 to 0.5 μg/min). A five-fold increase in the dose of both drugs in the mixture resulted in a response which was matched by that to a five-fold increase in the dose of adrenaline. The intra-arterial infusions of mixtures and of adrenaline both reduced the thermal conductivity of the skin of the forearm. This result suggests that blood vessels in skeletal muscle responded qualitatively in the same manner to these infusions. Mixtures of isoprenaline (2 μg/min) and noradrenaline (10 μg/min) were infused intravenously into the subjects. The response was an initial transient increase followed by a smaller but sustained increase in the flow of blood to the forearm, and a fall in the flow of blood to the hand. These responses resembled those to the intravenous infusion of adrenaline (10 μg/min). We conclude that the action of adrenaline in the human arm can be explained on the basis of the response of two types of catechol amine receptor.

The infusion of adrenaline (0.1 to 1.0 μg/min) into the brachial artery in man results in an immediate transient increase in forearm blood flow, followed by a decrease to or below the resting level (Duff & Swan, 1951). Similar doses of noradrenaline cause only a decrease in forearm blood flow (Barcroft & Swan, 1953) while smaller doses of isoprenaline cause a large transient increase followed by a smaller but sustained increase in flow (Cobbold, Ginsburg & Paton, 1960).

The effect of these sympathomimetic amines on the peripheral circulation in man has been explained in terms of separate constrictor and dilator "adrenotropic" receptors, as first proposed by Ahlquist (1948). After drugs such as phenoxybenzamine, which are thought to block the α- or "constrictor" receptors, the constrictor response to noradrenaline is abolished, the dilator response to isoprenaline is unaffected, and the response to adrenaline becomes purely dilator (Ginsburg & Cobbold, 1960). Recently, Glover, Greenfield & Shanks (1962) have shown that after administration of dichloroisoprenaline, which blocks the β- or "dilator" receptors, the dilator response to isoprenaline is abolished, the constrictor response to noradrenaline is unaffected, and the response to adrenaline becomes purely constrictor.

Consequently noradrenaline is assumed to act mainly on α-receptors, isoprenaline on β-receptors, and adrenaline on both. If this is so, we might expect that the peripheral vascular actions of adrenaline could be matched by the infusion of suitable mixtures of noradrenaline and isoprenaline. This hypothesis has been tested in the experiments described here.

METHODS

The experiments were carried out on healthy male subjects aged from 18 to 30 years. The subject lay supine on a couch in a laboratory maintained at a temperature of 21 to 22° C. Forearm, and in some experiments hand, blood flow was measured by venous occlusion plethysmography. In three experiments changes in the thermal conductivity of forearm skin were followed simultaneously with plethysmographic determinations using the heated thermocouple devices described by Hensel & Bender (1956). Intra-arterial infusions were made through an indwelling needle in the left brachial artery in the antecubital fossa; intravenous infusions were made through an indwelling catheter in an antecubital vein. Saline (0.9%, w/v), containing 0.003% of ascorbic acid as a preservative (Gaddum, Peart & Vogt, 1949), was infused throughout each experiment at the rate of 4 ml./min. Isoprenaline hydrochloride (Winthrop and I.C.I.), (−)-noradrenaline bitartrate (Bayer) or (−)-adrenaline hydrochloride (Parke-Davis) was added to the ascorbic acid-saline so that the dose per min was contained in 4 ml. Doses are expressed in terms of the salts.

RESULTS

Intra-arterial infusions

In the experiment illustrated in Fig. 1, isoprenaline (0.05 μg/min) was infused into one brachial artery. This resulted in a large initial increase in forearm blood flow followed by a smaller but sustained increase. When noradrenaline (0.25 μg/min) was infused the response was a fall in blood flow which persisted for the duration of the infusion. Fig. 1 (panel 3) shows the response to a mixture of the two drugs in these same amounts; there was a transient increase in flow followed quickly by a fall to below the resting level. As the infusion continued flow increased slightly towards the resting level, and at the end of the infusion rose slightly above it. This response bears a strong qualitative resemblance to the response to the infusion of adrenaline (0.25 μg/min) shown in Fig. 1 (panel 4).

