THE EFFECT OF ISOPRENALINE ON THE BLOOD FLOW THROUGH INDIVIDUAL SKELETAL MUSCLES IN THE ANAESTHETISED CAT

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The effects of intra-arterially and intravenously administered isoprenaline on the venous outflow from individual skeletal muscles in the hind limbs of cats under chloralose anaesthesia were studied. By intra-arterial injection isoprenaline was more powerful in causing vasodilatation than adrenaline. The dilator response to intravenously administered isoprenaline was shown by cross-circulation techniques and by the use of a blood pressure stabiliser, to be reflexly inhibited by a vasoconstriction initiated by the fall in blood pressure. In the innervated muscle when vasomotor tone was high, intravenously administered adrenaline was more potent than isoprenaline in producing vasodilatation. The reverse was true in the acutely denervated muscle. The dilator response to isoprenaline was shown to be the result of a direct action on the muscle blood vessels; no evidence was obtained of a reflex dilatation, such as has been demonstrated with adrenaline and noradrenaline.

Adrenaline has been shown to cause vasodilatation in the skeletal muscles of the cat by a direct action on the blood vessels and by an action which is mediated through the nerves[1]. The local action of noradrenaline is vasoconstriction, but it, too, can cause a weak vasodilatation in skeletal muscles by a mechanism which involves the nerves[1]. Isoprenaline is known to possess a direct vasodilator action in skeletal muscles as well as in most other tissues[2–5].

The present experiments were designed to compare the vasodilator actions of isoprenaline and adrenaline and to find out whether or not a direct action on the blood vessels is the only mechanism by which isoprenaline produces its effects.

Methods

Cats were anaesthetised with chloralose only (80 mg./kg.) injected into the subcutaneous vein of the fore-limb.

The methods used for recording the venous outflow from the tibialis anterior, the gastrocnemius-plantaris or the soleus muscle and for the preparation of cross-perfusion experiments, in which the gastrocnemius muscle of one cat is supplied entirely by blood from a donor cat, were identical with those previously described[1,6]. The sciatic nerve was exposed high in the thigh to denervate during the experiments. Blood pressure was recorded from the right common carotid artery, a blood pressure stabiliser[7] being connected when required. Drugs were injected intravenously through a cannula in the jugular vein or intra-arterially from a microsyringe into a needle cannula in the cut central end of a branch of the femoral artery. The maximum volume of any solution

administered intra-arterially was 0·01 ml. and control saline injections of the same volume were made throughout each experiment. (For further details see previous paper[1].)

Solutions for injection were made in 0·9 per cent w/v NaCl saline. The drugs used were isoprenaline sulphate and (−)-adrenaline bitartrate. The doses quoted in the text refer to the quantity of amine calculated as base.

Results

Throughout the experiments similar responses were obtained whatever the muscle under study. The results to be described, therefore, apply to all three muscles, the tibialis anterior, the gastrocnemius-plantaris and the soleus.

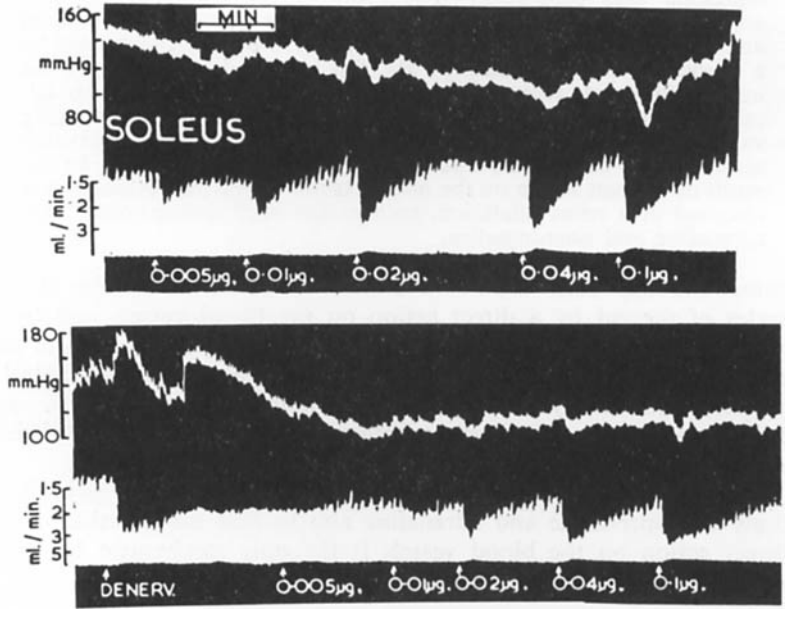

FIG. 1. Cat, 4·2 kg. The effect of intra-arterially administered isoprenaline in the innervated and acutely denervated muscle. Upper record: blood pressure recorded from carotid artery; lower record: venous outflow from soleus muscle.

