J. Physiol. (1958) 144, 92–107

THE EFFECTS OF ADRENALINE, NORADRENALINE AND ISOPRENALINE ON SKELETAL MUSCLE CONTRACTIONS IN THE CAT

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(*Received* 2 *April* 1958)

Adrenaline, noradrenaline and other sympathomimetic amines have been shown to increase the maximal twitch tension of unfatigued skeletal muscles (Oliver & Schaefer, 1895; Gruber, 1922*a*, *b*; Goffart & Brown, 1947; West & Zaimis, 1949; Brown, Goffart & Vianna Dias, 1950; Goffart & Ritchie, 1952; Huidobro, Cubillos & Eyzaguirre, 1952; Goffart, 1952, 1954; Montagu, 1955). This response, however, is not characteristic of all skeletal muscles. In fact the present experiments show that, in the cat, slow contracting muscles such as the soleus respond in a completely opposite way. A short account of the results has already been published (Bowman & Zaimis, 1955).

METHODS

Cats were anaesthetized either with chloralose only (80 mg/kg) or with a mixture of chloralose (80 mg/kg) and pentobarbitone sodium (6 mg/kg), injected into a subcutaneous vein of the forelimb or into the saphenous vein of the hind limb.

Recording of muscle contractions

The tibialis anterior and soleus muscles were prepared for recording and the hind limb was pinned and fixed horizontally to a Brown-Schuster myograph stand. When indirect stimulation of the muscles was required, shielded silver electrodes were placed on the sciatic nerve and the nerve was ligated central to the electrodes. Twitches and tetani were excited by square wave pulses of 0·2 msec duration and twice the strength required to evoke a maximal twitch. In experiments in which curarized muscles were directly excited, stimuli of maximal strength and 0·5 msec duration were applied between the tendon of the muscle and the drill in the femur. Electrical contact with the tendon was made through silver wire attached to a saline-soaked pad of cotton-wool. In order to ensure that the current supplied for direct stimulation was not short-circuited through the other tissues, the muscles were insulated by enclosing their bellies in a rubber fingerstall smeared with liquid paraffin. Muscle tension was recorded either on the smoked drum by means of an isometric steel-spring myograph or electrically using a capacitance strain gauge.

Recording of the venous outflow

An incision was made in the skin on the medial surface of the thigh to expose the femoral artery and vein, and, with the exception of the artery chosen for the intra-arterial administration of drugs, all branches of the femoral artery and vein down to the popliteal space were ligated and cut. This involved the removal of part of the gracilis muscle in order to tie off a few small branches of the artery and vein which supply this muscle.

An incision was then made in the skin along the mid line of the back of the leg to expose the popliteal space and the gastrocnemius muscle, and a further incision was made along the medial side of the leg to expose the tibialis posterior artery and vein lying between the soleus and flexor longus hallucis muscles.

Soleus muscle. For the recording of the venous outflow from the soleus muscle the popliteal artery and vein were tied below the tibialis posterior artery and vein. All branches arising from the two last-named, except those supplying the soleus muscle, were then ligated. The popliteal artery and vein pass between the two heads of the gastrocnemius muscle, near their origin, and at this point a small artery and vein arise carrying blood to and from this muscle. In order to overcome the difficulty of reaching these vessels, the medial head of the gastrocnemius was twice ligated near its origin, the muscle cut between the two ligatures and the exposed vessels tied. Finally, the remaining vessels supplying the muscles surrounding the popliteal space were ligated. Thus the blood flow in the femoral artery and vein was only that of the soleus muscle.

Tibialis anterior muscle. For the recording of the venous outflow from the tibialis anterior muscle the anterior tibial artery and vein were ligated near the ankle joint, thus cutting off the circulation of the foot. All branches and tributaries of the anterior tibial artery and vein were then tied, except those supplying the tibialis anterior muscle. Finally, all remaining branches of the popliteal artery and vein were ligated.

The skin was then sewn back into position and the leg mounted horizontally on a Brown-Schuster myograph stand. For the recording of the blood flow, the flowmeter described by Hilton (1952, 1953) was used. Ten minutes before the cannulation of the vein, heparin (1000 u./kg) was administered intravenously. At the end of each experiment indian ink was injected through the arterial cannula in order to ascertain that the blood flow was in fact only that of the muscle under study.

Administration of drugs

Drugs were injected intravenously or intra-arterially. For the intra-arterial administration a cannula made from a hypodermic needle was tied into the cut central end of a branch of the femoral artery, usually the small artery supplying the gracilis muscle. A micro-syringe was used for the administration of the drugs. Thus a minute volume could be injected straight into the blood stream of the femoral artery; 0·01 ml. was the maximum volume of any solution administered. The same volume of 0·9% saline was used as a control.

Stimulation of splanchnic nerves and of the lumbar sympathetic chain

When the effects of splanchnic stimulation were studied, the left splanchnic nerve was prepared and stimulated by means of silver hook electrodes. In experiments in which the effects of stimulation of the lumbar sympathetic chain were studied, muscle contractions were elicited by stimulation of the motor roots. The preparation was that described by Bülbring & Burn (1939).

