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THE PERIPHERAL VASCULAR EFFECTS OF PROPRANOLOL AND RELATED COMPOUNDS

BY

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Propranolol has been shown to block the inotropic and chronotropic responses produced by the intravenous administration of isoprenaline, adrenaline and noradrenaline in anaesthetized dogs (Shanks, 1966a). The vasodepressor action of isoprenaline was abolished and the pressor response to adrenaline potentiated. The latter effects were attributed to blockade of the peripheral vasodilator actions of isoprenaline and adrenaline which occur to a large extent in the vascular bed of skeletal muscle (Whelan, 1952; Bowman, 1959; Green & Kepchar, 1959; Whelan & de la Lande, 1963). The experiments to be described in this paper were carried out in an attempt to verify this hypothesis. The effects of propranolol on the changes in blood flow to the hind limb of the anaesthetized dog produced by isoprenaline, adrenaline and noradrenaline have been studied. The effects of propranolol on hind limb blood flow were compared with those of two other β-receptor blocking agents—I.C.I. 45,763 (Shanks, Wood, Dornhorst & Clark, 1966); and MJ 1999 (Lish, Weikel & Dungan, 1965). Drugs were injected directly into the external iliac artery to restrict their action to a large extent to the vessels of the hind limb and thus eliminate the effects of changes in heart rate, cardiac output, arterial pressure and baroreceptor reflexes.

METHODS

Dogs weighing 10–30 kg were anaesthetized by the intravenous injection of thialbarbitone (30 mg/kg) followed by chloralose (60 mg/kg); supplementary doses of chloralose were given during the course of experiments when necessary to maintain anaesthesia. A cuffed endotracheal tube was inserted to assist spontaneous respiration. The right external iliac artery was exposed through a lower abdominal incision. A 3-cm length of the artery proximal to the deep femoral branch was dissected free from surrounding tissues but the accompanying nerves were left intact. A snugly fitting probe for an electro-magnetic flowmeter (Medicon, K2000) was applied to this section of artery. A polythene snare was passed round the artery distal to the probe to occlude the artery for zero-flow baseline determinations, which were obtained before and at regular intervals during each experiment. The flowmeter probe was calibrated at the end of each experiment by cannulating the external iliac artery and timing the collection of samples of blood over a wide range of flow rates. Circulation through the paw was prevented by applying a tourniquet tightly to the leg above the paw. This reduced the proportion of flow supplying the skin of the leg so that changes in

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muscle flow would contribute to a larger extent to any observed response. In three dogs the left renal artery was exposed through an incision in the flank. A suitable probe for an electromagnetic flowmeter was applied to the artery; zero-flow baseline determinations and calibrations of the probe were obtained as described above. Arterial pressure was recorded from a cannula in the left carotid artery with an inductive type differential pressure transducer (New Electronic Products). Heart rate was measured by means of a cardiotachometer triggered by the electrical activity of the QRS complex of the electrocardiograph (Horsfall, 1965). Heart rate, arterial pressure, phasic and mean flow were continuously recorded on a multi-channel tape recorder (Ampex SP 300 or Precision Instruments PI 6108). Mean flow was obtained by electrically integrating phasic flow. At the completion of each experiment the tape recorder was re-run at eight or ten times the recording speed and a permanent record of the responses obtained on an ink-writing recorder (Mingograph, Elema-Schonander). During the course of the experiment responses were displayed on a four-channel oscilloscope (Airmec).

Drugs were injected into the right external iliac artery through a fine polyethylene catheter (PP30) inserted into the deep femoral artery until its tip lay in the main artery, and into the renal artery through a polyethylene catheter (PP30) attached to a needle (No. 20) inserted directly into the artery distal to the probe. The catheters were filled wih heparinized saline. Drugs were injected into the arteries in a volume not exceeding 0.3 ml. and washed in with 0.3–0.5 ml. heparinized saline. A polyethylene catheter was inserted into a jugular vein for the injection of supplementary doses of chloralose and in a number of dogs for the intravenous administration of propranolol.

The following drugs were used: (−)-adrenaline bitartrate (Burroughs Wellcome); (±)-isoprenaline sulphate (Burroughs Wellcome); (−)-noradrenaline bitartrate (Winthrop); (±)-propranolol hydrochloride (Inderal, Imperial Chemical Industries Limited); (+)-propranolol hydrochloride; (−)-propranolol hydrochloride; (±)-pronethalol hydrochloride (Alderlin, Imperial Chemical Industries, Limited); I.C.I. 45,763 [1-isopropylamino-3-(3-tolyloxy)-2-propanol hydrochloride]; phenoxybenzamine hydrochloride (Smith, Kline & French); bradykinin (Sandoz); dichloroisoprenaline; MJ 1999 (Mead Johnson). Drugs were dissolved in 0.9% saline at the required concentration; doses are expressed in terms of the salt.

RESULTS

Effects of propranolol

The changes in blood flow through the external iliac artery in an anaesthetized dog produced by the injection of propranolol into the artery are shown in Fig. 1. The injection of propranolol, 0.01 mg/kg, produced a transient increase in flow. Larger doses produced progressively greater increases in flow. After the larger doses flow did not return to the control level but remained slightly above it. The administration of a second dose of propranolol (1 mg/kg) increased flow but to a slightly smaller extent than the first dose (Figs. 1 and 3). No change in arterial pressure occurred when propranolol was injected into the iliac artery but after the administration of 1.0 mg/kg there was a slight reduction in resting heart rate. Similar observations were made in nine dogs in which increasing doses of propranolol 0.001, 0.005, 0.01, 0.1 and 1.0 mg/kg were injected at intervals of at least 10 min. The mean increases in flow expressed as ml./kg body weight/min in response to each dose is shown in Fig. 2.