Intra-arterially Administered Isoprenaline

Minimal effective doses of isoprenaline (0·002 to 0·01 μg.) caused vasodilatation in skeletal muscles and this response increased with increase in the dose up to a maximum with doses of 0·02 to 0·1 μg., after which further increase in the amount merely prolonged the effect. Figure 1 illustrates these results. The minimal effective doses of isoprenaline and adrenaline were similar but with increase in the dosage, the response to adrenaline gradually changed to vasoconstriction[1], whereas vasodilatation was produced by isoprenaline in all effective doses. With doses of equal size, the vasodilatation produced by isoprenaline was always longer lasting than that produced by adrenaline. During the hyperaemia

caused by acute denervation of the muscle, intra-arterially administered adrenaline only rarely caused vasodilatation. Isoprenaline, on the other hand, still caused a marked increase in venous outflow although the minimal effective doses were larger than those required in the innervated muscle (Fig. 1). After denervation, minimal effective doses of isoprenaline were equivalent in size to doses of adrenaline which, in the innervated muscle, produced the onset of vasoconstriction.

When administered intra-arterially, doses of adrenaline up to 3–4 μg. did not affect the general arterial blood pressure[1] but isoprenaline, administered by the same route, often caused a fall in blood pressure in doses as low as 0·05–0·1 μg. (Fig. 1).

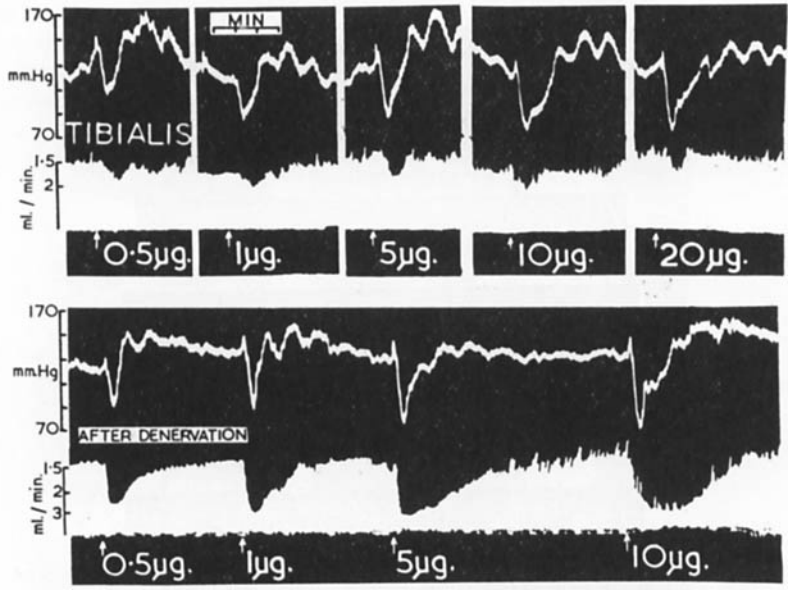

FIG. 2. Cat, 3·6 kg. The effect of acute denervation on the response to intravenously administered isoprenaline.

Intravenously Administered Isoprenaline

Intravenously administered isoprenaline caused a fall in blood pressure and vasodilatation in the skeletal muscles. Minimal effective doses which caused a fall in blood pressure were about 0·025 to 0·05 μg./kg. However, doses approximately four times larger were required to cause vasodilatation in the innervated skeletal muscles. In the acutely denervated skeletal muscles vasodilatation was produced by the smallest dose which caused a fall in blood pressure. In the innervated muscles the vasodilatation was invariably weak and hardly increased with increase in the dosage. It was often preceded by a brief passive reduction in flow as the blood pressure fell. After sectioning the sciatic nerve, intravenously administered isoprenaline produced a much greater increase in venous outflow and here the response increased with increase in dose

up to a maximum with doses of 3–4 μg./kg. after which any further increase merely prolonged the effect. The blood flow response to isoprenaline was increased after acute denervation whatever the original level of vasomotor tone in the muscle. Figure 2 illustrates an experiment in which the vasomotor tone in the innervated muscle was low as shown by the fact that acute denervation, later in the experiment, did not cause an increase in the rate of blood flow. In contrast, in the experiment illustrated by Figure 3, acute denervation caused a pronounced hyperaemia showing that vasomotor tone had originally been high. In both cases the vasodilator responses to isoprenaline were much more pronounced after denervation.