Drugs

The sympathomimetic amines used were L-adrenaline bitartrate, L-noradrenaline bitartrate and isoprenaline sulphate. The doses quoted in the text refer to the quantity of amine calculated as base. All solutions were made in 0·9% (w/v) NaCl saline.

RESULTS

Twitch

All three amines, adrenaline, noradrenaline and isoprenaline, administered intravenously or intra-arterially increased the twitch tension of the tibialis anterior and decreased that of the soleus muscle.

Fig. 1 illustrates an experiment in which the maximum twitch tension of the tibialis anterior and soleus muscles were recorded simultaneously on a

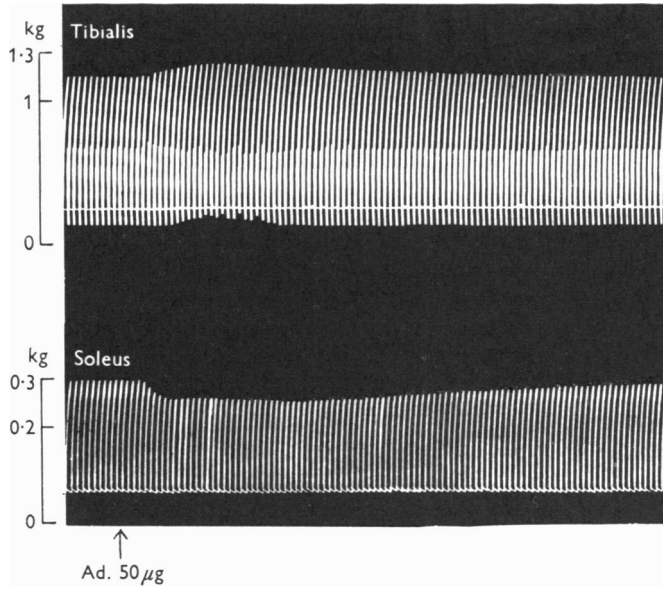

Fig. 1. Cat, 2·8 kg. Simultaneous recording of indirectly excited maximal twitches of the tibialis anterior and soleus muscles once every 10 sec. At arrow, 50 μg adrenaline administered intravenously.

smoked drum. 50 μg of adrenaline injected intravenously produced an increase in the twitch tension of the tibialis but a decrease in that of the soleus muscle. Figs. 2 and 3 show the effect of adrenaline on the time course of isometric twitches recorded electrically. In the experiment illustrated by Fig. 2 an intra-arterial injection of 10 μg of adrenaline increased the twitch tension of the tibialis anterior muscle by 13% and altered its time course; the rate of development of tension was slightly diminished, the time to peak tension was increased by 15% and the over-all duration of the twitch by 17%. On the other hand, in the experiment illustrated by Fig. 3 an intravenous injection of 5 μg/kg of adrenaline not only decreased the twitch tension of the soleus muscle by 18%, but markedly altered the time course of the contraction. The

time to peak tension was reduced by 25%, the duration of the twitch by 33% and the rate of relaxation was markedly increased. Results such as those illustrated by Figs. 2 and 3 are typical of all three sympathomimetic amines.

Of the three amines, isoprenaline was slightly more potent than adrenaline in producing these effects, and noradrenaline was the least potent. The minimal effective doses are shown in Table 1.

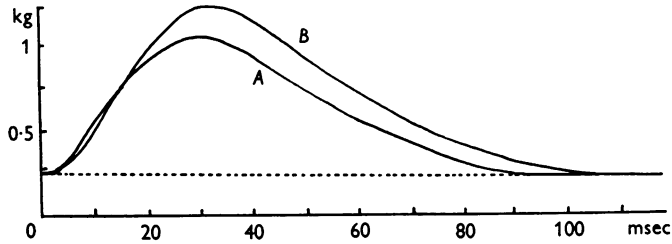

Fig. 2. Maximal twitches of the tibialis anterior muscle elicited by indirect stimulation once every 10 sec and recorded electrically, *A*, before adrenaline and *B*, 120 sec after the intra-arterial injection of 10 μg adrenaline.

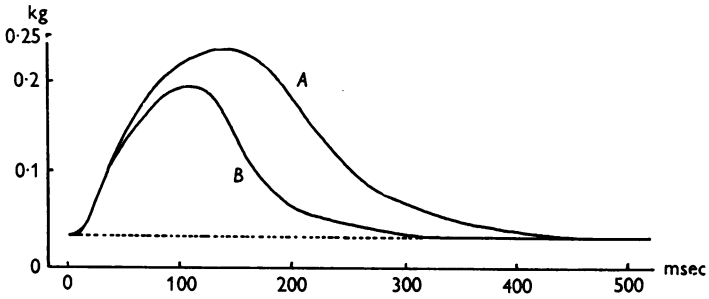

Fig. 3. Cat, 3·1 kg. Maximal twitches of the soleus muscle elicited by indirect stimulation once every 10 sec and recorded electrically, *A*, before adrenaline and *B*, 70 sec after the intravenous administration of 15 μg adrenaline.