The effect of varying the proportions of noradrenaline and isoprenaline in the mixture was studied in the experiments illustrated in Fig. 2. In each of the fifteen infusions the dose of isoprenaline was 0.05 μg/min. In five of these an equal amount of noradrenaline was added, in another five the dose of noradrenaline was 0.1 μg/min, and in the remaining five the dose was 0.25 μg/min, thus giving ratios of isoprenaline to noradrenaline of 1:1, 1:2 and 1:5 respectively. In all but one experiment the initial response was a transient increase in forearm blood flow. Allowing for individual variation, the responses to the 1:1 and 1:2 mixtures resemble the response to small doses of adrenaline (about 0.05 to 0.1 μg/min). The responses in four of the five experiments in which the ratio was 1:5 resemble the response to doses of adrenaline of the order of 0.25 to 0.5 μg/min.

In three experiments, illustrated in Fig. 3, the effect of increasing the doses of both drugs in the mixture was studied, their ratios being kept constant. The response to a mixture of isoprenaline (0.05 μg/min) and noradrenaline (0.1 μg/min) is shown

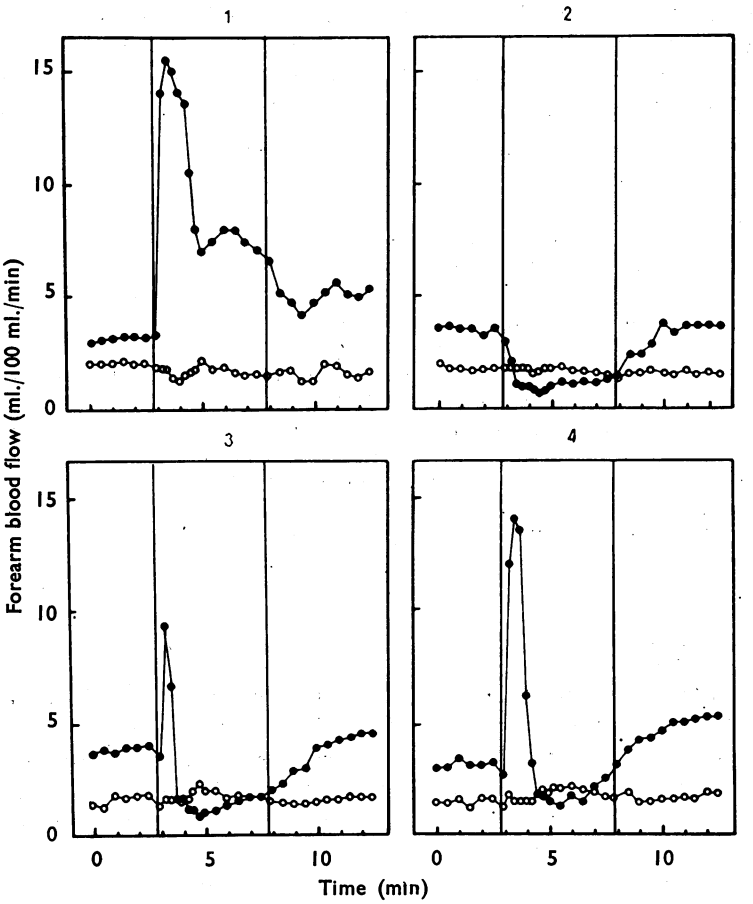

Fig. 1. The effects of intra-arterial infusions of (1) isoprenaline, 0.05 μg/min; (2) noradrenaline, 0.25 μg/min; (3) a mixture of isoprenaline, 0.05 μg/min, and noradrenaline, 0.25 μg/min; and (4) adrenaline, 0.25 μg/min, on forearm blood flow. The infusions were made during the periods represented between the vertical lines. ●——● Infused side; ○——○ control side. Reproduced, with permission, from Glover, Shanks & Stanford (1962).

in the third column. This response matches those to small doses of adrenaline (0.05 and 0.1 μg/min) shown in the first column. When the doses of both drugs in the mixture were increased fivefold, the ratio still being 1:2, the fall in flow after the initial increase was greater (last column). This response matches that to a fivefold increase in the dose of adrenaline, shown in column 2.