In three similar experiments increasing doses of (+)-propranolol were injected into the external iliac artery. The responses to (+)-propranolol were similar to those obtained with propranolol. The mean increase in flow for each dose of (+)-propranolol is given in Fig. 2. In two experiments (+)-propranolol (1 mg/kg) was injected after propranolol (1 mg/kg). The increases in flow produced by (+)-propranolol were similar to those obtained with propranolol (1 mg/kg) given after an initial loading dose of propranolol (Fig. 3). In two similar experiments (−)-propranolol (1 mg/kg) increased flow after propranolol to the same extent as (+)-propranolol (Fig. 3).

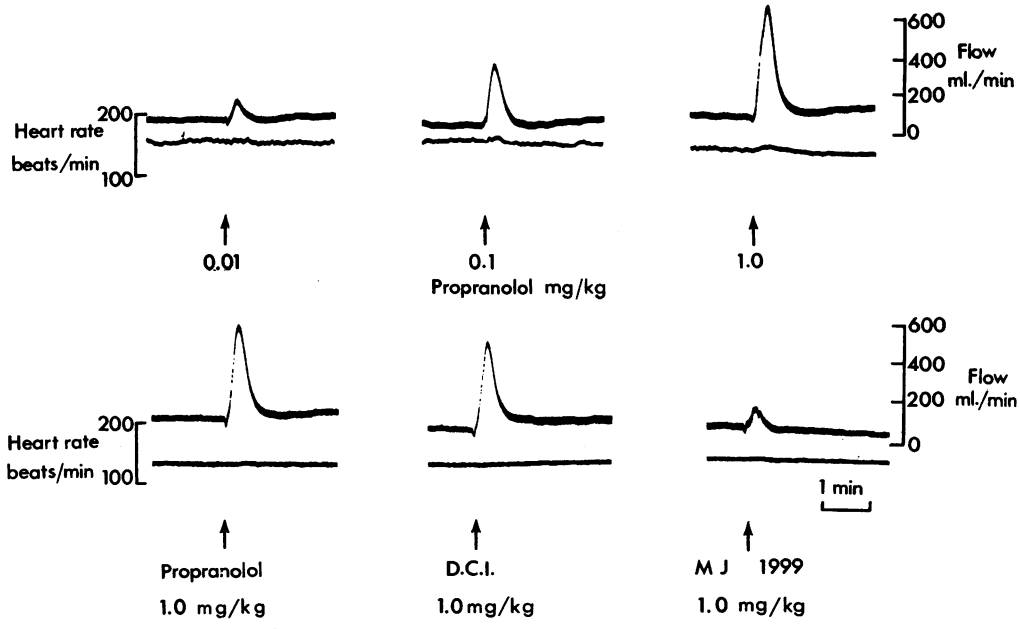

Fig. 1. Dog 15 kg, chloralose anaesthesia. Records of the rate of blood flow through the right external iliac artery and of heart rate. Responses produced by the injection into the artery of propranolol, dichloroisoprenaline (DCI) and MJ 1999.

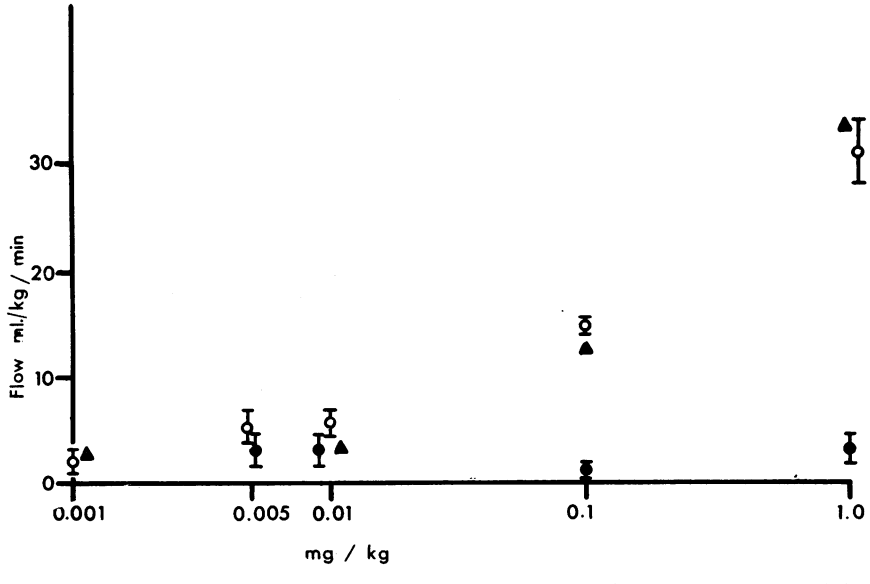

Fig. 2. Increases in hind-limb blood flow (ml./kg body weight/min) produced by the injection into the external iliac artery of propranolol (○), (+)-propranolol (▲) and MJ 1999 (●); mean of observations in 10, 4 and 3 dogs respectively.