TABLE 1

	Minimal effective intravenous dose (μg/kg) of		
Muscle	Adrenaline	Noradrenaline	Isoprenaline
Tibialis anterior	3–10	5–15	2–8
Soleus	0·06–0·5	5–20	0·06–0·4

Although the sensitivity of the soleus to adrenaline and isoprenaline is much greater than that of the tibialis anterior muscle, there is little difference between the doses of noradrenaline required to affect them. This makes the soleus muscle approximately 50 times less sensitive to noradrenaline than to adrenaline and isoprenaline.

The time course of the effects of all three amines is similar in both muscles. The effect usually starts 20–40 sec after the intravenous or intra-arterial

administration of the drug and reaches its peak 40–60 sec later. The duration of the effect depends on the magnitude of the dose and may last 12–15 min after amounts producing maximum responses have been administered. 16% was the maximum increase in twitch tension recorded from the tibialis anterior and 20% the maximum decrease from the soleus muscle.

Tetanus

As was expected from the results obtained with the single twitch all three amines increased the submaximal tetanic tension (maximum tension developed during an incomplete tetanus) of the tibialis anterior and decreased that of the soleus muscle. In the experiment illustrated by Fig. 4 the response of the

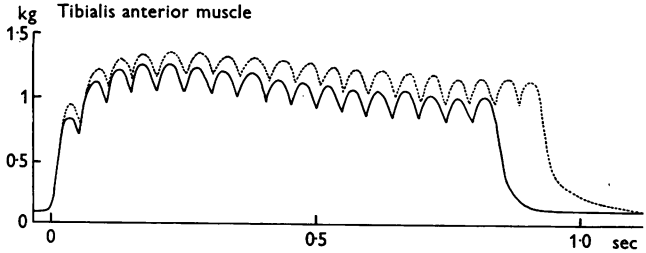

Fig. 4. Cat, 2 kg. Electrically recorded tetani of the tibialis anterior muscle elicited indirectly with supramaximal shocks at a frequency of 20/sec. ———, before adrenaline; – – – –, 140 sec after the intravenous administration of 30 μg of adrenaline.

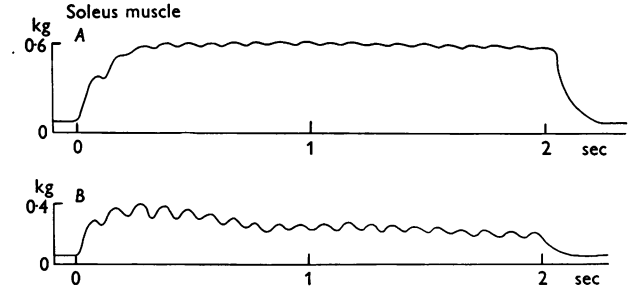

Fig. 5. Cat, 2·5 kg. Electrically recorded tetani of the soleus muscle elicited indirectly with supramaximal shocks at a frequency of 10/sec, *A*, before adrenaline; and *B*, 140 sec after intravenous administration of 12 μg of adrenaline.

tibialis anterior muscle to a stimulation frequency of 20/sec was electrically recorded before and after adrenaline. After adrenaline the tension developed was greater and fusion was facilitated. Fig. 5 illustrates the results of a similar experiment on the soleus muscle. After adrenaline the tension developed was less and the degree of fusion markedly decreased. Fig. 6 illustrates similar effects on the soleus muscle with isoprenaline. Tetani of 3 sec duration and 14/sec frequency were recorded every 30 sec on a rapidly revolving smoked

drum. After 5 μg/kg of isoprenaline had been administered intravenously, the tension and the degree of fusion progressively decreased so that 90 sec later the muscle relaxed almost completely between stimuli.

The lower the frequency of stimulation the more marked the effects obtained. For example, in one experiment 30 μg of adrenaline, administered intravenously, increased the submaximal tetanic tension of the tibialis anterior muscle by 11·5% when the frequency of stimulation was 14/sec, by 3·6% when the frequency was 20/sec and by 1% when the frequency was 50/sec. In another experiment, the intravenous administration of 15 μg of isoprenaline decreased the submaximal tetanic tension of the soleus muscle by 36% when the frequency of stimulation was 10/sec, by 18% when the frequency was 14/sec, by 7% when the frequency was 23/sec and was without effect when the frequency was 30/sec.

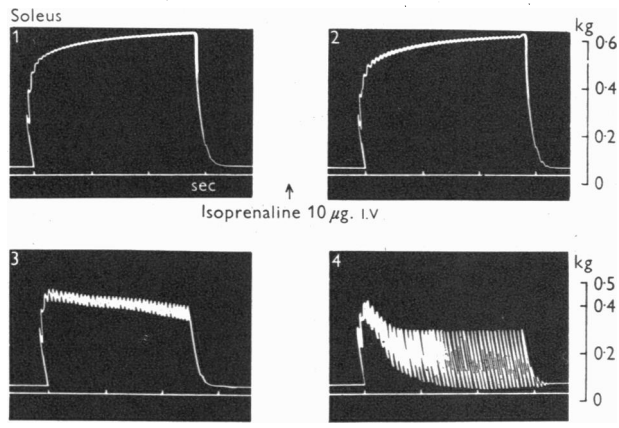

Fig. 6. Cat, 2·2 kg. Electrically recorded tetani of the soleus muscle elicited indirectly every 30 sec by stimulation with supramaximal shocks at a frequency of 14/sec. 1, before isoprenaline; 2, 3 and 4, after the intravenous administration of 10 μg of isoprenaline.