In three experiments changes in the thermal conductivity of the skin of the forearm were followed during the intra-arterial infusion of a mixture of isoprenaline (0.05 μg/min) and noradrenaline (0.25 μg/min) and during the infusion of adrenaline (0.25 μg/min), using the Hensel-Bender heated thermocouple skin device. Total forearm blood flow was measured simultaneously by venous occlusion plethysmography. The responses were qualitatively the same in each experiment, and a

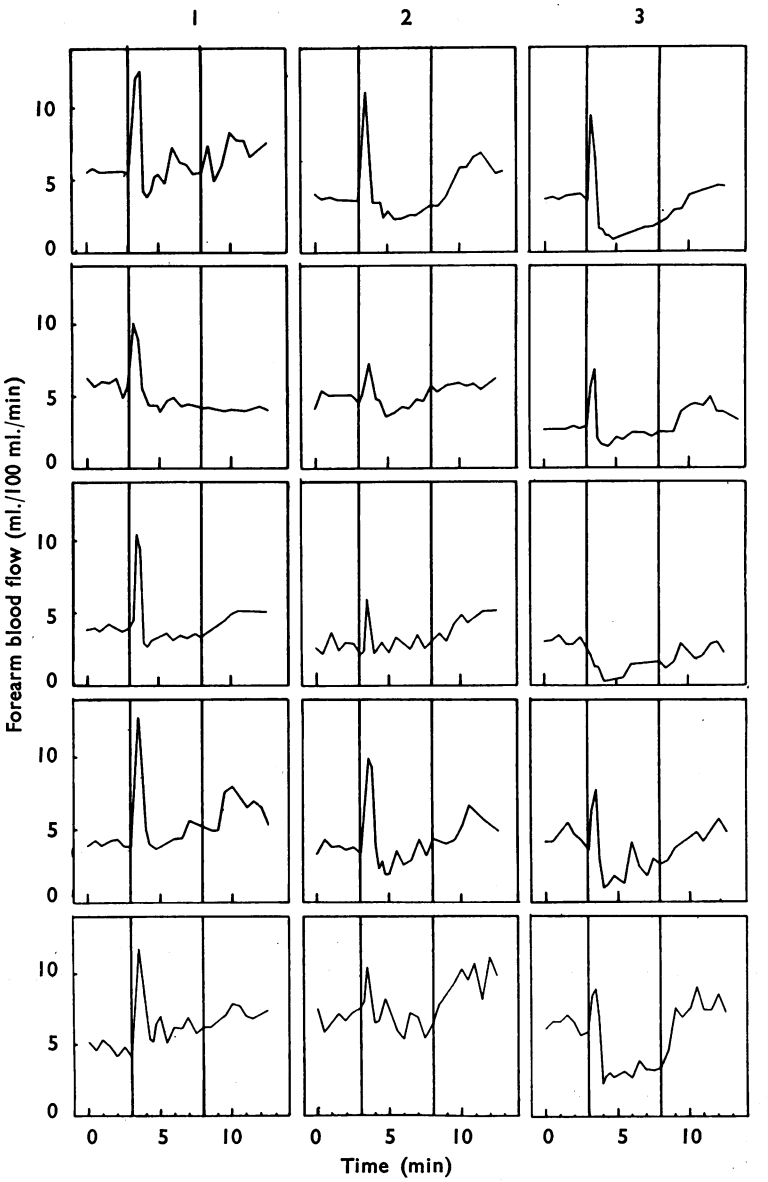

Fig. 2. The effects of intra-arterial infusions of mixtures of isoprenaline, 0.05 μg/min, and noradrenaline in doses of 0.05 μg/min (column 1), 0.1 μg/min (column 2) and 0.25 μg/min (column 3), on forearm blood flow. The infusions were made during the periods represented by the vertical lines.

typical experiment is illustrated in Fig. 4. The usual biphasic changes in total forearm blood flow occurred in response to the mixture and to adrenaline. During both infusions there was a fall in the thermal conductivity of the skin. It is assumed that this effect indicates a fall in skin blood flow in both instances. Since the response