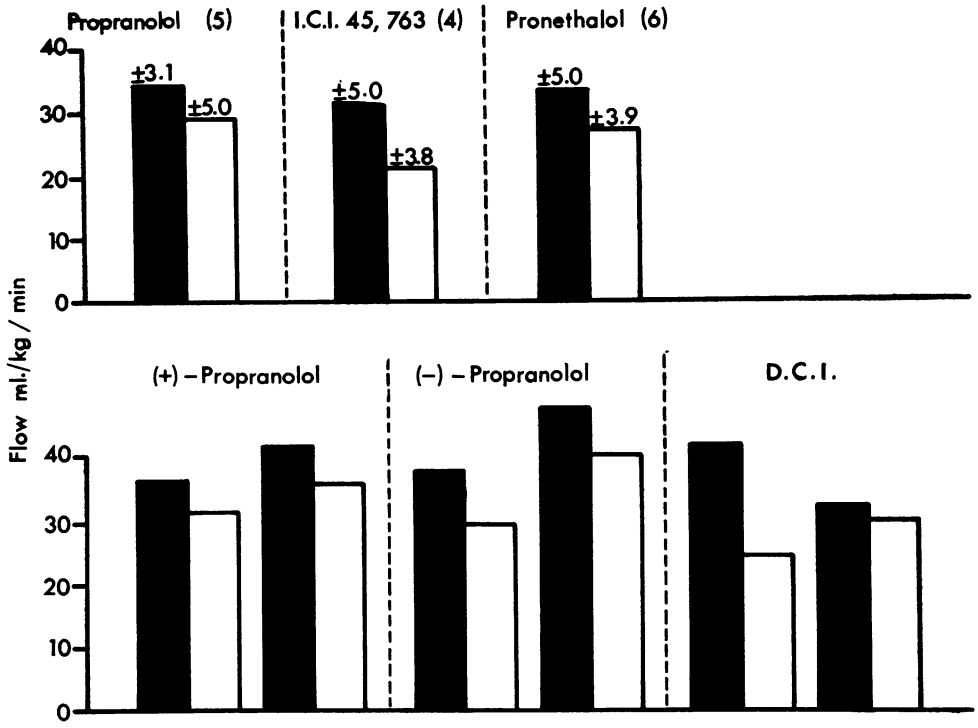

Fig. 3. Increases in flow (ml./kg body weight/min) to the hind limb of dogs produced by the injection into the external iliac artery of propranolol, 1 mg/kg (black column) followed by the same dose of either propranolol, I.C.I. 45,763, pronethalol, (+)-propranolol, (−)-propranolol or DCI (open column). The results in the upper panel are the mean of observations from the number of dogs shown in brackets; the standard errors of the mean are given. In the lower panel the results from two dogs for each compound are given.

In one dog propranolol, 0.1 and 1.0 mg/kg, was injected into the right external iliac artery after the leg was acutely denervated by cutting the right sciatic and femoral nerves. The injection of propranolol increased blood flow to the same extent as in a normal leg. In four dogs the administration of phenoxybenzamine (5 mg/kg) into the artery did not affect the vasodilator responses to propranolol. In another dog arterial inflow and venous outflow from the leg were measured by placing probes for electromagnetic flow-meters on both external iliac artery and vein. Propranolol was injected into the artery through a catheter in the deep femoral artery. The increases in arterial inflow produced by propranolol were accompanied by identical changes in venous outflow. Observations were also made in a dog in which the skin was completely removed from the right hind leg from the groin to the ankle and the leg then wrapped in warmed damp cotton wool. The usual vasodilator response was obtained when propranolol was injected into the external iliac artery.

The administration of MJ 1999 produced an increase in flow which was independent of the dose and much less than the maximum produced by propranolol (Figs. 1 and 2). In two separate experiments and in several experiments in which small doses of

propranolol had been given, a single dose (1 mg/kg) of pronethalol, I.C.I. 45,763 and dichloroisoprenaline (DCI), were given after propranolol (1 mg/kg). Pronethalol, I.C.I. 45,763 and DCI increased flow; the pattern of the response was similar to that obtained with propranolol except that after DCI it did not return to the control level (Fig. 1). The increases in femoral flow were always slightly less than that due to propranolol. These results are summarized in Fig. 3 which gives the increases in flow (ml./kg/min) produced by these three compounds and by the preceding dose of propranolol. In three experiments blood flow to the left kidney was measured. The injection of propranolol (1 mg/kg) into the left renal artery increased blood flow to the kidney. The maximum increases in flow were 5.45, 9.6 and 4.28 ml./kg body weight/min which is less than those obtained in the hind limb. The vasodilator response was more prolonged in the renal circulation and lasted approximately 90 sec.

Effect of propranolol on the responses to isoprenaline

Observations were made in eight dogs and the results of a typical experiment are shown in Fig. 4. A series of doses of isoprenaline were injected into the external iliac

