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THE EFFECT OF ADRENALINE ON THE CONTRACTION OF HUMAN MUSCLE

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SUMMARY

1. Infusions of adrenaline in physiological amounts alter human muscle contractions evoked by nerve stimulation.

2. Adrenaline shortens the duration of the slow calf muscle twitch, but has no effect on the fast twitch of adductor pollicis.

3. Adrenaline decreases unfused tetanic tension and increases the oscillation of tension in 10/sec tetani of calf muscle and adductor pollicis. The usual rise of tension and decrease in oscillation in unfused tetani ('ramp' phenomenon) is abolished.

4. Adrenaline has no effect on maximal tetanic tension or maximal rate of rise of tension in a fused tetanus of adductor pollicis.

5. The effects of adrenaline on human muscle are due to stimulation of β-adrenotropic receptors, for they are abolished by the β-adrenotropic antagonist DL-propranolol (but not by D-propranolol), and are mimicked by isoprenaline but not by noradrenaline.

6. The effect of adrenaline on adductor pollicis is abolished by local β-blockade of one arm with intra-arterial DL-propranolol, indicating that the responsible β-receptors lie peripherally.

7. The changes in muscle contraction observed cannot be explained by altered muscle temperature, for this falls during adrenaline infusion; nor are they due to an action on neuromuscular transmission, for these small doses of adrenaline do not affect the muscle action potential. The evidence points to a direct action of adrenaline on muscle.

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INTRODUCTION

It is a commonplace that fright causes people to shake, and there is good reason to suppose that this is due to liberation of adrenaline, for injection of adrenaline brings on a similar state of tremor. Recently, Marsden, Foley, Owen & McAllister (1967) established that adrenaline tremor is not a central effect but is due to stimulation of peripheral adrenotropic β-receptors, for they found that the increase in the amplitude of the normal tremor of the outstretched fingers during intravenous infusion of adrenaline in healthy subjects could be prevented in an arm, and in that arm alone, by injection of a small dose of DL-propranolol (an adrenotropic β-blocking agent) into the brachial artery.

Of the numerous known effects of adrenaline on the peripheral neuromuscular apparatus the two that appear most likely to be relevant in explaining adrenaline tremor are the abbreviation of the twitch of the cat soleus muscle by physiological doses of adrenaline, discovered by Bowman & Zaimis (1958), and the sensitization of muscle spindles to stretch by adrenaline, investigated by Calma & Kidd (1962). Bowman & Zaimis themselves suggested that their effect might be responsible for human adrenaline tremor and their case was strengthened by the observation of Marsden, Meadows, Lange & Watson (1967) that adrenaline still accentuated hand tremor in an arm that had been surgically deafferented by section of dorsal roots C5–T2, thus ruling out all reflex effects, in particular those from muscle spindles. A direct effect of adrenaline on the parameters of contraction seemed the only explanation. The present paper brings forward further evidence for the suggestion of Bowman & Zaimis (based on their results on cat muscle), by showing that adrenaline speeds up contraction of human muscle too.

It should be made clear at the outset, however, that the matter may be more complicated than Bowman & Zaimis originally thought, for in the deafferented patient investigated by Marsden *et al.* (1967) adrenaline and isoprenaline increased tremor considerably more in the normal arm than in the deafferented arm. Sensitization of the stretch reflex by adrenaline (Hodgson, Marsden & Meadows, 1969) by an effect on muscle spindles (or some other different reflex effect) may, therefore, contribute to adrenaline tremor, but we offer no further evidence as yet on this possibility. (That peripheral factors, acting reflexly, may influence or determine the frequency of tremor was shown by Robson (1959) and has recently been emphasized by Lippold (1969) with new experimental support.) Some of our results presented here have already been communicated to the Physiological Society (Marsden & Meadows, 1968).

METHODS

The subjects studied were ourselves or colleagues. The effect of intravenous adrenaline on the contraction of triceps surae and adductor pollicis was investigated.

Two methods were used for recording contraction of the calf muscles. In the main series of experiments the subject lay face downward on a bed with his feet clear of the end. One foot was securely strapped to a rigid footplate, at right angles to the leg, through which the tension developed during contraction of triceps surae under approximately isometric conditions was transmitted as a bending movement to a stiff aluminium bar incorporating two silicon strain gauges (Ether Ltd., type 2A-1A-350P). The latter formed two arms of a bridge circuit, the output of which was displayed on a Tektronix 502A oscilloscope. The contraction of triceps surae was expressed in terms of the pressure exerted on the footplate under the ball of the foot (the level of the first metatarsophalangeal joint), the system being calibrated by placing weights at this position on the footplate with the footplate horizontal. The output was linear up to 15 kg.

A few later experiments on the calf muscles were done at the Physiological Laboratory, Cambridge, with Dr P. A. Merton. In these experiments the subject sat on a chair with his thigh horizontal and his knee bent to a right angle. The foot was again strapped to a footplate, force being recorded by a strain gauge of small compliance and referred, as before, to the pressure exerted at the ball of the foot. The footplate was designed to swivel about the same axis as the ankle joint, the alignment of the axes being finally secured by careful adjustment of the fore and aft position of the foot on the footplate and of the height of the foot (by placing packing pieces between it and the footplate) until both contraction of the extensors of the knee and resting a 20 kg weight upon the knee gave no output from the strain gauge. The 20 kg weight was then left in position on the knee to prevent the heel from lifting off the footplate during contraction of the calf muscles.

With both recording arrangements single twitches and incomplete (i.e. unfused) tetani of the calf muscles were evoked by supramaximal cathodal stimulation of the medial popliteal nerve in the popliteal fossa with brief shocks delivered via a fixed silver surface electrode about 1 cm in diameter. The tension developed must have been mainly due to contraction of soleus and gastrocnemius (triceps surae), with inevitable smaller contributions from plantaris, tibialis posterior, flexor digitorum longus and flexor hallucis longus. In some experiments the first differential of the tension signal, corresponding to velocity of contraction, was also recorded. In other experiments the muscle action potential was led off by two surface electrodes strapped approximately 4 cm apart on the belly of the muscle.