The doses of the three sympathomimetic amines needed to affect a tetanus were similar to those needed to affect the single twitch. Adrenaline, noradrenaline and isoprenaline administered intravenously or intra-arterially in doses not causing a marked vasoconstriction were without effect on the maximum tetanic tension of either muscle.

Concomitant blood-flow changes. The majority of workers have concluded that the effects of the sympathomimetic amines on skeletal muscles are independent of blood-flow changes; in most cases, however, the evidence is indirect. In order to obtain more direct information, in the present experiments the action of the sympathomimetic amines on the blood flow through the muscle under study was simultaneously recorded.

Isoprenaline, injected intravenously or intra-arterially, always increased the

blood flow through the muscle. On the other hand, whereas an intra-arterial injection of noradrenaline always decreased the blood flow, an intravenous one produced, according to its magnitude and its effect on the general blood pressure, either a decrease or a biphasic response. Finally, adrenaline produced an increase, a decrease or a biphasic response by either route of administration, again according to the dose and the general blood-pressure effect.

Whatever the blood-flow response the effects of the three sympathomimetic amines on the single twitch remained unaltered. Such results are illustrated by Figs. 7 and 8. In another series of experiments, in which the vasoconstrictor

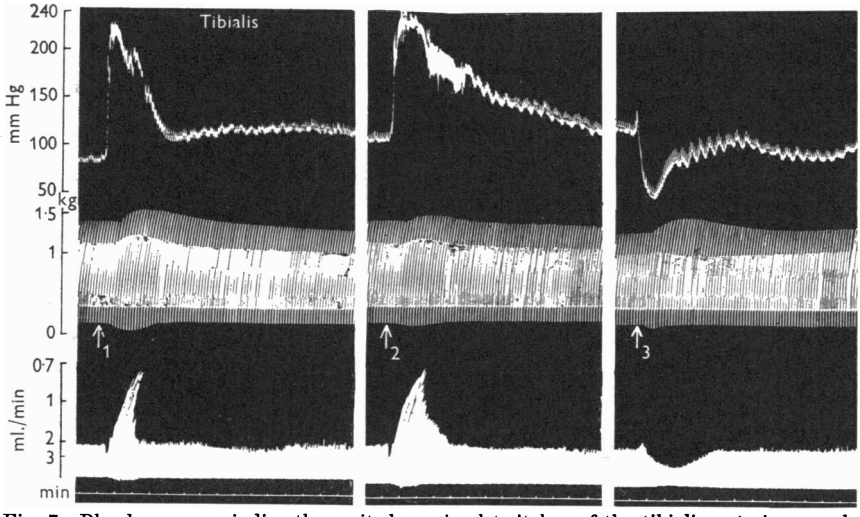

Fig. 7. Blood pressure, indirectly excited maximal twitches of the tibialis anterior muscle and venous outflow from the tibialis anterior muscle recorded simultaneously. At arrow (1), 50 μg of adrenaline; at arrow (2), 50 μg of noradrenaline and at arrow (3), 50 μg of isoprenaline administered intravenously at intervals of 1 hr.

action of adrenaline and noradrenaline was abolished by the previous administration of dibenamine or phentolamine, the sympathomimetic amines produced the usual effects on muscle contraction.

Tetanic contractions, however, may be altered by a powerful vasoconstriction. For example, adrenaline or noradrenaline in large doses may cause depression of the submaximal or maximal tetanic tension of the tibialis anterior muscle. Fig. 9 illustrates this effect. Both vasoconstriction and reduction of tetanic tension were more pronounced after noradrenaline. That this reduction of the tetanic tension is due to a decreased blood flow was further confirmed in experiments in which dibenamine or phentolamine were previously administered. In such experiments when the vasoconstrictor action of adrenaline and noradrenaline was reduced or abolished, the reduction of the tetanic tension did not occur. The maximum tetanic tension of the soleus