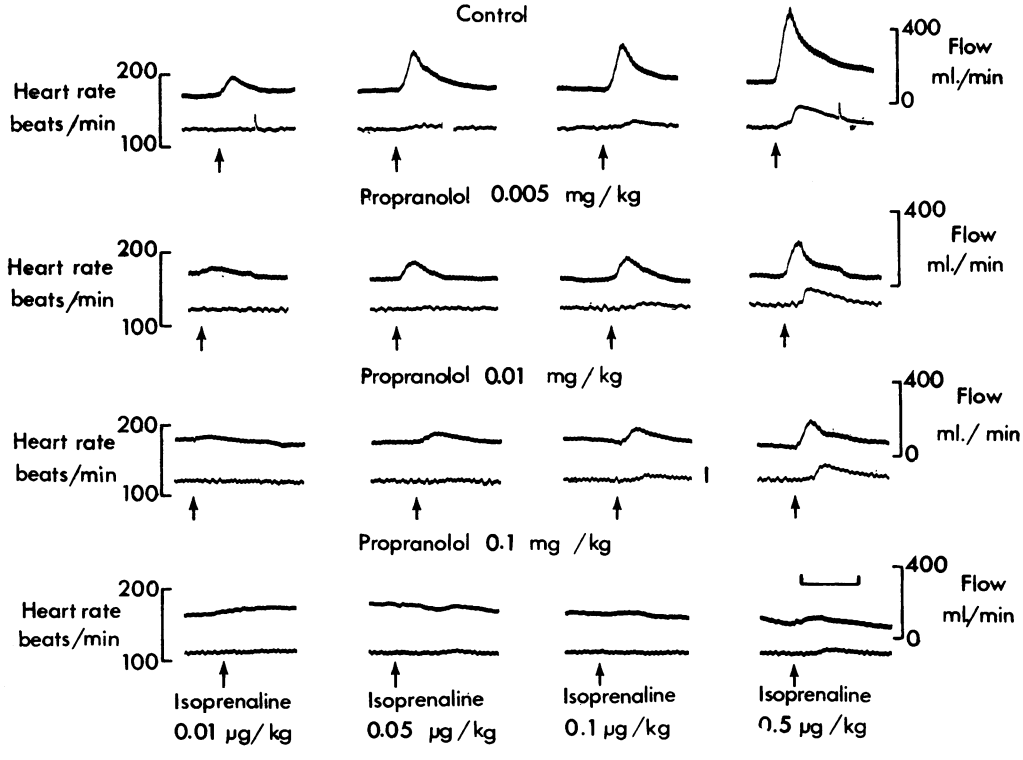

Fig. 4. Dog, 20 kg, chloralose anaesthesia. Records of blood flow through the right external iliac artery and of heart rate. Isoprenaline, 0.01, 0.05, 0.1 and 0.5 µg/kg was injected into the artery as indicated by the arrows. Responses to isoprenaline were obtained, from above downwards, during the control period and after the intra-arterial injection of propranolol 0.005, 0.01 and 0.1 mg/kg.

artery at 5–7 min intervals before and after the intra-arterial injection of each dose of propranolol. Isoprenaline increased blood flow ; the magnitude of the increase depended on the dose. The increases in flow were reduced after the administration of 0.005 and 0.01 mg propranolol/kg and abolished by 0.1 mg/kg. In each of the eight experiments five doses of isoprenaline in the range 0.005 to 1.0 μg/kg were given before and after 0.005, 0.01 and 0.1 mg propranolol/kg. The increases in flow expressed as ml./kg body weight/min produced by isoprenaline before and after propranolol in all the experiments have been averaged and some of the results are shown in Fig. 5. The effects of

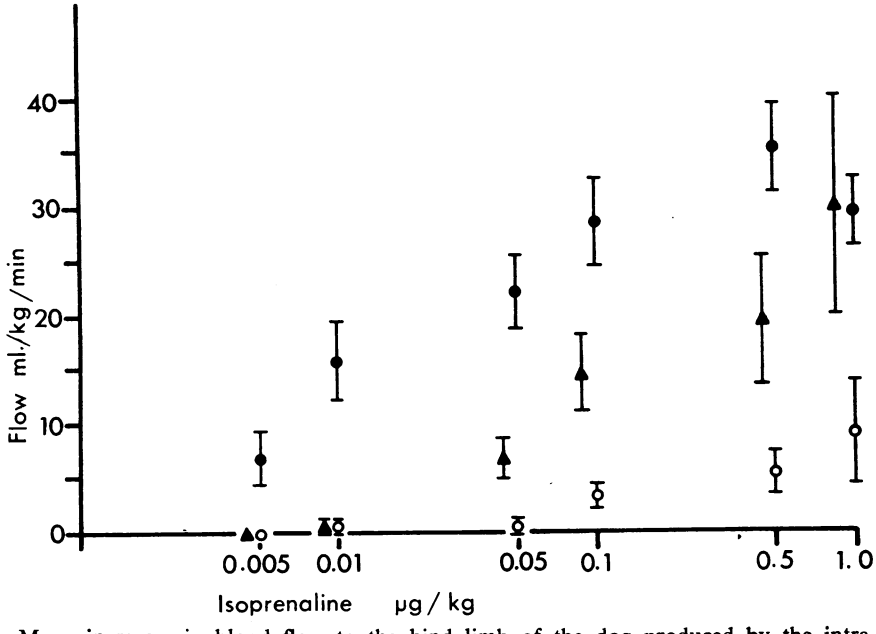

Fig. 5. Mean increases in blood flow to the hind limb of the dog produced by the intra-arterial injection of isoprenaline before (●) and after the intra-arterial injection of propranolol 0.01 (▲) and 0.1 (○) mg/kg. Standard errors of the mean are included.

propranolol (0.005 mg/kg) were not significantly less than those of 0.01 mg/kg. Propranolol (0.1 mg/kg) almost completely abolished the vasodilator responses to isoprenaline. In the experiment illustrated in Fig. 4 heart rate was recorded: the two larger doses of isoprenaline increased heart rate, presumably as a result of isoprenaline passing from the hind limb into the general circulation. These increases in heart rate still occurred after the administration of propranolol (0.005 and 0.01 mg/kg), when the vasodilator responses to isoprenaline were greatly reduced. When the dose of propranolol was increased to 0.1 mg/kg both resting heart rate and the isoprenaline tachycardia were reduced, indicating that with this dose an effective amount of propranolol also was entering the systemic circulation.

Similar observations were made in three dogs in which the effects of (+)-propranolol on the increases in femoral flow produced by isoprenaline were studied. In each dog five doses of isoprenaline (0.001, 0.005, 0.01, 0.05, 0.1 μg/kg) were injected intra-arterially at 6-min intervals before and after each dose of (+)-propranolol (0.01, 0.1 and 1.0 mg/kg).

The mean increases in flow in response to isoprenaline before and after each dose of propranolol in the three dogs are given in Fig. 6. The blocking effect of (+)-propranolol was much less than that of propranolol; the results indicate that (+)-propranolol had less than one-twentieth the blocking action of propranolol.