With either type of recording arrangement single maximal twitches of the calf muscles are not smooth but exhibit one or more bumps on the rising phase, e.g. Fig. 8. (The records chosen for the Figures are, of course, the smoothest.) After taking great care with both types of apparatus to exclude free play, sideways movements and similar mechanical troubles that can undoubtedly cause the appearance of bumps on twitch records, we are left with the strong impression that some of the bumps seen are not artefactual and probably reflect the different rates of contraction in different muscles participating, e.g. slow soleus and fast gastrocnemius.

The experiments on the hand muscle, adductor pollicis, were carried out in Cambridge, using a modified form of the equipment described by Merton (1951). The main difference was that action potentials were recorded by surface electrodes, one on the palm about 2 cm medial to the first metacarpophalangeal joint and the other on the fourth finger. The ulnar nerve was stimulated at the wrist and muscle tension recorded by a strain gauge and direct-coupled amplifier.

Other neurophysiological techniques employed are described in the Results. The delivery of nerve stimuli was programmed by a Devices Instruments Ltd Digitimer and supplementary Logic Unit 3080, both designed by Mr H. B. Morton of the National Hospital, Queen Square.

Intravenous infusions were administered via a needle inserted in an antecubital vein at rates varying from 2–4 ml./min, by a constant-rate infusion pump. Solutions of catecholamines were diluted in isotonic saline to which 0·03 % ascorbic acid was added to prevent oxidation. The dosages of adrenaline (l-adrenaline bitartrate) and of noradrenaline (l-noradrenaline bitartrate) are given in terms of the base, but of isoprenaline (isopropylnoradrenaline sulphate) as the salt. Blockade of β-adrenotropic receptors was produced by intravenous or intra-arterial DL-propranolol (Inderal, I.C.I.). In a few control experiments D-propranolol (I.C.I. 47,319) was given.

In all experiments the effects of infused catecholamine were compared with control values obtained during prior infusion of isotonic saline alone, usually for many minutes. With few exceptions, which are referred to specifically, all observations on the effects of catecholamines were made between the third and sixth minute of infusion. Statistical analysis was by Student's t test on paired samples.

RESULTS

The effect of adrenaline on the calf muscle twitch

Adrenaline consistently altered the shape of the isometric twitch of triceps surae evoked by supramaximal nerve stimulation. The experiment illustrated in Fig. 1 is taken from the main series of experiments in which the dose of adrenaline was always 10 μg/min. Control twitches during the initial saline infusion are compared with twitches recorded during the fifth minute of a subsequent intravenous infusion of adrenaline. Adrenaline increased the peak tension developed by 2·7 %; decreased the time taken to develop peak tension from 95 to 87 msec; and decreased the time taken to reach half-relaxation from 184 to 155 msec. Table 1 gives the results obtained in this and eight similar experiments on five subjects. Adrenaline always reduced the duration of the twitch. The time to half-relaxation decreased by a mean of 28·7 msec (S.E. of mean $\pm$ 2·6 msec; $P < 0{\cdot}001$). Adrenaline also appeared to decrease the time to peak tension as measured from the twitch records, by a mean of 7·5 msec (S.E. of mean $\pm$ 1·26 msec; $P < 0{\cdot}005$). It was often difficult to determine the exact point at which peak tension was achieved in twitch records, but records of the first differential of the twitch confirmed that it was reached earlier during adrenaline. Adrenaline always shortened relaxation time much more than contraction time. Maximum tension was variably affected; it was decreased in six experiments, increased in two, and unchanged in one. Adrenaline had similar effects on triceps surae twitches evoked by constant submaximal nerve shocks. After adrenaline infusions the twitch returned to its previous shape within about 30 min. Sufficient observations were made at these late

intervals to establish this point, but the long duration of the adrenaline action explains why its effects were normally only compared with control records taken immediately beforehand.

Observations were later made both on calf twitch and on calf tremor with much smaller doses of adrenaline, using the Cambridge equipment. The standard dose of adrenaline, 10 μg/min, may increase tremor in the

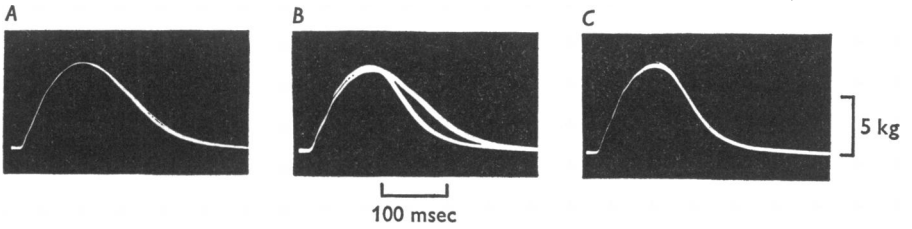

Fig. 1. The effect of adrenaline (10 μg/min intravenously) on calf muscle twitch. (*A*) Six superimposed twitches during prior infusion of saline, (*B*) six twitches during adrenaline superimposed on six twitches during saline, (*C*) six twitches during adrenaline. In this and some subsequent Figures, rapid transients in the signal photographed have been retouched for the sake of clarity.

TABLE 1. Effect of adrenaline (10 μg/min intravenously) on (A) peak tension, (B) time to peak tension, (C) time to half-relaxation of calf muscle twitch in nine experiments on five subjects

	(A) Peak tension (kg)		(B) Time to peak tension (msec)		(C) Time to half-relaxation (msec)	
Subject	Saline*	Adrenaline†	Saline*	Adrenaline†	Saline*	Adrenaline†
1	5·96	5·78	91	84	160	136
	5·26	5·79	100	93	185	106
	6·82	7·00	95	87	184	155
	6·14	5·92	106	104	197	160
2	7·31	7·31	100	89	175	142
	7·91	6·37	107	93	207	164
3	6·11	6·00	64	62	162	140
4	3·55	3·45	136	129	225	198
5	4·70	4·60	118	109	178	160

* Mean values during 3 min prior saline infusion.
† Mean values during fifth min of adrenaline infusion.

calf so much that in some subjects the muscles break into violent clonus. As it seemed implausible that such a striking oscillation could be precipitated merely by a change in muscle dynamics of the degree just demonstrated, smaller doses of adrenaline were tried to see whether an increase in tremor could be produced without detectable abbreviation of the

muscle twitch. Tremor-recording runs at a demanded force of 5 kg (to be described in detail in a subsequent paper) were alternated with records of maximal twitches during adrenaline infusion. Somewhat to our surprise the smallest doses of adrenaline that increased tremor also distinctly abbreviated the twitch. Thus, in three experiments, adrenaline (only 1·25 μg/min) decreased the time taken to reach half-relaxation from a mean of 218 msec to a mean of 204 msec, a change of 14 msec.