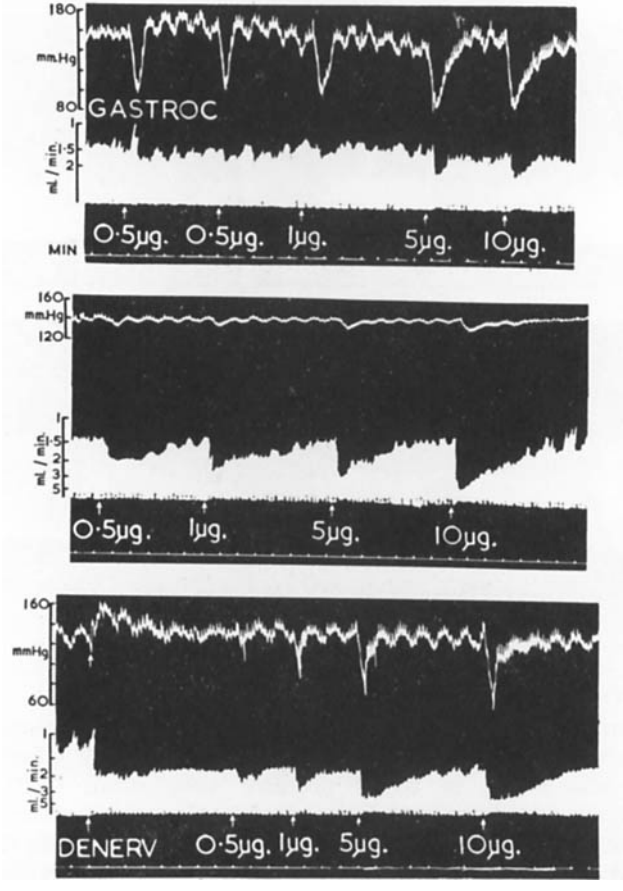

FIG. 3. Cat, 3·0 kg. The effect of stabilising the blood pressure (middle tracing) and of acute denervation (lower tracing) on the response to intravenously administered isoprenaline.

When the blood pressure stabiliser was connected to the carotid artery, the fall in blood pressure produced by intravenously administered isoprenaline was prevented and the vasodilatation produced in the innervated

muscle was very much greater than that which occurred when the blood pressure was allowed to fall (Fig. 3). These results combined indicate that vasodilatation produced by intravenously administered isoprenaline is inhibited in the innervated muscle by reflexes initiated by the fall in blood pressure. This conclusion was confirmed in cross-circulation experiments in which the muscle of one cat was perfused entirely by blood from a donor cat so that the only connection between the recipient cat and the muscle under study was by way of the nerves. In such experiments the intravenous administration of isoprenaline to the recipient cat caused a fall in blood pressure and vasoconstriction in the skeletal muscle. When the fall in blood pressure was prevented by means of the blood pressure stabiliser a similar administration to the recipient cat was without effect on the muscle blood flow. The intravenous administration of isoprenaline to the donor cat caused pronounced vasodilatation in the perfused muscle which was preceded by a short-lasting passive reduction in venous outflow as the blood pressure of the donor cat fell.