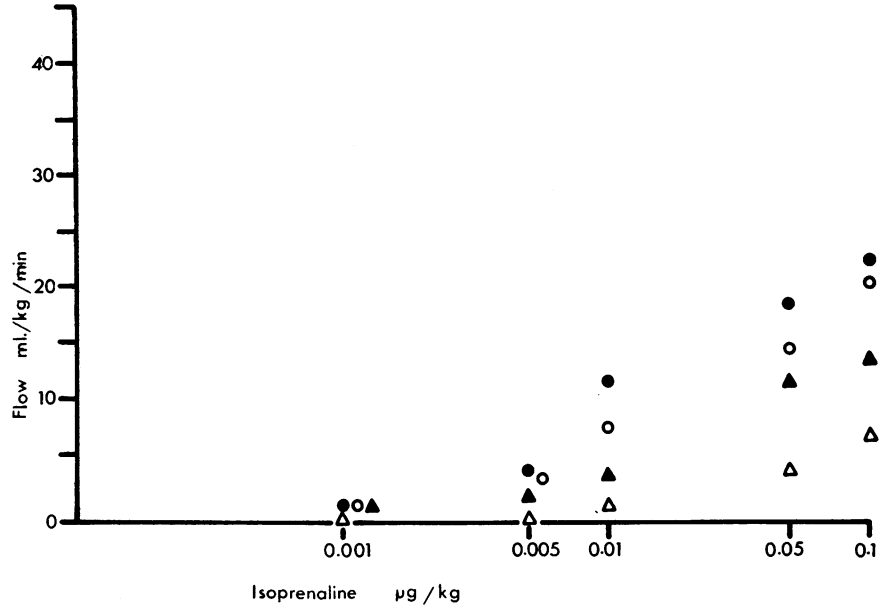

Fig. 6. Mean increases in hind-limb blood flow produced in three dogs by the intra-arterial injection of isoprenaline before (●) and after (+)-propranolol 0.01 (○), 0.1 (▲) and 1.0 (△) mg/kg.

Effect of propranolol on the responses to adrenaline

The changes in blood flow to the hind limb produced by the injection of adrenaline into the external iliac artery depended on the amount administered as is shown in Fig. 7, which contains the results of a typical experiment. The intra-arterial injection of adrenaline (0.01 μg/kg) produced a transient increase in flow followed by a fall to below the control level. A dose of 0.1 μg/kg produced an initial vasoconstriction followed by a marked increase in flow, which has been termed the " after-dilatation." A similar type of response was obtained after 1.0 μg/kg but the reduction in flow was more prolonged and the after-dilatation increased. These three doses of adrenaline were again given at 5-min intervals 5 min after the injection of propranolol (0.1 mg/kg) into the artery. Propranolol abolished the initial transient vasodilatation in response to adrenaline (0.01 μg/kg) and reduced the after-dilatation produced by 0.1 and 1 μg/kg. The vasoconstriction in response to the three doses of adrenaline was prolonged. After a larger dose of propranolol (1 mg/kg) the after-dilatation was abolished and the vasoconstrictor responses prolonged. Phenoxybenzamine 5 mg/kg, was then injected into the external iliac artery over a 5-min period. The subsequent injection of the three doses of adrenaline produced little change in flow. Similar results were obtained in three