The effect of adrenaline on the adductor pollicis twitch

The adductor pollicis twitch was of shorter duration than that of the calf muscles. For the adductor pollicis, time to half-relaxation averaged 112 msec calculated from the figures in Table 2; for calf muscles, time to

TABLE 2. Effect of adrenaline (10 μg/min intravenously) on (A) peak tension, (B) time to peak tension, (C) time to half-relaxation of adductor pollicis twitch in eight experiments on three subjects

	(A) Peak tension (kg)		(B) Time to peak tension (msec)		(C) Time to half-relaxation (msec)	
Subject	Saline*	Adrenaline†	Saline*	Adrenaline†	Saline*	Adrenaline†
1	0·80	0·87	60	60	122	122
	1·02	1·02	55	56	114	112
	0·99	0·98	53	62	115	116
	0·75	0·76	58	61	97	106
2	0·90	0·90	63	63	127	126
	1·04	1·01	69	71	122	124
	1·03	1·03	63	63	113	120
3	1·05	1·00	46	48	90	90

* Mean values during 3 min prior saline infusion.
† Mean values during fifth min of adrenaline infusion.

half-relaxation averaged 186 msec (Table 1) when the knee was extended, and 218 msec when the knee was flexed to 90°.

In contrast to its effect on the calf muscle twitch, intravenous adrenaline had no detectable effect on the peak tension or the duration of the adductor pollicis twitch (Table 2).

The effect of adrenaline on incomplete tetani of the calf muscles

As was expected from the results obtained with single twitches, adrenaline had marked effects on the tension developed by triceps surae during stimulation of the medial popliteal nerve at 10/sec. This rate of stimulation was chosen because grouping of muscle action potentials at about 10 c/s is seen during contraction of human calf muscle (Lippold,

Redfearn & Vučo, 1957) and has been held to be responsible for the peak at about 10 c/s which is conspicuous in the spectrum of physiological tremor. An increased oscillatory response to a 10/sec tetanic stimulation would lead one to expect an increased response to action potentials grouped at 10/sec and could therefore help to explain the elevation of the 10 c/s peak in adrenaline tremor.

Figure 2*A* illustrates such an experiment. Before infusion of adrenaline, 10/sec supramaximal stimulation produced a peak tension of 13·3 kg at the end of 2 sec. The tetanus was unfused and the peak-to-trough oscillation in tension at the end of 2 sec amounted to about 0·67 kg, or 5·0 % of

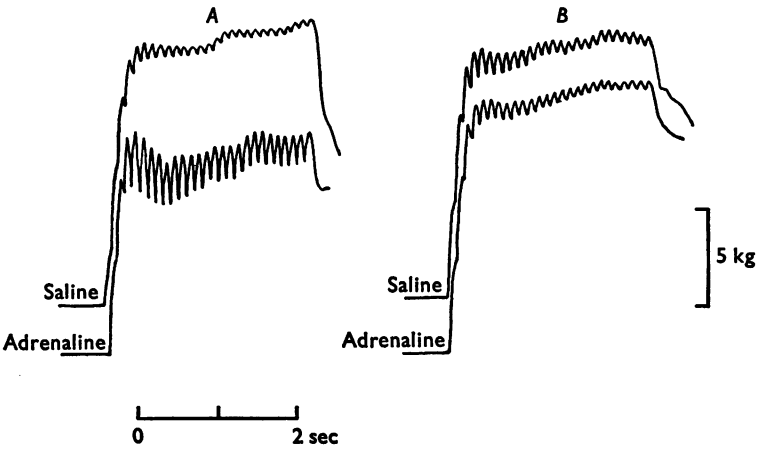

Fig. 2. The effect of adrenaline (10 μg/min intravenously) on calf muscle tetani at 10/sec (*A*) before, and (*B*) after, 5 mg DL-propranolol intravenously. In both *A* and *B* the base line was lowered during the adrenaline infusion.

the peak tension developed. During the fifth minute of intravenous infusion of adrenaline at a rate of 10 μg/min, the peak tension fell to 11·2 kg and the oscillation increased to about 2·72 or 24·3 % of peak tension. The results of a series of six similar experiments on two subjects are summarized in Table 3*A*. The tension developed during the final second of a 2 sec tetanus at 10/sec decreased, while the peak-to-trough oscillation in tension increased during adrenaline infusion.

Such experiments are painful and the difficulty of ensuring complete voluntary relaxation leads to some irregularity in the records, which do not, however, conceal the main phenomena, although the 'ramp' (see below) is less convincingly seen than in adductor pollicis. Higher frequencies of stimulation proved impracticable, so we are unable to say what the effect of adrenaline is on the maximal tetanic tension of triceps surae.