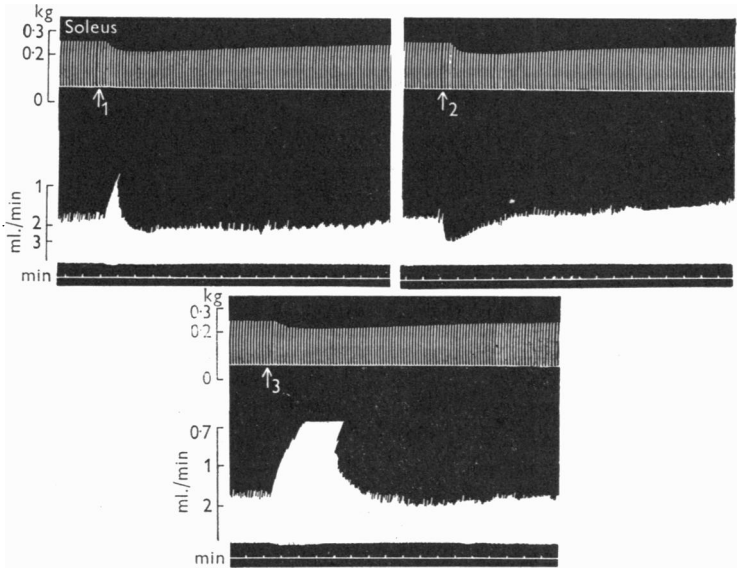

Fig. 8. Cat, 4·5 kg. Indirectly excited maximal twitches and venous outflow from the soleus muscle recorded simultaneously. At arrow (1), 1 μg of adrenaline; at arrow (2), 1 μg of isoprenaline and at arrow (3), 5 μg of noradrenaline administered intra-arterially at intervals of 30 min.

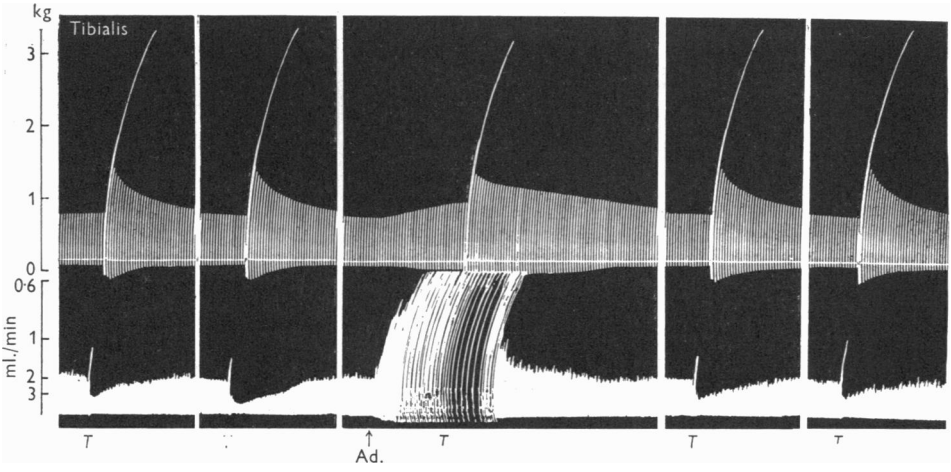

Fig. 9. Cat, 3·3 kg. Maximal twitches elicited by indirect stimulation every 10 sec and venous outflow from the tibialis anterior muscle recorded simultaneously. *T* = tetanus of 2 sec duration and 120/sec frequency, interpolated every 15 min; at arrow, 10 μg of adrenaline administered intra-arterially.

muscle, however, was never reduced even in the presence of a marked vasoconstriction.

Direct stimulation. In order to study the effects of the three sympathomimetic amines on the twitch and tetanic tensions of the directly stimulated tibialis and soleus muscles, the drugs were administered after neuromuscular transmission was completely blocked by a slow continuous infusion of tubocurarine. In both muscles the effects produced were similar to those obtained when the contractions were elicited by indirect stimulation.

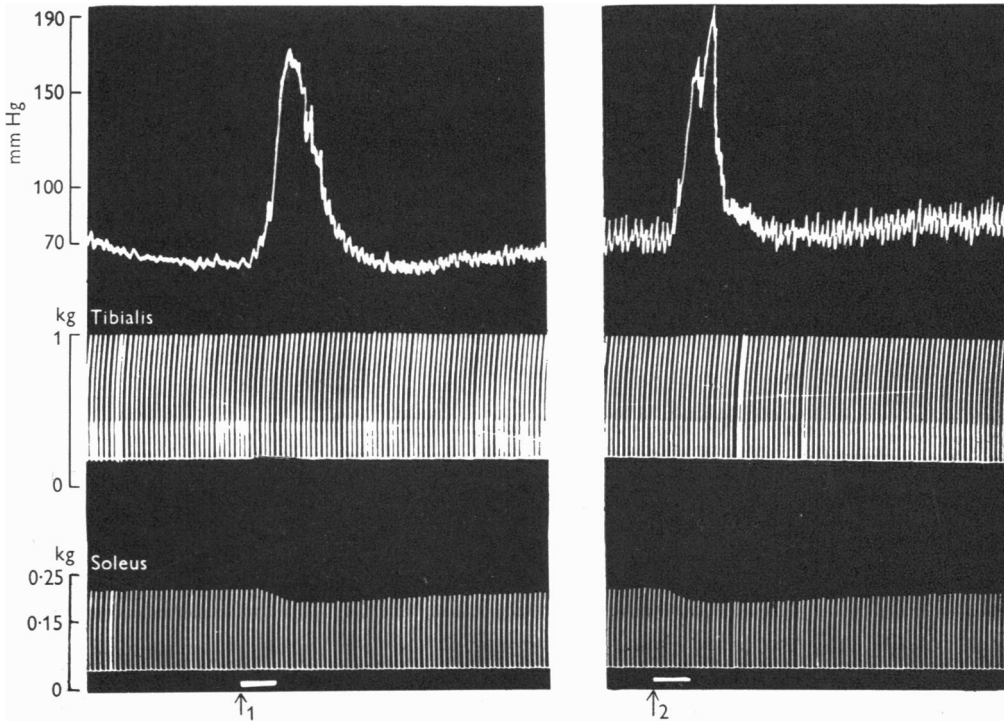

Fig. 10. Cat, 2·3 kg. Blood pressure and indirectly excited maximal twitches of the tibialis anterior and soleus muscles recorded simultaneously. At arrow (1) stimulation of the left splanchnic nerve for 60 sec at a frequency of 20/sec; at arrow (2) 10 μg of adrenaline administered intravenously during 60 sec.