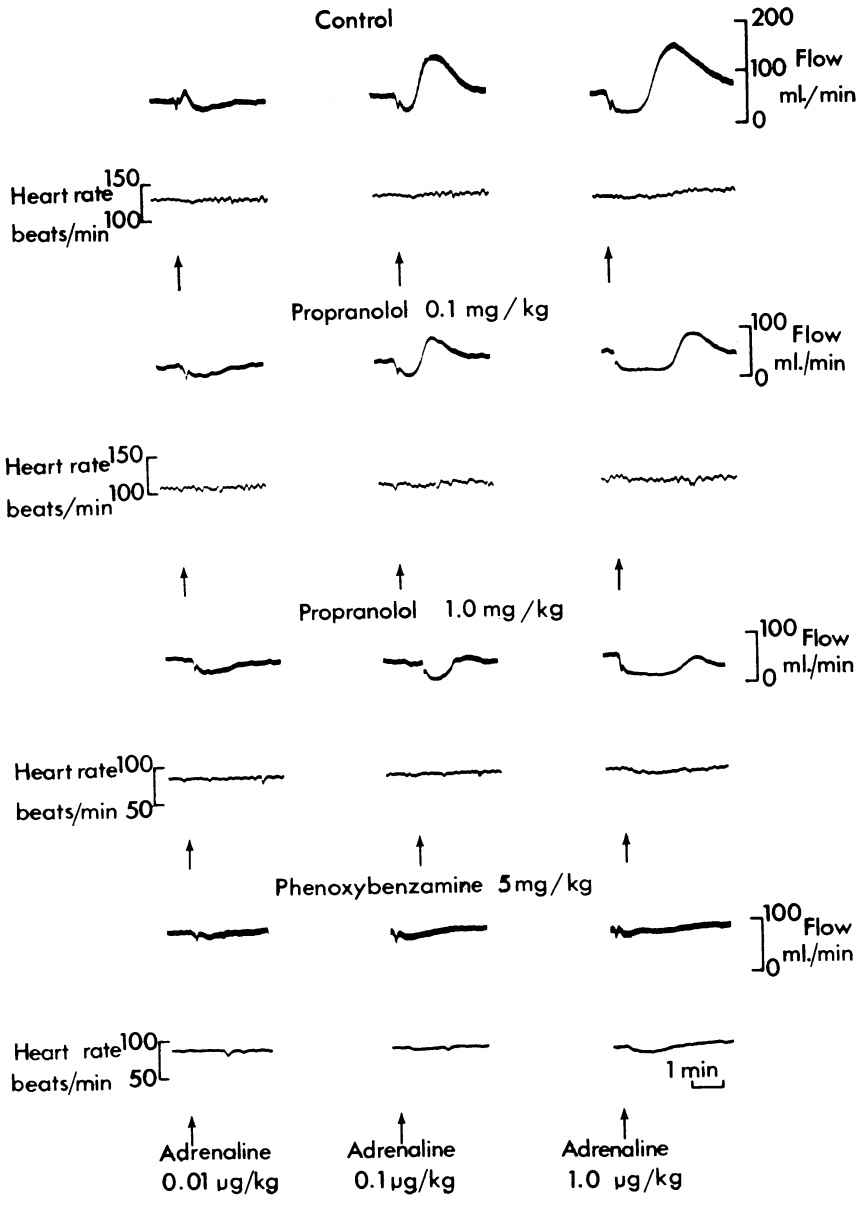

Fig. 7. Dog, 10 kg, chloralose anaesthesia. Records as in Fig. 2. Adrenaline, 0.01, 0.1 and 1.0 µg/kg was injected intra-arterially as indicated by the arrows. Responses were obtained, from above downwards, during the control period, after propranolol 0.1 and 1.0 mg/kg and after phenoxybenzamine 5 mg/kg. Propranolol and phenoxybenzamine were administered by intra-arterial injection.

other experiments. The small transient changes in flow occurring at the beginning of a response shown in the records in Fig. 7 are artifacts caused by washing in the test drug. Similar changes were produced by the injection of saline alone and are also seen in Figs. 1 and 9.

In five further experiments the changes in hind-limb blood flow produced by the intra-arterial injection of adrenaline (0.01, 0.1 and 1 μg/kg) were first recorded (Fig. 8). Phenoxybenzamine (5 mg/kg) was then injected slowly. When adrenaline was again injected each dose produced an increase in flow. After the intra-arterial injection of propranolol (0.01 mg/kg), the vasodilator responses to adrenaline were reduced; after

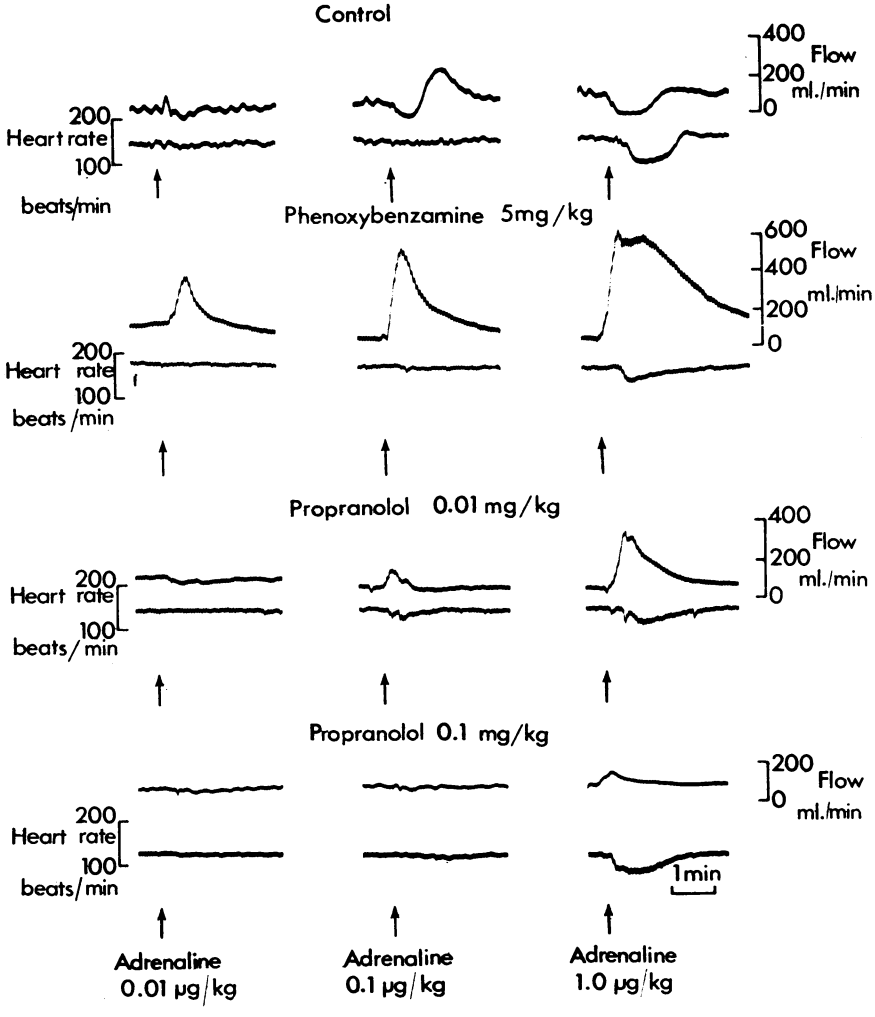

Fig. 8. Dog, 13 kg, chloralose anaesthesia. Records as in Fig. 2. Adrenaline, 0.01, 0.1 and 1.0 μg/kg was injected intra-arterially as indicated. Responses were obtained, from above downwards, during the control period, after phenoxybenzamine, 5 mg/kg, and after propranolol 0.01 and 0.1 mg/kg. Phenoxybenzamine and propranolol were injected intra-arterially.

propranolol (0.1 mg/kg) the injection of adrenaline (0.01 and 0.1 μg/kg) produced no change in flow and 1 μg/kg a slight increase. Similar observations were made in the other dogs. The mean increases in flow produced by each dose of adrenaline after phenoxybenzamine before and after propranolol (0.01 and 0.1 mg/kg) are shown in Fig. 9. Propranolol 0.1 mg/kg reduced the vasodilator responses to adrenaline to the same extent as it reduced the responses to isoprenaline.