The effect of adrenaline on incomplete tetani of the adductor pollicis

Although adrenaline did not alter the single twitch of adductor pollicis, it did change the response to repetitive stimulation. In the experiment illustrated in Fig. 3*A* supramaximal shocks at 10/sec were delivered to the ulnar nerve for periods of 4 sec. (Each tetanus was preceded and followed by isolated single twitches.) In the control tetanus the tension rises progressively and the peak-to-trough oscillation of tension diminishes, both

TABLE 3. Effect of adrenaline (10 μg/min intravenously) on 10/sec tetani of (A) calf muscle (mean of six experiments) and (B) adductor pollicis (mean of ten experiments)

(A) Calf muscle

	Median tension* during final second of 2 sec tetanus (kg)		Peak-to-trough oscillation as % of peak tension	
n	Saline	Adrenaline	Saline	Adrenaline
6	10·91	8·58	15·1	29·2
	$t = 3{\cdot}5$, $P < 0{\cdot}02$		$t = 9{\cdot}3$, $P < 0{\cdot}001$	

(B) Adductor pollicis

	Median tension* during final second of 4 sec tetanus (kg)		Peak-to-trough oscillation as % of peak tension	
n	Saline	Adrenaline	Saline	Adrenaline
10	2·27	1·41	40·2	60·1
	$t = 4{\cdot}9$, $P < 0{\cdot}001$		$t = 6{\cdot}2$, $P < 0{\cdot}001$	

* Calculated as the midpoint between the peak and the trough of oscillations.

absolutely and relatively. This conjunction of a rising tetanic tension with a diminishing oscillation is here called the 'ramp' phenomenon. It can also be seen in calf muscles in the control record in Fig. 2*A* and in both records in Fig. 2*B*. During longer periods of stimulation of adductor pollicis at 10/sec the ramp continued, the oscillation gradually fading until the tetanus was almost fused at a tension some two to three times that achieved during the initial second of stimulation.

The relation of the ramp to the classical post-tetanic potentiation of the twitch is uncertain. The latter is attributable to an initial increase in the response of the contractile material itself, followed by prolongation of the duration of the active state of the contractile mechanism of the muscle (Ritchie & Wilkie, 1955; Close & Hoh, 1968).

Adrenaline did not alter the initial twitch of a 10/sec tetanus but, as can be seen in Fig. 3*A*, it changed subsequent events by preventing the rise in tension and fall in oscillation. Before adrenaline, the peak tension achieved

after 4 sec of stimulation was 3·34 kg and the peak-to-trough oscillation in tension was 0·77 kg or 23·0 % of peak tension. During the fifth minute of adrenaline infusion the peak tension was 1·42 kg and peak-to-trough oscillation was 0·91 kg or 64·0 % of peak tension. The results of a series of ten such experiments on three subjects are summarized in Table 3*B*. Adrenaline consistently reduced or abolished both components of the ramp phenomenon on repetitive stimulation of adductor pollicis and the same was true of the calf muscles.

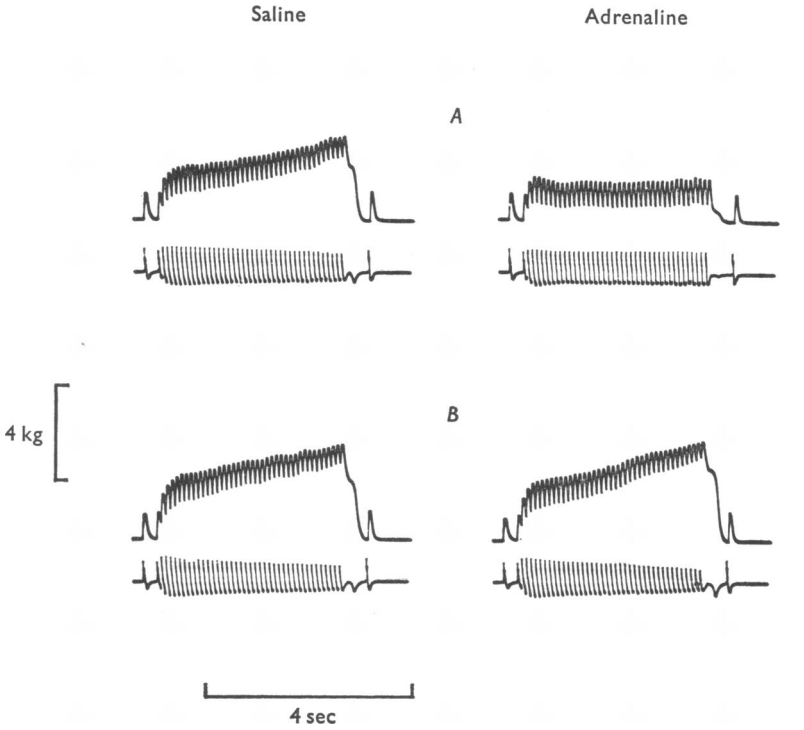

Fig. 3. The effect of adrenaline (10 μg/min intravenously) on adductor pollicis tetani at 10/sec. Below the tension trace in each record is the first differential of the tension signal. (*A*) Before propranolol and (*B*) after injection of propranolol (0·5 mg) into the brachial artery of the same subject. Single twitches before and after each tetanus are also shown.

The effect of adrenaline on tetani of adductor pollicis evoked by greater rates of stimulation was also studied in three subjects. Single twitches and 3 sec periods of stimulation at 10/sec, 12/sec, 15/sec, 20/sec and 50/sec in a programmed sequence once every 2 min were given before and during adrenaline infusion at the usual dose of 10 μg/min. Sample records are shown in Fig. 4 and the mean values for the three subjects are plotted in Fig. 5.

The peak tension of a single twitch was, as already stated, unaltered by adrenaline. The mean tension achieved after 3 sec tetani at 10, 12, 15, and 20/sec was decreased by adrenaline, the effect becoming less marked the greater the rate of stimulation. Adrenaline increased the relative peak-to-trough oscillation of tension after 3 sec stimulation, the effect again becoming less obvious as stimulation frequency increased. At 50/sec, the

