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THE EFFECT OF ADRENALINE ON THE CONTRACTION OF MAMMALIAN SKELETAL MUSCLE

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Brown, Bülbring & Burns (1948) showed that the main site of action of adrenaline on the fatigued mammalian muscle is the muscle fibre itself, and that adrenaline can augment the twitch tension under circumstances in which no failure of neuromuscular transmission can be demonstrated. A fatigued state of the muscle is not necessary for the demonstration of the potentiating action of adrenaline on the mammalian muscle twitch (Goffart & Brown, 1947). Evidence has been provided that the effect is dependent on the ionic balance in the fluid surrounding the muscle (Goffart & Brown, 1947; Goffart, 1949) and in the muscle itself (Goffart, 1947). Other effects of adrenaline are an increase in demarcation potential (Brown, Goffart & Vianna Dias, 1950) and a decrease in K^+ loss from the muscle (Goffart & Perry, 1951). These effects run roughly parallel to the changes in tension developed by single maximal twitches, but neither of these two last factors seems to be directly responsible for the mechanical potentiation induced by adrenaline. We have no knowledge of the precise mechanism whereby adrenaline exerts its effect, and we therefore thought it might be of value to study the action of this hormone on various mechanical characteristics of the muscle. We have reached the conclusion that adrenaline prolongs the active state (Hill, 1949*b*), and that this accounts for the increase in tension obtained in maximal twitches.

METHODS

In some experiments cats were used; they were anaesthetized with chloralose, the tibialis anterior was prepared for close arterial injection and tension recorded on the smoked drum (Brown, 1938).

Most of the experiments were made on the isolated phrenic-diaphragm preparation of the rat (Bülbring, 1946) and the original technique was followed closely except that strips of muscle 5–11 mm. in width were employed. The muscle was clamped at its rib end and mounted under slight tension on a multielectrode assembly similar to that described by Hill (1949*b*), and by Abbott & Ritchie (1951*b*). The muscle pulled vertically through a light inextensible chain attached to a piezo-electric crystal (Abbott & Ritchie, 1951*a*). Under these conditions the tension recorded was strictly isometric; the Rochelle salt crystal ('bender type') held at the ends, gave an output of 0·23 V. for a tension of 1000 dynes suddenly applied in the middle with a movement of only

2·2 μ. The time constant of the crystal was 200 msec. The voltage produced in it was fed through a cathode follower into a d.c. amplifier, displayed on a cathode-ray tube and photographed on film.

A crystal, though it accurately follows rapid tension changes, alters the form of the recorded tension-time curve of a muscle twitch. In later experiments therefore it was replaced by an R.C.A. 5734 mechano-electronic transducer valve.

Isotonic twitches were also recorded by means of a light lever and a twin photocell system described by Hill (1949*a*).

The muscle was stimulated with maximal nerve volleys at 10 or 20 sec. intervals for a period of between 2 min. and 1 hr. before the experiment proper began. Stimulation was then applied to the nerve or directly to the curarized muscle. The direct stimulation was made either through electrodes at one end of the muscle or through a series of cathodes and anodes disposed alternately 3 mm. apart along the length of the muscle. The stimulating current was derived from an electronic stimulator described by Attree (1950). Throughout the experiment the muscle was immersed in Tyrode's solution usually at 37° C. and a mixture of 5% CO_2 and 95% O_2 was bubbled through the bath.

Adrenaline hydrochloride prepared from the base or the 'Parke, Davis and Co.' adrenaline solution was used in the final concentration of 1×10^{-6} (w/v). For curarization, D-tubocurarine 2×10^{-6} (w/v) was employed.

RESULTS

Action of adrenaline on maximal tetanic tension

Adrenaline is known to increase the maximal twitch tension of the unfatigued mammalian muscle, but there is no clear information on what it does to the peak tetanic tension, in other words, to the maximal force a normal muscle can develop. A cat's tibialis muscle was excited through its nerve by maximal nerve volleys every 10 sec. A tetanus of 2 sec. duration and at a frequency of 100 or 200 per sec. was interpolated. The tetanus was followed by the ordinary post-tetanic potentiation (Feng, Lee, Meng & Wang, 1938; Brown & Euler, 1938), and, when this had disappeared, similar tetanic stimulation was applied. After three such controls, a close arterial injection of 10 μg. adrenaline was made and 2–5 min. later, when the potentiation of the single twitch reached its maximum, a similar tetanus was produced. After half an hour the adrenaline effect had completely disappeared and three more records of tetani were then obtained at 15 min. intervals as controls. Fig. 1 shows that a dose of adrenaline which increases the single twitches by 15%, very slightly decreased the maximal tetanic tension. The first tetanus after the effect of adrenaline on the single twitches had disappeared was still depressed, but later tetani recovered.

Using the same technique, we found that close arterial injection of 1·5 mg. potassium chloride or 5–10 mg. caffeine, or a previous tetanus—processes which are known to increase the twitch tension without inducing repetitive responses—did not significantly alter the peak tetanic tension. These experiments confirm the results of Huidobro & Amenabar (1945) with caffeine, but, whereas we found in our experimental conditions that potassium chloride did not affect a subsequent tetanus, Aubert & de Loof (1948) showed that after

half an hour's equilibrium of a frog's sartorius with a Ringer's solution with doubled potassium concentration the tetanic tension was reduced by 9%.

Thus we are dealing with a process in which the twitch tension is increased, but the tetanic tension is unaltered or even slightly decreased.