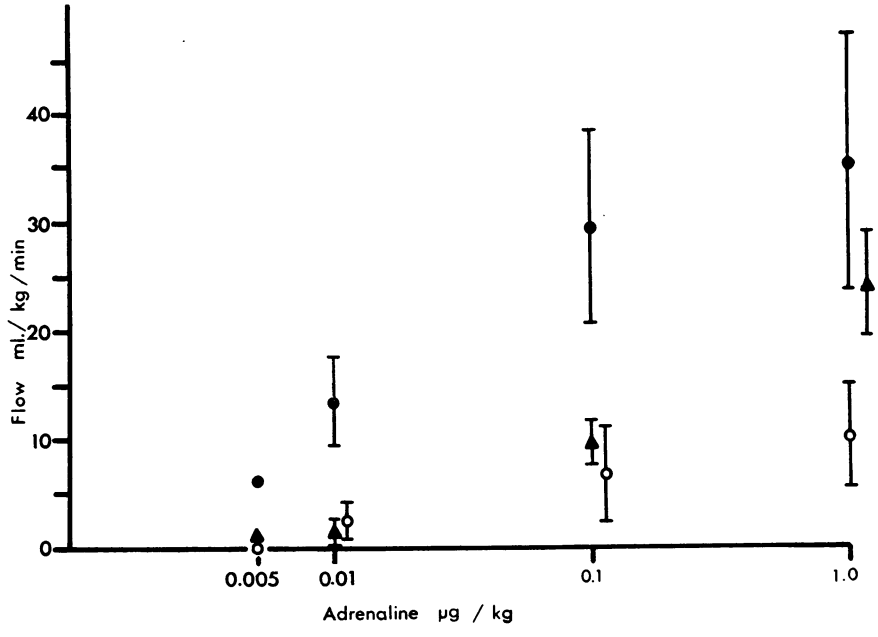

Fig. 9. Mean increases in blood flow produced by the intra-arterial injection of adrenaline in hind-limbs of dogs pretreated with phenoxybenzamine before (●) and after propranolol 0.01 (▲) and 0.1 (○) mg/kg. Standard errors of the mean are shown.

Effect of propranolol on the responses to noradrenaline

The injection of noradrenaline (0.001, 0.01, 0.1 and 1 μg/kg) into the external iliac artery reduced flow to the hind limb. These responses were not altered after the administration of propranolol. After treatment of the hind-limb with phenoxybenzamine (5 mg/kg) the intra-arterial injection of noradrenaline (0.01, 0.1, 1 and 5 μg/kg) increased blood flow. These vasodilator responses were reduced by the administration of propranolol. The mean increases in flow produced by each dose of noradrenaline before and after propranolol in four dogs are given in Fig. 10. Propranolol 0.1 mg/kg almost abolished the vasodilator response to noradrenaline.

Effect of propranolol on the responses to bradykinin

To see if the inhibition produced by propranolol of the vasodilator responses to isoprenaline and to adrenaline and noradrenaline after phenoxybenzamine was due to specific blockade of adrenergic β-receptors, the effect of propranolol on the vasodilator

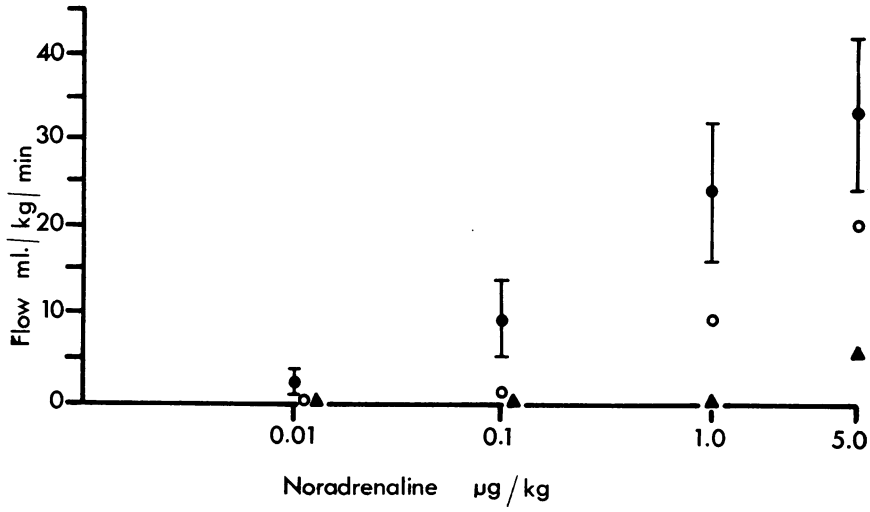

Fig. 10. Mean increases in blood flow produced by the intra-arterial injection of noradrenaline in hind-limbs of dogs pretreated with phenoxybenzamine before (●) and after propranolol 0.01 (○) and 0.1 (▲) mg/kg.

action of bradykinin has been studied. Observations were made in three dogs in which bradykinin (0.1 μg/kg) was injected into the external iliac artery before and after propranolol (0.1 mg/kg). Bradykinin increased blood flow to the hind limb; the percentage changes in the response to bradykinin after propranolol in the three experiments were −10, +10 and 0. These results indicate that propranolol did not inhibit the vasodilator action of bradykinin.

DISCUSSION

Dichloroisoprenaline (DCI) and pronethalol, unlike propranolol, possesses intrinsic sympathomimetic activity in addition to their action in blocking adrenergic β-receptors as they increase heart rate and produced a peripheral vasodilatation (Moran & Perkins, 1958; Black & Stephenson, 1962; Donald, Kvale & Shepherd, 1964; Black, Duncan & Shanks, 1965). In the present experiments the injection of propranolol into the external iliac artery increased hind-limb blood flow. A similar response was observed by Nakano & Kusakari (1965). This effect was not due to stimulation of adrenergic β-receptors as propranolol on repeated administration always increased flow. In addition the injection of the (+)- and (−)-isomers of propranolol, which have respectively one-fortieth and twice the β-blocking activity of propranolol (Howe & Shanks, 1966), increased blood flow to almost the same extent as propranolol. Similar patterns of response were obtained with pronethalol, DCI and I.C.I. 45,763 (Shanks *et al.*, 1966) when they were given after a loading dose of propranolol to abolish their sympathomimetic properties. The injection of MJ 1999, which has one-fourth the β-blocking activity of propranolol, produced little change in flow. Direct injection of propranolol into the renal artery increased renal blood flow, although the response was much smaller than

that in the hind-limb; vasodilator responses generally are smaller in the renal circulation (McNay & Goldberg, 1966). The vasodilator response to propranolol occurred in the skinned and in the acutely denervated leg and after complete blockade of adrenergic α-receptors.