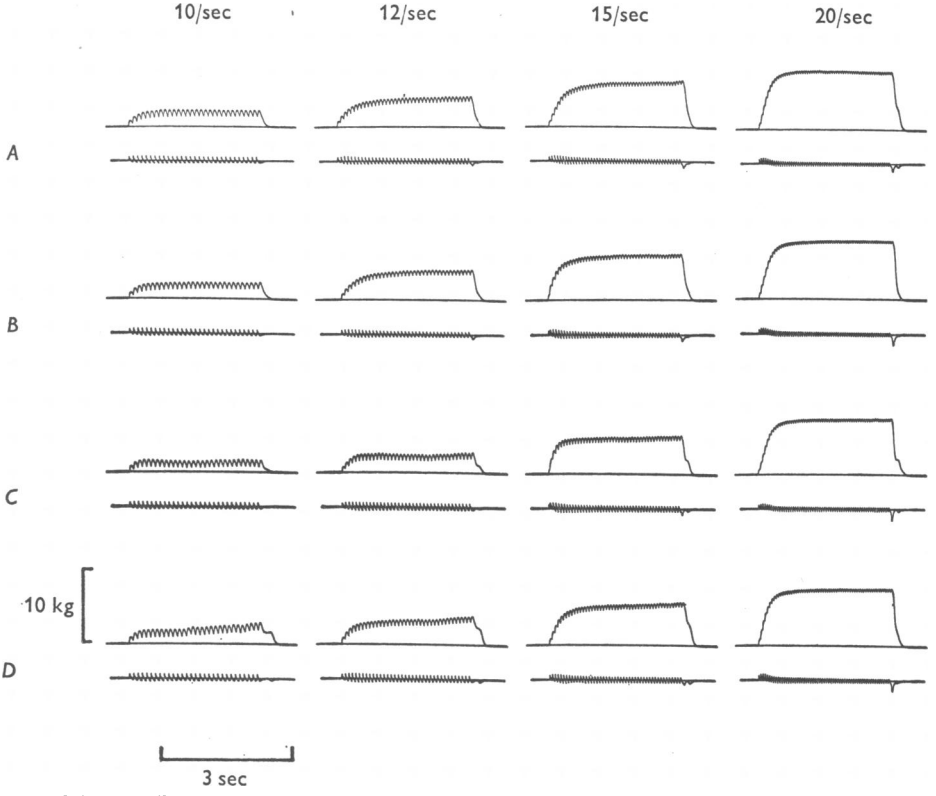

Fig. 4. The effect of adrenaline (10 μg/min intravenously) on adductor pollicis tetani at 10, 12, 15 and 20/sec. Below the tension trace in each record is the first differential of the tension signal. (*A*) and (*B*) recorded at an interval of 7 min during prior saline infusion, (*C*) during adrenaline, and (*D*) 25 min after adrenaline infusion.

tetanus appeared fused and adrenaline had no effect on the tension achieved. Higher rates of stimulation were also studied, and it was concluded that adrenaline had no effect on the maximum tetanic tension of adductor pollicis (which appears to be achieved at a frequency of 100/sec). Measurement of the rate of rise of tension using the differentiated tension signal indicated that adrenaline did not alter the maximum velocity of contraction of adductor pollicis at the start of a fused tetanus, at 50/sec or 100/sec.

The type and site of the adrenotropic receptors responsible for the effect of adrenaline

The criteria for identification of a β-adrenotropic action are that the effect of adrenaline should be mimicked by isoprenaline but not by noradrenaline, and prevented by DL-propranolol but not by D-propranolol. Howe & Shanks (1966) have shown that D-propranolol has only about one sixtieth of the β-blocking activity of the racemic mixture, although it retains the latter's local anaesthetic and cardiac anti-arrhythmic properties.

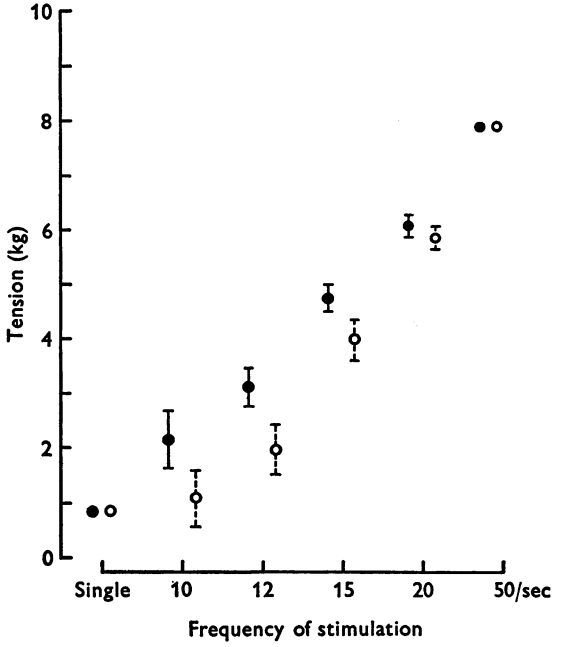

Fig. 5. The effect of adrenaline (10 μg/min intravenously) on adductor pollicis tetani at 10, 12, 15, 20 and 50/sec. Median tension after 3 sec of stimulation before (filled circles) and during adrenaline (open circles) is shown, as well as peak tension in a single twitch. The peak-to-trough oscillation in tension after 3 sec of stimulation is shown before (continuous lines) and during adrenaline (interrupted lines). The results shown comprise the mean of those obtained in three subjects.

All these criteria are satisfied for the effect of adrenaline on the calf muscle twitch. Isoprenaline, in doses of 5–10 μg/min intravenously, caused a characteristic decrease in twitch duration, whereas 10 μg/min of noradrenaline intravenously did not (Fig. 6). The effects of adrenaline and of isoprenaline were both abolished by prior β-blockade with 5 mg DL-propranolol intravenously, but not by 5 mg of D-propranolol intravenously.

In addition Fig. 2*B* shows that the effect of adrenaline on a 10/sec tetanus of the calf muscles was abolished by DL-propranolol, thus confirming that the change in the ramp phenomenon after adrenaline is also due to stimulation of β-adrenotropic receptors.