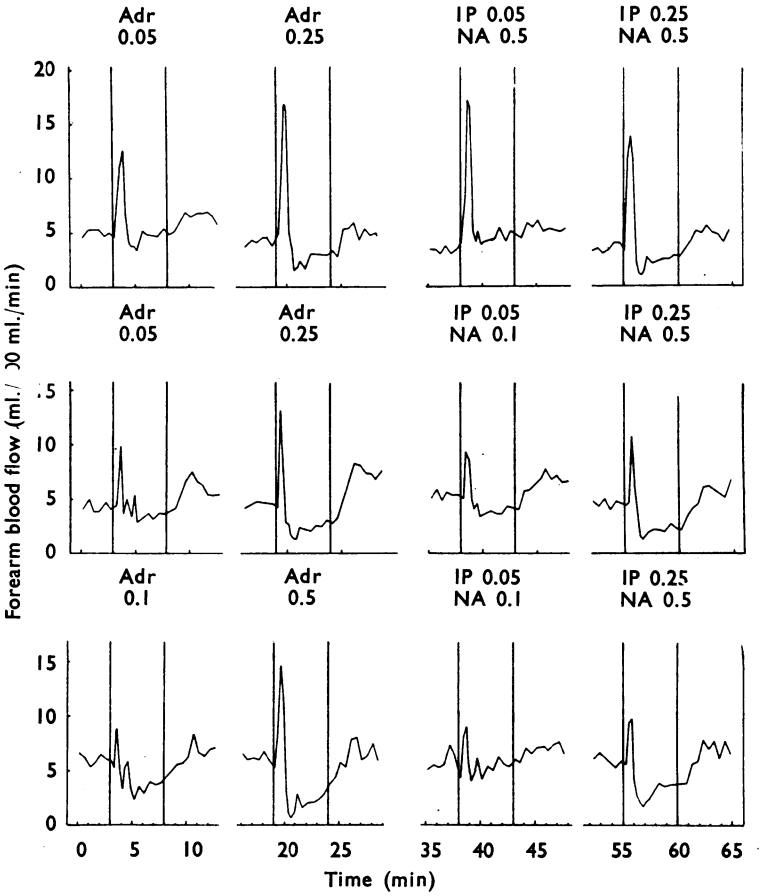

Fig. 3. The effects of intra-arterial infusions of adrenaline (Adr), 0.05 or 0.1 μg/min (column 1) and 0.25 or 0.5 μg/min (column 2), and of mixtures of isoprenaline (IP), 0.05 and 0.25 μg/min, and noradrenaline (NA), 0.1 and 0.5 μg/min (columns 3 and 4 respectively) on forearm blood flow.

of the forearm as a whole is similar, it is highly likely that the muscle vessels respond qualitatively in the same manner both to infusions of adrenaline and to infusions of the mixture.

The effect of starting the infusion of noradrenaline before adding isoprenaline to the mixture was studied in two experiments; the results of one are shown in Fig. 5 and a similar response was seen in both experiments. Noradrenaline (0.25 μg/min) was infused into the brachial artery; this caused the usual decrease in forearm blood flow. After 2 min isoprenaline (0.05 μg/min) was added to the infusion. A transient increase in blood flow followed, resembling the "spike" normally seen at the beginning of the infusion of a mixture; flow then rapidly fell to the former level. We conclude that the initial spike is not due to isoprenaline reaching its site of action before, or causing a more immediate response than, noradrenaline.