The effect of splanchnic stimulation. In five experiments stimulation of the splanchnic nerve at frequencies of 10 and 20/sec for periods of 1–2 min was accompanied by a decrease of the maximal twitch tension of the soleus muscle. In four out of the five experiments and only with the higher frequency of stimulation the maximal twitch tension of the tibialis anterior muscle was increased. The effects of splanchnic stimulation could be closely imitated by the intravenous administration of 3–5 μg/kg/min of adrenaline (Fig. 10).

The effect of stimulation of the lumbar sympathetic chain. In a further series of five experiments maximal twitches of the tibialis anterior and the soleus muscles were elicited by stimulation of the motor roots. Stimulation of the lumbar sympathetic chain at frequencies of 10 and 20/sec for periods up to 5 min produced no change in the maximal twitch tension of the tibialis anterior muscle. In one animal, however, the maximal twitch tension of the soleus muscle was slightly decreased by stimulation at 20/sec.

DISCUSSION

Oliver & Schaefer (1895) were the first to show that extracts of the adrenal medulla increased skeletal muscle contractions. Since then many workers have obtained similar results with adrenaline (Gruber, 1922*a*, *b*; Goffart & Brown, 1947; West & Zaimis, 1949; Brown *et al.* 1950; Goffart & Ritchie, 1952; Goffart, 1952; Huidobro *et al.* 1952; Montagu, 1955); with noradrenaline (West & Zaimis, 1949; Brown *et al.* 1950; Huidobro *et al.* 1952; Goffart, 1952, 1954); and with isoprenaline (Brown *et al.* 1950; Goffart, 1952; Huidobro *et al.* 1952).

The present experiments on the tibialis anterior muscle confirm these findings and at the same time show that the increase in twitch tension produced by the three sympathomimetic amines is associated with a slight decrease in the rate of development of tension and an increase in the time to peak, the over-all duration of the twitch being prolonged. Goffart & Ritchie (1952) reported similar changes with adrenaline in the time course of the maximal twitch of the isolated diaphragm of the rat.

As was expected from the results on the single twitch, all three sympathomimetic amines facilitate fusion and increase the submaximal tetanic tension; the maximal tetanic tension, however, is not increased. When adrenaline and noradrenaline are administered in doses producing a marked vasoconstriction they may depress both submaximal and maximal tetanic tensions. That vasoconstriction is the cause of this depression is supported by the following results: (1) adrenaline and noradrenaline, only in doses which cause an almost complete arrest of the local blood flow, decrease the maximal tetanic tension; (2) noradrenaline is more potent than adrenaline in reducing tetanic tension and at the same time more powerful in decreasing the blood flow through the muscle; (3) isoprenaline, a pure vasodilator, never depresses tetanic tension; and (4) adrenergic blocking substances in doses reducing the vasoconstrictor action of both adrenaline and noradrenaline prevent the depression of tetanic tension. Submaximal tetanic contractions were shown in the present experiments to be more sensitive to vascular changes than maximal tetanic contractions. Similar results were obtained by Dolgin & Lehmann (1930) who showed that in human subjects weak contractions were more sensitive to ischaemia than strong contractions.

Goffart & Ritchie (1952) concluded that adrenaline can depress the maximal tetanic tension of the tibialis anterior muscle. In their experiments, however, they used large doses of adrenaline injected intra-arterially. The present results suggest that the reduction of the maximal tetanic tension they obtained was not due to a direct effect of adrenaline on the muscle contraction but to a simultaneous powerful vasoconstriction.

The results obtained on the soleus muscle show that skeletal muscles vary in their responses to sympathomimetic amines. In contrast to the effects on the tibialis anterior, isoprenaline, adrenaline and noradrenaline decreased the maximal twitch tension of the unfatigued soleus muscle. Electrical records showed that this response is associated with a decrease in the contraction time, a marked increase in the speed of relaxation and a reduction in the over-all duration of the twitch. As a consequence of these effects on the single twitch the degree of tetanic fusion is decreased and the submaximal tetanic tension reduced.