In the arm, intra-arterial propranolol was used to show that the relevant β-receptors are in the periphery. In one subject a dose of 0·5 mg DL-propranolol, intended as a control, was injected intravenously, but it appeared

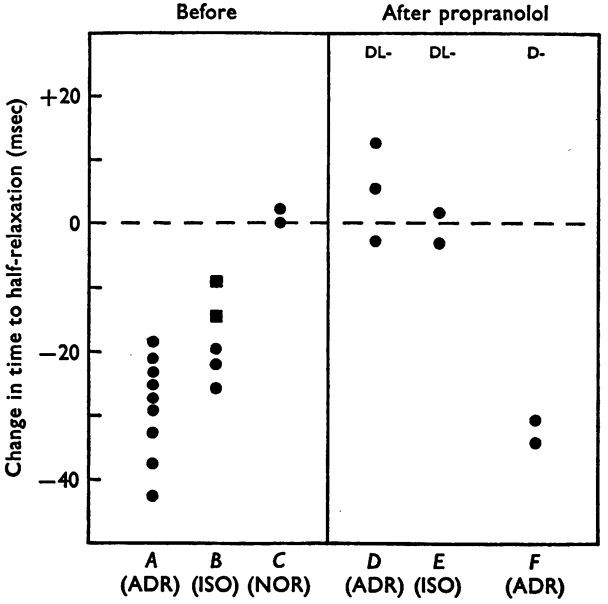

Fig. 6. Change in time to half-relaxation of calf muscle twitch produced by intravenous infusion of (*A*) adrenaline (10 μg/min), (*B*) isoprenaline (5 μg/min, squares; 10 μg/min, circles), (*C*) noradrenaline (10 μg/min), (*D*) adrenaline (10 μg/min) after DL-propranolol (5 mg I.V.), (*E*) isoprenaline (10 μg/min) after DL-propranolol (5 mg I.V.), (*F*) adrenaline (10 μg/min) after D-propranolol (5 mg I.V.).

to cause some reduction in the effect of adrenaline on the 10/sec tetanus of adductor pollicis. The following day 0·25 mg intravenously was without detectable blocking action, so, after another 24 hr interval, this dose was given into the brachial artery of the arm from which records were being taken. The effect of adrenaline on the 10/sec tetanus of the adductor was then found to be abolished. As the same dose had been without effect intravenously this experiment indicates that the responsible β-receptors lie in the distribution of the brachial artery; thus they are of the same type and in the same location as those responsible for the increase of tremor after adrenaline. Previous experiments on two other subjects had shown

that 0·5 mg intra-brachial DL-propranolol completely blocked the effect of adrenaline on the 10/sec tetanus of the adductor pollicis. One of these experiments is illustrated in Fig. 3*B*.

Precisely in what structures these peripheral β-receptors lie we have not established, but the likelihood is that they are in the muscle fibres themselves. The experiments that follow attempt to support this view by offering evidence to exclude other possible sites and modes of action.

Control observations on various factors that alter the muscle twitch

Muscle temperature. Adrenaline has complex effects on muscle blood flow, but it is difficult to see how these could be relevant to the present phenomenon except by altering muscle temperature. Bowman & Zaimis (1958) did, indeed, find that the effect of adrenaline on the cat soleus was independent of concomitant changes in blood flow. In a number of experiments we measured muscle temperature by means of a needle thermocouple thrust into the first dorsal interosseus muscle for about 1 cm towards the adductor pollicis. During the intravenous infusion of adrenaline muscle temperature consistently fell by 0·3 to 0·9° C and remained low at a time when records were taken showing an abolition of the ramp phenomen. To explain the decreased degree of tetanic fusion during adrenaline the temperature would have to rise, not fall (we have checked this assertion). Hence it appears that temperature changes cannot account for the effects of adrenaline we observe.

Changes in resting length and tension. As discussed by Buller & Lewis (1963) changes in the initial length or tension in a muscle can alter the shape of the recorded twitch. There were no changes in initial length of the calf muscles during the adrenaline infusion, nor were changes in resting tension observed. Furthermore, during adrenaline infusions, alterations in the tension applied to the footplate by making a small voluntary contraction, or alterations in the angle of the foot relative to the footplate, did not restore the twitch to its pre-adrenaline shape; nor did such manoeuvres reproduce the effects of adrenaline.

The muscle action potential. Although adrenaline lowers the electrical threshold of nerve (Bülbring & Whitteridge, 1941; Goffart & Holmes, 1962) and has complex effects on neuromuscular transmission (Bowman & Raper, 1966, 1967), it is difficult to see how these actions can be involved in the changes in mechanical response described above. We have, however, confirmed (Fig. 7) that, at a time when the usual abbreviation of the triceps surae twitch had occurred, during adrenaline infusion there was no alteration in the maximal action potential recorded from the calf with surface electrodes. Furthermore, in a series of experiments on five subjects, adrenaline did not alter consistently either the action potential recorded

from abductor pollicis brevis on supramaximal stimulation of the median nerve or individual motor unit action potentials recorded with concentric needle electrodes from the thenar muscles on minimum voluntary effort. Motor nerve conduction velocity in the median nerve between the elbow and wrist, measured by conventional techniques, was not affected by adrenaline.

The 'back response' of muscle. Elimination of the back response of the muscle during a mechanical twitch, discovered by Merton (1954) and analysed by Brown & Matthews (1960), produces changes in twitch shape

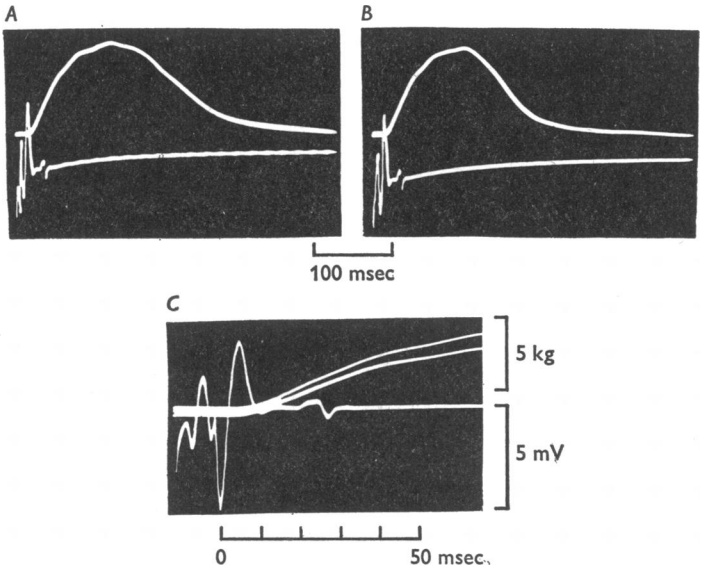

Fig. 7. Effect of adrenaline (10 μg/min intravenously) on triceps surae twitch (above) and evoked electromyographic action potential (below). Six superimposed traces during (*A*) saline and (*B*) adrenaline. In (*C*) six action potentials during saline are superimposed on those during adrenaline at a faster sweep speed. Despite the usual changes in the twitch, the muscle action potential was unaltered by adrenaline.