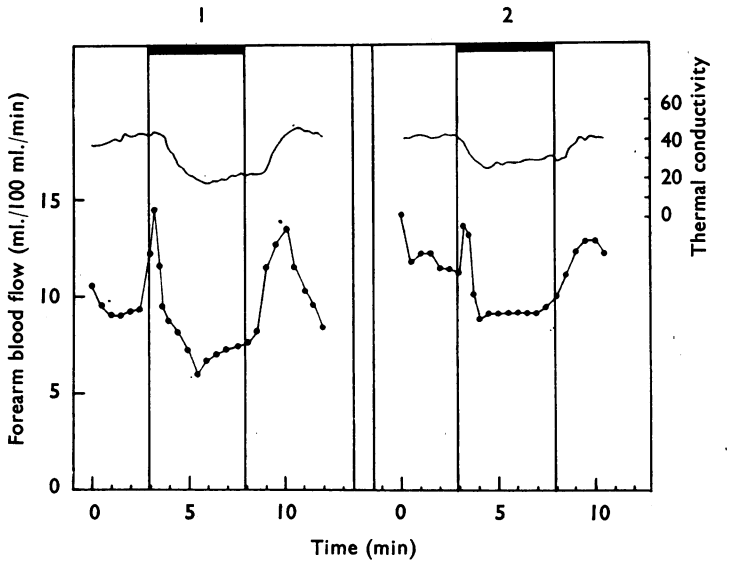

Fig. 4. The effects of intra-arterial infusions of adrenaline, 0.25 μg/min (panel 1), and of a mixture of isoprenaline, 0.05 μg/min, and noradrenaline, 0.25 μg/min (panel 2), on forearm blood flow and on the thermal conductivity of the skin of the forearm. ●——● Forearm blood flow; —— thermal conductivity of skin (arbitrary units, zero corresponds to zero flow).

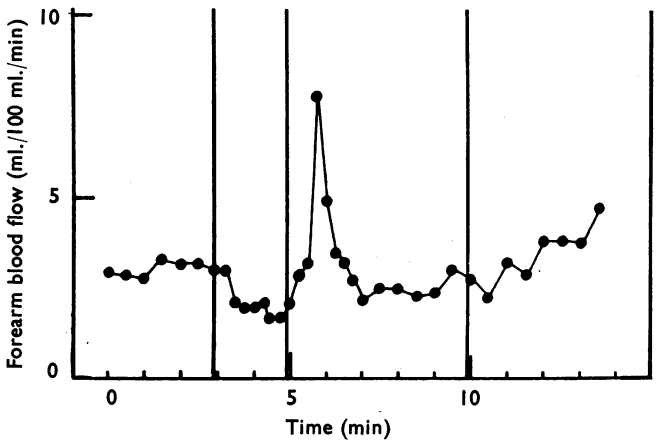

Fig. 5. The responses of forearm blood flow to the intra-arterial infusion of noradrenaline, 0.25 μg/min (commencing at time 3 min), and isoprenaline, 0.05 μg/min (commencing at time 5 min). The infusion ended at time 10 min.

Intravenous infusions

In four experiments blood flow to the forearm was measured on one side of the body, and blood flow to the hand on the other. A typical experiment is illustrated in Fig. 6. The intravenous infusion of isoprenaline (2 μg/min) caused an increase in forearm blood flow but no change in flow to the hand. Noradrenaline (10 μg/min) caused a fall in hand blood flow but no change in flow to the forearm. Fig. 6