The tibialis anterior muscle is known to consist mainly of white or fast-contracting fibres while the soleus consists mainly of red or slow-contracting fibres. In a few experiments the plantaris and gastrocnemius were used in order to study the effect of the sympathomimetic amines on muscles containing a more even mixture of red and white fibres. The twitch tension of the gastrocnemius muscle was increased by the amines but to a less extent than that of the tibialis anterior muscle, whereas the twitch tension of the plantaris was decreased but to a less extent than that of the soleus muscle. Thus the effect of the amines on the twitch tension appears to depend on the proportion of red and white fibres in the muscle. The contraction of muscles such as the gastrocnemius and plantaris is little affected, possibly because neither type of fibre predominates greatly and the opposite actions on the two types of fibre tend to cancel each other. Goffart (1952), from experiments on muscles containing a mixture of red and white fibres (diaphragm of rat and tenuissimus muscle of cat), concluded that the effect of adrenaline must be the same on both red and white fibres, and he postulated that the postural tone of the soleus muscle would be improved. The results obtained in the present experiments, performed directly on the soleus muscle, give no support to such conclusions.

When considering the possible significance of these results, it is important first of all to find out whether physiological concentrations of sympathin are large enough to affect muscle tension. Several workers have attempted to determine the upper limit of the rate of impulse discharge in the sympathetic nervous system. Bronk, Ferguson, Margaria & Solandt (1936) recorded action potentials from individual sympathetic fibres and concluded that the discharge rate of sympathetic nerve cells never exceeds, even in stress, 10–20 impulses/sec. Others (Rosenblueth, 1932, 1950; Bacq, 1935) determined the frequency of nerve stimulation to which the corresponding effector cells give a maximum

response. In mammals this was found to be between 10 and 25 impulses/sec. Folkow (1952*a*, *b*) recorded the blood flow from a limb and matched the vasoconstriction produced by strong reflex excitation of the vasomotor centre with the effect produced by stimulation of the vasoconstrictor nerves themselves at various frequencies. He concluded that the normal peripheral resistance of the small vessels is maintained by quite a low rate of impulse discharge, probably around 1–2 impulses/sec, and that the average rate of impulse discharge accompanying a strong reflex excitation of the vasomotor centre is about 3–5 impulses/sec, the maximum discharge ever obtained being 6–8 impulses/sec. According to Celander (1954) and Folkow (1955) the rate of discharge in sympathetic nerves never exceeds 10 impulses/sec in the intact animal.

In the resting condition the adrenal medullae release approximately 0·1 μg/kg/min of a mixture of adrenaline and noradrenaline (Kaindl & von Euler, 1951; Duner, 1953; Folkow & von Euler, 1954). Celander (1954), assuming that the maximum rate of discharge in the splanchnic nerves is 10 impulses/sec, has calculated that the absolute maximum physiological output of sympathin from the adrenal glands when all cells are simultaneously activated is 5 μg/kg/min. According to him this amount represents the theoretical upper limit of amine secretion in the cat; it is considerably higher than that found during various types of reflex activation. Strong reflex excitation of the vasomotor centre causes the release of 0·2–0·5 μg/kg/min (Kaindl & von Euler, 1951) and in prolonged asphyxia, which appears to be the most powerful physiological stress, only 1–2 μg/kg/min is discharged (von Euler & Folkow, 1953; Celander, 1954). Intense pain-fibre stimulation in lightly anaesthetized cats causes the release of 0·6–0·7 μg/kg/min (von Euler & Folkow, 1953). From these results, Folkow (1955) has reached the conclusion that a rapid injection of 1 μg of adrenaline or noradrenaline administered intravenously to an average sized cat is, from a physiological point of view, a very large dose, creating a peak concentration which in the intact animal might possibly be reached only in extreme stress.

At first sight an increase in muscle tension appears to be more advantageous than a decrease. It is questionable, however, whether the concentration of circulating amines under any circumstances ever reaches a sufficiently high level to affect muscles like the unfatigued tibialis anterior. The present experiments show that the minimal effective intravenous dose of adrenaline necessary to increase the tension of the tibialis anterior muscle is usually between 3 and 10 μg/kg. Such concentrations are considerably greater than those considered by Folkow to be within physiological limits.

In four out of five experiments stimulation of the left splanchnic nerve caused a slight increase in the maximal twitch tension of the tibialis anterior muscle. These results confirm the finding of Gruber (1922*a*) and Goffart (1952).

In the present experiments, in order to produce this effect, it was necessary to stimulate the nerve at a frequency of 20/sec, stimulation at 10 impulses/sec being without effect in all five experiments. Stimulation of the left splanchnic nerve at a frequency of 20/sec may be assumed to cause the liberation of about the same amount of sympathin as is liberated by stimulation of both left and right splanchnic nerves at a frequency of 10/sec, that is, according to Celander (1954) and Folkow (1955), the maximum possible rate of discharge under physiological conditions. The effects of splanchnic stimulation at this frequency were closely imitated by the intravenous administration of 3–5 μg/kg/min of adrenaline. These quantities are in agreement with those found by Celander (1954). Stimulation of the lumbar sympathetic chain, as Goffart (1952) also showed, was without effect on the twitch tension of the unfatigued tibialis anterior muscle.

Thus from the results described it appears unlikely that the effect of sympathomimetic amines on the contractions of muscles such as the tibialis anterior has any physiological significance. However, if it has it will only be during conditions of extreme stress when the amounts of circulating amines might possibly reach a concentration equivalent to that produced by minimal effective doses of adrenaline.