similar to those caused by adrenaline. Although, as already mentioned, adrenaline lowers the threshold of nerve, and would therefore be expected to augment the back response rather than abolish it, we confirmed by experiment that adrenaline has its usual effect when the muscle is stimulated in such a way that back responses are prevented. This experiment depends on the observation that the back response may be abolished by applying a second maximal nerve stimulus at an interval less than the absolute refractory period of the muscle fibres (Brown & Matthews, 1960). The second volley has no effect on the muscle, but renders the intra-

muscular nerve fibres refractory to a 'back response' restimulation by the muscle action potential. Accordingly, the effect of adrenaline on twitches elicited by paired stimuli of 200 μsec duration was compared with that on twitches elicited by a single shock. When the two stimuli were separated by an interval of 2 msec or more, the resulting twitch was larger than that produced by a single stimulus. The twitch evoked by stimuli separated by 500 μsec to 1 msec was smaller and briefer, suggesting that at these intervals a double shock was occluding a 'back response'. Adrenaline shortened the time to half-relaxation of twitches evoked by a single stimulus, and of the twitches evoked by paired stimuli separated by intervals of 500 μsec to 4 msec. The extent of the twitch shortening was proportionately the same irrespective of whether a single or double stimulus was used, or of the interval between two stimuli. While it cannot be claimed as certain that any 'back response' in the muscle has been wholly occluded by the paired stimuli used, this experiment makes it most unlikely that adrenaline is exerting its action on the twitch by inhibiting the 'back response'.

The H reflex and the F wave. Both the H reflex (Magladery & McDougal, 1950) and the F wave (Dawson & Merton, 1956; McLeod & Wray, 1966) are spinal responses elicited by nerve stimulation in intact subjects and could both result in distortion of the twitch by delayed activation of motor units. The H reflex is antidromically blocked by maximal motor nerve stimulation, and ought therefore to have been absent in our experiments. We demonstrated on one subject that when the H reflex was elicited by suitably chosen submaximal stimuli, it was not altered in latency, duration or amplitude by adrenaline. The F wave is not blocked by supramaximal stimuli, but it is always small and inconstant and has not been observed to change during adrenaline infusion (see Fig. 7).

A control experiment with nerve block. In one subject, to obtain a true uncontaminated twitch, the H and F responses were prevented by pressure block of the sciatic nerve, as described by Brindley (1962), while back responses were eliminated by paired stimulation. The experiment is illustrated in Fig. 8. The subject sat on a metal bar positioned under his sciatic nerve with the leg extended parallel to the ground, and the foot strapped to the footplate, which for this experiment was inverted. After 50 min, voluntary power in the calf muscles had almost disappeared and the leg felt numb in the distribution of the sciatic nerve. Total nerve block could not be achieved, for slight power remained in the peronei and cutaneous sensation was not wholly abolished. The triceps surae twitch was then elicited by supramaximal stimulation of the medial popliteal nerve in the popliteal fossa with paired pulses separated by 500 μsec. Such a double stimulus had previously been shown to reduce twitch duration

by 4 msec when compared with a single shock in this subject, which we interpret as occlusion of the 'back response'. The shape of the muscle twitch so produced did not change significantly during the period of sciatic nerve pressure, but was somewhat shorter than that usually recorded in this subject, probably as a result of the change in mechanical arrangements necessary to record the twitch in the sitting position. The twitch elicited after 50 min of sciatic nerve pressure was speeded up by adrenaline in the usual manner, the time to half-relaxation falling by

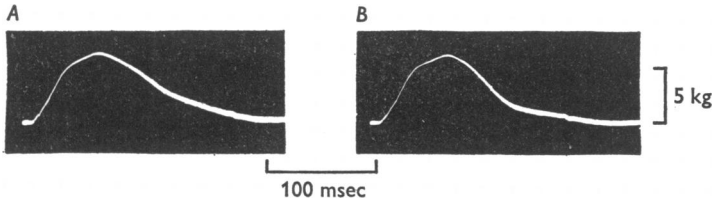

Fig. 8. The effect of adrenaline (10 μg/min intravenously) on calf muscle after prolonged sciatic nerve pressure. (*A*) Six superimposed twitches before adrenaline, (*B*) six twitches during adrenaline.

15 msec from 115 msec, a change of 13 %. In two previous experiments on this subject using the standard procedure, adrenaline in the same dose shortened the time to half-relaxation by about 19 %. The smaller effect of adrenaline during nerve block is still well within the range obtained in the group of subjects studied.

DISCUSSION

The effects of adrenaline in speeding up the contraction of human muscle are very similar to those observed by Bowman & Zaimis (1958) on cat soleus muscle, but less marked. In both cases the effects are β-adrenotropic. The chief difference is that adrenaline causes a substantial reduction in twitch tension in cat soleus, but no unequivocal change in the human calf. Their doses (single intravenous injections of 0·06–0·5 μg/kg) were similar to ours (10 μg/min, equivalent to roughly 0·15 μg/kg.min).