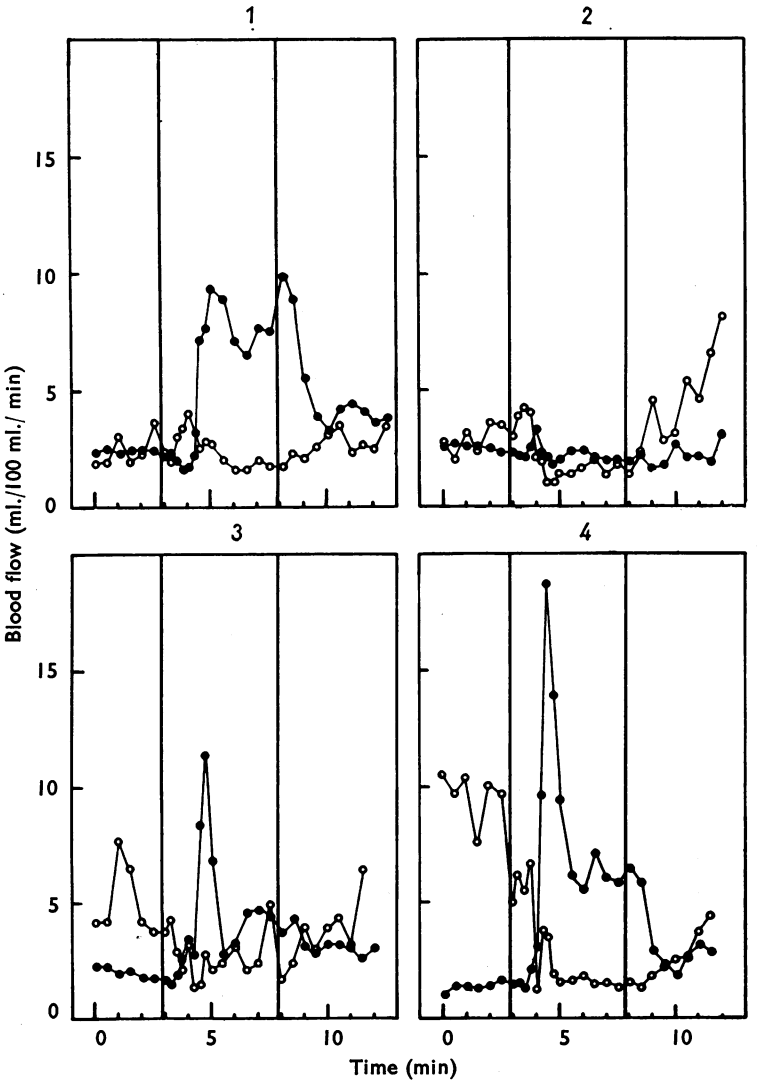

Fig. 6. The effects of intravenous infusions of (1) isoprenaline, 2 μg/min; (2) noradrenaline, 10 μg/min; (3) isoprenaline, 2 μg/min, and noradrenaline, 10 μg/min; and (4) adrenaline, 10 μg/min, on the flow of blood to the forearm (●——●) and the hand (○——○).

(panel 3) shows the response to a mixture of the two drugs in these same amounts. In the forearm there was an initial transient increase followed by a smaller sustained increase in flow. In the hand there was a decrease in flow during the period of the infusion. The responses were qualitatively the same in each of the four experiments, and the averaged results are shown in Fig. 7, which also shows the averaged responses to intravenous infusions of adrenaline (10 μg/min) in the four subjects. This result clearly demonstrates the strong resemblance between the responses to the mixtures and to adrenaline which is seen with both the forearm and the hand.