On the other hand, the soleus muscle is considerably more sensitive to adrenaline than the tibialis anterior muscle. This indicates that if adrenaline has any physiological action in relation to unfatigued muscle contractions it will be the slow-contracting or red fibres which are first affected. The present experiments show that the minimal effective intravenous doses of adrenaline necessary to affect this muscle are of the order of 0·06–0·5 μg/kg, doses producing concentrations which are within the range of the physiological output from the adrenal glands. In all experiments stimulation of the left splanchnic nerve at frequencies of 10/sec caused a marked decrease in the twitch tension; the decrease produced by stimulation at 20/sec approached the maximum effect obtained with injected adrenaline. Furthermore, doses of adrenaline which just affect the general blood pressure frequently decrease the tension of the soleus muscle. It seems probable, therefore, that some physiological significance should be attached to the effect on this muscle.

In only one out of five experiments stimulation of the lumbar sympathetic chain at a frequency of 20 impulses/sec caused a very small decrease in the twitch tension of the soleus muscle. Stimulation at 10 impulses/sec was without effect in all experiments. It can be concluded therefore that the sympathetic nerves do not influence the contractions of this muscle under physiological conditions. Since the transmitter of these adrenergic nerves is noradrenaline (Folkow & Uvnäs, 1948) and since the soleus muscle is relatively insensitive to this amine, this result might be expected. Noradrenaline is about 50 times less active than adrenaline on the soleus muscle. This lack of sensitivity

to noradrenaline is not surprising, for if the soleus muscle were sensitive to noradrenaline every increase in the activity of the vasoconstrictor nerves would be accompanied by a decrease in the tension of the muscle.

An explanation must be sought, therefore, as to how the effect on muscles like the soleus is of assistance to the over-all skeletal muscle performance. Human muscles are known to consist of a mixture of slow- and fast-contracting fibres and it is possible that in emergencies a speeding up of the slow-contracting fibres would facilitate muscle work by producing a more uniform contraction.

Goffart (1952) concluded that during emergency states adrenaline and noradrenaline would increase the postural tone, improve the respiration and increase the contractions of other muscles. This was probably because at that time it was not realized that the amounts of amines needed to increase the muscle tension were much larger than those normally found under physiological conditions, and also because it was not known that skeletal muscles differ in their responses to sympathomimetic amines.

Denny-Brown (1929) showed that postural tone is maintained in the soleus muscle by rates of firing from 5 to 25/sec, frequencies well within the range affected by adrenaline. During emergency states the tension of the soleus and similar muscles may be decreased by the circulating adrenaline. This may be the cause of the well known feeling of weakness in the limbs experienced as an effect of fright. Barcroft & Swan (1953), describing the effects of an intravenous infusion of adrenaline in man, report that the subjects experience a feeling of fatigue in the back and in both legs and that a coarse tremor of the extremities is common. The same authors, however, were unable to record such effects with noradrenaline. Among the symptoms in patients with phaeochromocytoma, body tremors are described (Pickering, 1955). Usually in such cases paroxysms are produced by the sudden release into the circulation of relatively large amounts of mixtures of noradrenaline and adrenaline, the former tending to predominate. Litchfield & Peart (1956) describe a rather uncommon case of phaeochromocytoma in which the tumour contained more adrenaline than noradrenaline. This patient exhibited unusually pronounced muscle tremors during the attacks (personal communication by Professor Peart). All these skeletal muscle effects could be explained by an action of adrenaline similar to that described in the present experiments on the soleus muscle.

SUMMARY

1. In the cat, adrenaline, noradrenaline, isoprenaline and splanchnic stimulation increase both the indirectly and the directly excited maximal twitches of the tibialis anterior but decrease those of the soleus muscle. Stimulation of the lumbar sympathetic chain is usually without effect on either muscle.

2. Electrical recordings show that the effects on the tension are accompanied

by changes in the time course of the maximal twitch. In the tibialis anterior muscle the rate of development of tension is slightly diminished, whereas the time to peak tension and the duration of the whole twitch are increased. In the soleus muscle, on the other hand, the time to peak tension and the duration of the twitch are reduced and the rate of relaxation markedly increased.

3. All three sympathomimetic amines facilitate fusion and increase the tension of a submaximal tetanus of the tibialis anterior but decrease the tension and the degree of fusion in the soleus muscle. Maximal tetanic tension of both muscles, however, is not affected.

4. Simultaneous recording of the blood flow through the individual muscles shows that these effects are independent of vascular changes.

5. The soleus muscle is considerably more sensitive to adrenaline and isoprenaline than the tibialis anterior muscle but there is little difference in their sensitivities to noradrenaline.

6. The observations have led to the conclusion that whereas physiological concentrations of adrenaline are unlikely to affect fast-contracting muscles they may well influence the activity of slow-contracting muscles.

Grateful acknowledgement is made of a grant by the Medical Research Council (to E.Z.) for technical assistance. The authors are indebted to Ciba Laboratories Limited for their generous gift of phentolamine.

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