Using doses some fifty times larger (3–10 μg/kg), Bowman & Zaimis (1958) found that the effect of adrenaline on tibialis anterior was to increase both the tension and the duration of the twitch. (A similar effect in the rat diaphragm was described by Goffart & Ritchie (1952) but their dosage, 10^{-6} w/v in the bathing fluid, was three orders of magnitude larger than ours.) In the cat, soleus is a slow (red) muscle and tibialis anterior a fast (pale) muscle. Bowman & Zaimis hence concluded that adrenaline has opposite effects on slow and fast muscle. In man the distinction between fast and slow muscles is less definite than in lower animals, and information about the speed of contraction of different muscles is not easily to be found in the literature. The question as to

whether human muscles contain a mixture of slow and fast motor units, as do animal muscles, is still unanswered. We have found that the adductor pollicis twitch is only about two thirds of the duration of the calf muscle twitch, and when the knee is bent so as to decrease the contribution of gastrocnemius to the calf twitch the resulting 'soleus' twitch is longer than the twitch obtained with the knee straight. The faster calf twitch produced by adrenaline could be accounted for if adrenaline decreased the contribution from slow soleus and increased that from fast gastrocnemius. This seems unlikely as adrenaline shortened the calf twitch obtained both with the knee straight and with it bent.

In our experiments adrenaline did not have opposite effects on calf muscle and adductor pollicis, but the differences we observed in their responses to adrenaline are at any rate in the direction to be expected from the results of Bowman & Zaimis. Adrenaline did not actually lengthen the contraction of the faster muscle, adductor pollicis, but its action in speeding up contraction was much smaller than in the slow calf muscles. Thus the single twitch of adductor was unchanged by adrenaline, while its effect in abolishing the ramp phenomenon may mean merely that adrenaline prevents that prolongation of the mechanical responses to successive volleys in a tetanus that appears to cause the ramp, rather than that it actually shortens these responses.

There may, of course, be fast muscles in the human other than adductor pollicis whose contraction would be prolonged by adrenaline. However, in four experiments (not mentioned in Results) the twitch of the human anterior tibial muscles elicited by stimulation of the common peroneal nerve was slightly shortened by adrenaline in doses of 10 μg/min; doses comparable with those found by Bowman & Zaimis to lengthen the twitch of this muscle in the cat would be unphysiological and unsafe in humans.

Our experiments do not conflict with the plausible view that the β-receptors responsible for the effects of adrenaline are in the muscle fibres themselves. Sutherland and his colleagues (Robison, Butcher & Sutherland, 1967) have provided cogent reasons for believing that the enzyme adenyl cyclase is itself the β-receptor. Stimulation of the β-receptor increases the concentration of adenyl cyclase, which catalyses the conversion of ATP to adenosine 3′,5′-cyclic monophosphate (cyclic 3′,5′-AMP). Adrenaline increases the amount of cyclic 3′,5′-AMP in skeletal muscle, and this substance activates the enzymes necessary for break-down of muscle glycogen (Posner, Stern & Krebs, 1962, 1965). Independently of this particular theory, infusion of adrenaline into the human brachial artery has been shown to increase glycogenolytic activity in forearm muscles in man (De la Lande, Manson, Parks, Sandison, Skinner & Whelan, 1961). The time course of this effect was similar to the time

course of the effect of adrenaline on contraction that we have observed. It is not improbable that the two effects may be causally related. It is planned to test this hypothesis in two ways, first by studying the effects of cyclic 3′,5′-AMP on human muscle dynamics, and, secondly, by looking at the effect of adrenaline in cases of McArdle's syndrome, in which muscle glycogenolysis is effectively non-existent owing to a congenital absence of striated muscle phosphorylase (McArdle, 1951).

As regards the changes brought about in the contractile mechanism itself, our results, showing a reduction of the time to half-relaxation of the twitch, are consistent with the view that adrenaline shortens the duration of the active state in the calf muscles. This of itself, as discussed by Close (1965), would lead to a decrease in twitch tension as well as in twitch duration, but, in the human subject, we found that the height of the calf muscle twitch was often not reduced. To explain this would require some other parameter to change as well as the active state duration. One possibility is an increase in the intrinsic speed of shortening. Close (1965) has presented evidence that, in muscles in general, speed of shortening increases as the duration of the active state gets shorter. Our results would be accounted for if a reciprocal change of this nature was induced in the calf muscles by adrenaline. Following from what was said above, the lesser effect of adrenaline on adductor pollicis may merely be to prevent or delay a change of these parameters in the opposite direction during a tetanus.

The consequences of the effect of adrenaline on the twitch and tetanus of triceps surae and similar muscles in man were discussed by Bowman & Zaimis (1958). They pointed out that the tension developed by such muscles for a given rate of firing of the anterior horn cells must be decreased by circulating adrenaline, an effect that might account for the well known feeling of weakness in the limbs experienced during fright and during adrenaline infusion in man. The increase in tremor of the limbs and particularly of the outstretched hands in similar circumstances, which is also a peripheral β-adrenotropic effect (Marsden *et al.* 1967), may, in part, have a similar explanation. Thus, we have shown that adrenaline increases the oscillatory component of tension during a 10/sec tetanus. If the peak in the tremor spectrum near 10 c/s is due to bursts of motor impulses at 10/sec (as claimed by Lippold *et al.* 1957) then it seems clear that adrenaline would tend to increase the amplitude of tremor oscillations near 10 c/s by its direct action on the muscle. This, or something closely similar, would seem to be the only possible explanation for the increase of tremor after adrenaline in the deafferented arm of the patient studied by Marsden *et al.* (1967). It would not be the only instance of a relation between tremor and muscle dynamics, for C. D. Marsden, J. C. Meadows, G. W. Lange & R. S. Watson (in preparation) have found that the amplitude of finger

tremor is directly related to the duration of the muscle twitch in patients with thyroid disease. However, for reasons given in the Introduction, it is not likely that adrenaline tremor of healthy subjects can be wholly accounted for by the effect of adrenaline on muscle dynamics. Some peripheral action of adrenaline working reflexly to accentuate tremor seems to be required. The most likely candidate is the stretch reflex, see e.g. the vibration experiments of Hodgson *et al.* (1969). In view of the demonstrable action of adrenaline on the main contractile (extrafusal) fibres it is interesting to speculate on the possibility that adrenaline modifies the stretch reflex by some similar action on the contraction dynamics of the intrafusal fibres of the muscle spindles.

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