The mechanism of this vasodilator action of propranolol is not clear. Propranolol has properties which do not result from blockade of adrenergic β-receptors (Somani & Lum, 1965; Howe & Shanks, 1966). It is a potent local anaesthetic as are pronethalol and I.C.I. 45,763 (Morales-Aguilerá & Vaughan Williams, 1965; Shanks, 1966b). This action is not a consequence of blockade of β-receptors as the local anaesthetic activity of the (+)- and (−)-isomers of propranolol are the same, while MJ 1999 is devoid of local anaesthetic activity (Lish *et al.*, 1965). In the present experiments the injection into the external iliac artery of adrenergic β-receptor antagonists which had local anaesthetic activity produced a vasodilatation. As this suggested that the vasodilator and local anaesthetic properties were related, we examined the vascular effects of procaine hydrochloride. The intra-arterial administration of procaine hydrochloride (1 and 10 mg/kg) to two dogs increased blood flow to the hind limb slightly; the response was more prolonged than that seen with propranolol (Shanks, unpublished). It can only be concluded that the vasodilator action of propranolol does not result from an effect on adrenergic β-receptors but may arise from its local anaesthetic properties. Propranolol has been shown to reduce arterial pressure in patients with hypertension (Prichard & Gillam, 1964), although its mode of action is not clear. It probably does not result from the vasodilator action described in the present experiments as this only occurred with the intra-arterial and not the intravenous injection of propranolol and was of short duration.

After the intra-arterial injection of small doses of propranolol (0.005 and 0.01 mg/kg) which produced no change in heart rate or arterial pressure, blood flow returned after the transient vasodilatation to the previous resting level. These results suggest that under the conditions of the present experiments there was no tonic activity of adrenergic β-receptors contributing to the control of peripheral vascular resistance. Similar findings were obtained in experiments on the human forearm (Brick, Hutchison & Roddie, 1966). On the other hand Nakano & Kusakari (1965) found that a vasoconstriction followed the vasodilator response to propranolol. Their observations were made in dogs with a thoracotomy and, as a result, under stress. This may increase circulating levels of adrenaline (von Euler, 1964) which would stimulate adrenergic β-receptors.

In the present experiments there was no evidence that isoprenaline stimulated adrenergic α-receptors as complete blockade of its vasodilator response did not unmask a vasoconstriction. Similar observations were made by Waelan, Sonneville, Ariëns & Simonis (1964). Adrenaline stimulates both α- and β-receptors in the peripheral vessels. The β-receptors appear to be more sensitive and to respond more rapidly to adrenaline, as smaller doses produce only a vasodilatation of rapid onset and when there is a biphasic response the vasodilatation occurs first. There is however concomitant stimulation of α-receptors with small doses of adrenaline, which is seen as a vasoconstriction after propranolol. The situation is reversed with larger doses of adrenaline when the α-receptor action—vasoconstriction—overrides the effect on β-receptors, which are still being stimulated as shown by the marked vasodilatation after treatment of the limb

with phenoxybenzamine. There is probably a critical dose of adrenaline above which the vasoconstrictor effect will override the vasodilatation. The dominance of the α-receptor effect may result from an excess of α-receptors or to a more powerful action when more than a critical number have been activated.

Although noradrenaline has been shown to stimulate adrenergic β-receptors in the heart (Ahlquist, 1948; Shanks, 1966a) and in tracheal smooth muscle (Foster, 1966) it has generally been accepted that it has no effect on these receptors in skeletal muscle vessels (Bowman, 1959; Green & Kepchar, 1959; Ginsburg & Cobbold, 1960; Waelen *et al.*, 1964). Youmans, Green & Denison (1955) showed in the hind-limb of the dog treated with phenoxybenzamine that noradrenaline produced a weak vasodilator response but this may not have resulted from stimulation of β-receptors as it was abolished by atropine and by larger doses of phenoxybenzamine. Recently Brick, Hutchison & Roddie (1966) have shown in the human forearm treated with phentolamine that noradrenaline increased blood flow, due to stimulation of adrenergic β-receptors. Similar findings have been made in the present experiments. Normally the effect of noradrenaline on adrenergic α-receptors completely overrides its weaker effect on β-receptors.

SUMMARY

1. Drugs were injected directly into the external iliac artery and the changes in the rate of blood flow through the artery recorded.

2. Propranolol produced a transient vasodilatation which was dependent on the dose.

3. After an initial dose of propranolol, the administration of 1 mg/kg propranolol, (+)-propranolol, (−)-propranolol, pronethalol, dichloroisoprenaline and I.C.I. 45,763 increased flow to the same extent. It is suggested that this effect may result from the local anaesthetic action of these compounds, as MJ 1999 produced little change in flow.

4. Propranolol was at least 10 times more active than its (+)-isomer in abolishing the vasodilator action of isoprenaline.

5. Propranolol blocked the vasodilatation produced by adrenaline and potentiated its vasoconstrictor effect. The vasodilatation in response to adrenaline and noradrenaline after phenoxybenzamine treatment was inhibited by propranolol.

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