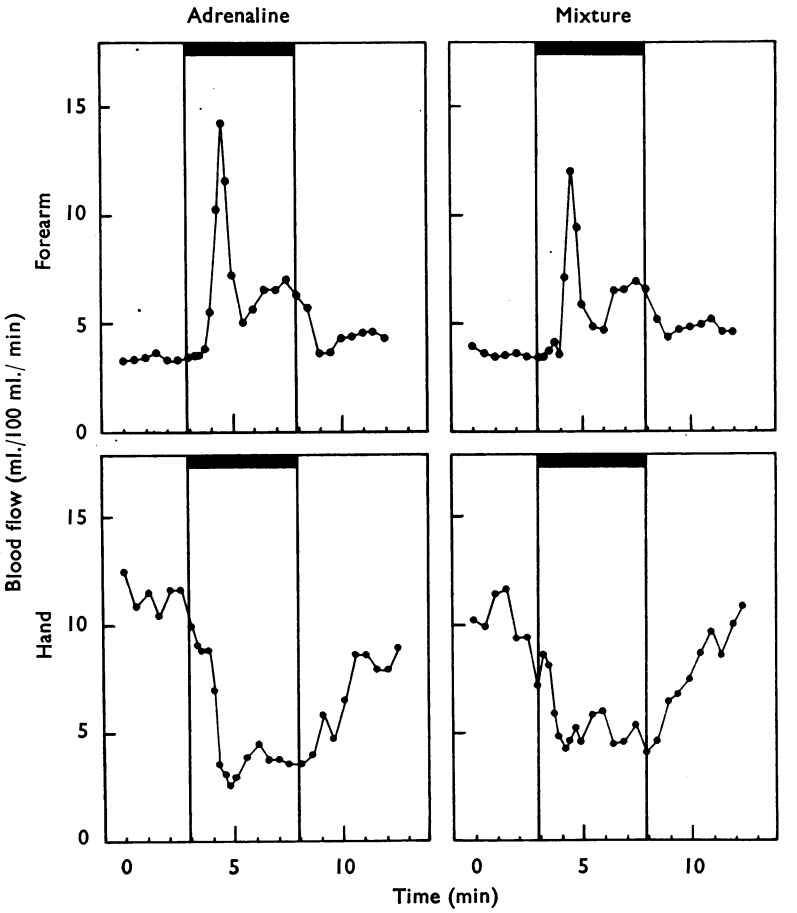

Fig. 7. The effects of intravenous infusions of adrenaline, 10 μg/min (left column), and a mixture of isoprenaline, 2 μg/min, and noradrenaline, 10 μg/min (right column), on the flow of blood to the forearm (above) and to the hand (below). Average of four experiments.

DISCUSSION

These experiments show that when a mixture of noradrenaline and isoprenaline is infused into the brachial artery the response strongly resembles that to the intra-arterial infusion of adrenaline. Because of the transient nature of the initial increase in blood flow no conclusions can be made from its size, but it appears that the subsequent fall to or below the resting level depends on the ratio of isoprenaline to noradrenaline in the mixture. As the dose of adrenaline is increased above 0.1 μg/min the vasoconstrictor effect becomes more marked. If the action of adrenaline on the blood vessels of the forearm is, as the experiments with blocking agents suggest, a balance between its vasoconstrictor and vasodilator effects, it appears that in this dose range (0.1 to 1.0 μg/min) the vasoconstrictor effect increases at a faster rate with increasing dose than the vasodilator effect. This conclusion

is supported by the fact that increasing the dose of both drugs in the mixture leads to an increased vasoconstriction.

It is known that the blood vessels to the skeletal muscle and to the skin of the forearm respond independently to many stimuli. Although the biphasic response to adrenaline does not appear to be due to the summation of independent changes occurring in these vessels (Allen, Barcroft & Edholm, 1946), it seemed possible that such a mechanism could account for the response to infusion of the mixtures of noradrenaline and isoprenaline. However the similarity of the responses to the mixtures and to adrenaline was also demonstrated in the experiments in which changes in thermal conductivity of the forearm skin were used to follow changes in blood flow in the vesels of the skin. These results indicate that the vessels of the skin responded in a similar manner to both infusions ; it is therefore assumed that the blood vessels in the skeletal muscles do likewise.

When adrenaline is infused intravenously in doses calculated to give approximately the same concentration in the blood reaching the forearm as is obtained during an infusion into the brachial artery, the initial increase in forearm blood flow is followed by a smaller but sustained increase in flow. In the hand such an infusion causes a fall in flow. Both these responses were matched in the present experiments by that to the intravenous infusion of a mixture of isoprenaline and noradrenaline.

Thus the actions of adrenaline on the forearm circulation can be explained on the basis of two types of catechol amine receptor as proposed by Ahlquist (1948). Ginsburg & Cobbold (1960) suggested that the action of adrenaline when given intra-arterially was due to initial stimulation of β-receptors followed by stimulation of α-receptors. This possibility is confirmed by our results, which alsc suggest that the initial response to stimulation of the β-receptors is greater than either the initial or the sustained response to stimulation of the α-receptors.

The mechanism of the sustained increase in forearm blood flow during the intravenous infusion of adrenaline has been the subject of much speculation. Lowe & Robinson (1963) suggest that adrenaline in low concentration causes vasodilatation and in high concentration vasoconstriction. On intra-arterial infusion the concentration of the drug varies with the response, thus favouring vasoconstriction ; on intravenous infusion the vasodilatation is no longer limited by a fall in concentration. A similar mechanism could explain the responses to intra-arterial and intravenous infusions of the mixture. This hypothesis therefore appears more attractive than the alternative suggested by Whelan (1952), namely, that some other vasodilator substance appears in the blood during the intravenous infusion of adrenaline.

Our results do not throw any light on the nature of the sympathetic receptors. It would be interesting to know if other actions of adrenaline in man and animals can be reproduced by mixtures of isoprenaline and noradrenaline.

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