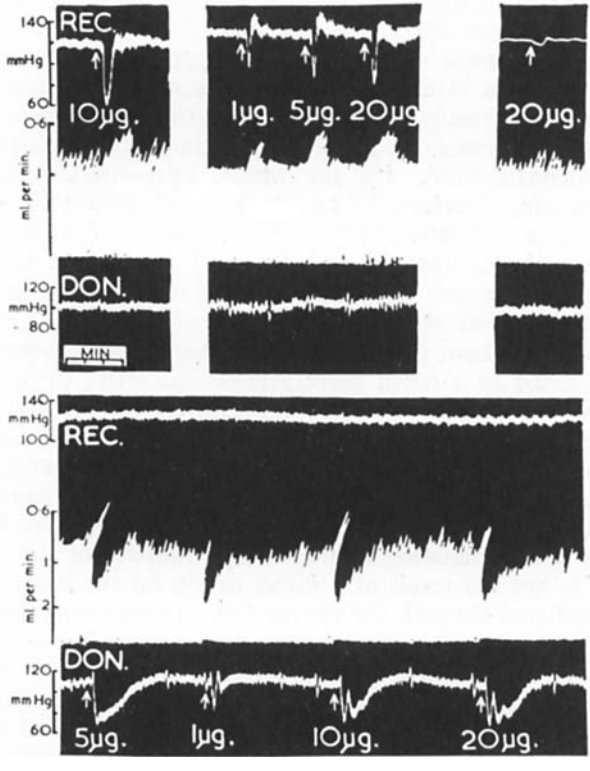

FIG. 4. Recipient cat, 3·5 kg.; donor cat, 2·7 kg. Cross-circulation experiment. REC, blood pressure of recipient cat; middle record, venous outflow from cross-perfused muscle; DON, blood pressure of donor cat. The doses of isoprenaline are marked under the blood pressure record of the cat to which they were intravenously administered. The upper tracing on the extreme right shows the effect of isoprenaline after stabilising the blood pressure of the recipient animal.

After acute denervation of the perfused muscle, the administration of isoprenaline to the recipient cat was without effect on the blood flow, while its administration to the donor cat caused effects similar to those produced before denervation. Figure 4 illustrates the results of a typical cross-perfusion experiment.

In the innervated muscle, particularly when vasomotor tone was high, intravenously administered adrenaline was much more powerful in producing vasodilatation than similar doses of isoprenaline. The reverse was true, however, in the acutely denervated muscle.

Discussion

The results obtained on intra-arterial administration confirm the finding by other workers[2–5] that isoprenaline causes vasodilatation in skeletal muscles by direct action on the blood vessels. When vasomotor tone is high, the degree of vasodilatation produced by small intra-arterial doses of isoprenaline is roughly equal to that produced by similar doses of adrenaline, although the effect with isoprenaline is slightly longer lasting. With larger doses, the response to adrenaline is converted to a reduction in venous outflow[1], while isoprenaline continues to cause pure vasodilatation in all doses. When vasomotor tone is low, either naturally or as a result of acute denervation, isoprenaline still causes vasodilatation whereas, in such circumstances, adrenaline frequently causes vasoconstriction[1]. On the whole, intra-arterially administered isoprenaline can, therefore, be said to be more potent than adrenaline in producing vasodilatation in the skeletal muscles of the cat. Working on human subjects, Barcroft and Konzett[4] found that intra-arterially infused isoprenaline was slightly less potent in producing vasodilatation than similar infusions of adrenaline.

The weak vasodilator response to intravenously administered isoprenaline is converted to a much more pronounced effect by sectioning the sciatic nerve. By the use of a blood pressure stabiliser and cross-circulation techniques, the dilator response to intravenously administered isoprenaline in the innervated muscle was shown to be reflexly inhibited by a vasoconstriction initiated by the fall in blood pressure.

Adrenaline and, to a smaller extent, noradrenaline have been shown to produce a vasodilatation in the skeletal muscles of the cat and the dog which is not the result of a direct action on the blood vessels but which is mediated through the nerves[1,8–12]. In cross-circulation experiments, the administration of adrenaline or noradrenaline to the recipient animal causes vasodilatation in the perfused muscles[1,8–12]. The present experiments showed, on the other hand, that a similar administration of isoprenaline causes vasoconstriction. When the blood pressure of the recipient cat is stabilised, the vasoconstriction is abolished but there is still no evidence of vasodilatation. It must be concluded, therefore, that vasodilatation produced by isoprenaline in the skeletal muscles of the cat is entirely the result of a direct action on the blood vessels.

Gruhzit, Freyburger and Moe[12] have provided evidence that in the dog vasodilatation produced by intravenously administered adrenaline

and noradrenaline is mainly brought about by a reflex mechanism, the afferent source of which is mechanoreceptors along the wall of the thoracic aorta, activated by the inotropic cardiac action of these amines.

The inotropic cardiac action of isoprenaline has been shown to be more powerful than that of adrenaline[2,13,14] and yet no reflex vasodilatation could be demonstrated with this substance in the present experiments on the cat. The results obtained with isoprenaline, therefore, supply evidence that it is not the inotropic cardiac action of adrenaline and noradrenaline which is responsible for the nervously activated vasodilatation produced in the skeletal muscles of this species. Taylor and Page[15] demonstrated a reduction in pressure in the trunk when adrenaline or noradrenaline was administered to the perfused head, the only connection between the head and the trunk being the spinal cord. Since the response was independent of pressure changes they concluded that it was due to chemoreceptors in the cephalic circulation. Such a mechanism might be the explanation of the reflex vasodilatation produced in the skeletal muscles of the cat by adrenaline and noradrenaline.

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