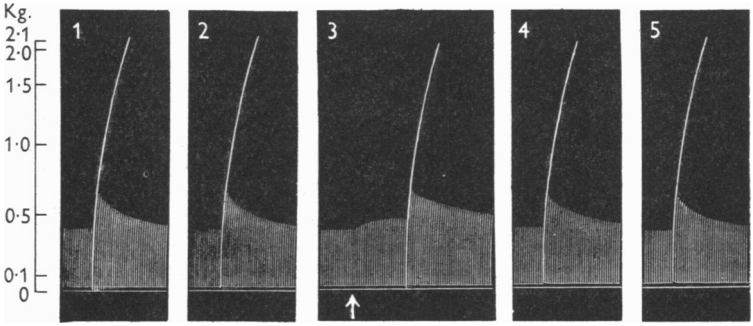

Fig. 1. Cat, 2·3 kg. Chloralose. Tibialis anterior stimulated maximally every 10 sec. through its nerve. 1, 1·19 p.m. 2 sec. tetanus at a frequency of 100 per sec.; 2, 1·31 p.m. as in 1; 3, 1·48 p.m. at arrow 10 μg. adrenaline injected close arterially, followed 4 min. later by the same tetanus as in 1; 4, 2·19 p.m. as in 1; 5, 14·35 p.m. as in 1.

Some characteristics of the rat diaphragm preparation

The isolated phrenic-diaphragm preparation of the rat was chosen as one convenient for a more detailed study of the effects of adrenaline on the various mechanical characteristics of the muscle twitch. The fibres of this muscle lie parallel to each other, and strips can be isolated without any great damage to the fibres. The dissected strips were generally 15–17 mm. long. A strip 7 mm. wide, weighing 52·5 mg. developed 8 g. tension in a single maximal twitch, under 1·2 g. initial tension; the greatest force exerted in a tetanus by this strip was 50 g. This represents a force of 1·62 kg./sq. cm. cross-section, a value which compares favourably with that of about 2 kg./sq. cm. found by Hill (1939) in the frog's sartorius. The tetanus/twitch ratio for the rat diaphragm is thus much higher than that of some other mammalian muscles at body temperature; it has varied from 6 to 10, the mean of ten experiments being 7·3.

The time from the stimulus to the peak of the twitch tension curve was 16–21 msec.; this includes a latency of about 3 msec. when the stimulus was applied to the nerve and a latency of about 1·5 msec. when the muscle was directly stimulated simultaneously at many points (see Fig. 4). The figures for contraction time and tetanus/twitch ratio agree with the results of Cooper & Eccles (1930) who found that muscles with a short contraction time have a high tetanus/twitch ratio. The contraction time of the rat diaphragm falls between those of the extensor digitorum longus and internal rectus of the eye in the cat. The rat diaphragm is a quicker muscle than the rapid fibres of the cat's tibialis

which have a contraction time of 32 msec. (Gordon & Holbourn, 1949). For this latter muscle we found a tetanus/twitch ratio of 4 to 5.

Relation between slowing of the conduction of the excitation wave and tension

Brown *et al.* (1948) have shown that adrenaline slows the contraction wave along the muscle fibre, and recently Goffart (1950) suggested that this slowing, by prolonging the twitch, and by increasing the time available for stretching of the series elastic component of the muscle, might result in a greater tension being reached.

We have tested this hypothesis in the following way. If slowing of the propagation wave were an important factor in the increase of tension produced by adrenaline, the increase in tension would be reduced when the necessity for distant propagation of the muscle impulse was diminished by simultaneous excitation of the muscle at several points.

A strip of diaphragm, 5 mm. in width, was mounted on a multielectrode apparatus in Tyrode's solution containing 2 μg. D-tubocurarine per ml. When curarization was complete, as checked by indirect stimulation, 'maximal' stimuli of 0·25–0·5 msec. duration were applied every 20 sec. directly to the muscle, alternately at one end, and at many points simultaneously. The tension was recorded by a piezo-electric crystal. It was more difficult to obtain maximal twitches by direct stimulation in mammalian muscle than in the frog sartorius at 0° C. (see below). We tried to meet this difficulty by lifting the assembly into a layer of paraffin floating on the Tyrode, to reduce the short circuiting by the surrounding fluid, and applied to the muscle a voltage which gave approximately the same tension as that obtained in the twitch produced by a maximal nerve volley before curarization. After ten control twitches adrenaline was added to the bath, so that it reached a concentration of 1×10^{-6} and changes in twitch tension were followed every minute for 10 min.

Stimulation at one point near the end of the muscle produced about the same peak tension as the all-over stimulation. Fig. 2*A* shows the relations between the contractions induced by 'all-over' and 'one-end' stimulation recorded under isometric conditions. Similar experiments were done under isotonic conditions and the shortening curves displayed similar characteristics to those described by Abbott & Ritchie (1951*b*) in the frog sartorius. In this muscle, with parallel fibres running from end to end, they showed that the 'one-end' shortening curve had about the same height as the 'all-over' shortening curve but was displaced to the right by half the propagation time. The 'one-end' isometric twitch of the diaphragm is similarly delayed and runs parallel to the 'all-over' twitch in the middle of the rising phase.

The contractions in Fig. 2*A* were recorded before adrenaline was added to the bath and those in Fig. 2*B*, 5 min. after the adrenaline had begun to act.

Both 'all-over' and 'one-end' contractions were potentiated by adrenaline and it can be seen that the augmentation produced with the 'all-over' stimulation was actually greater than that with the 'one-end' preparation, although the propagation time with the 'all-over' stimulation must have been much less than in the 'one-end' condition. The increase in propagation time produced by adrenaline (Brown *et al.* 1948) cannot, therefore, be an important factor in the adrenaline effect on skeletal muscle.

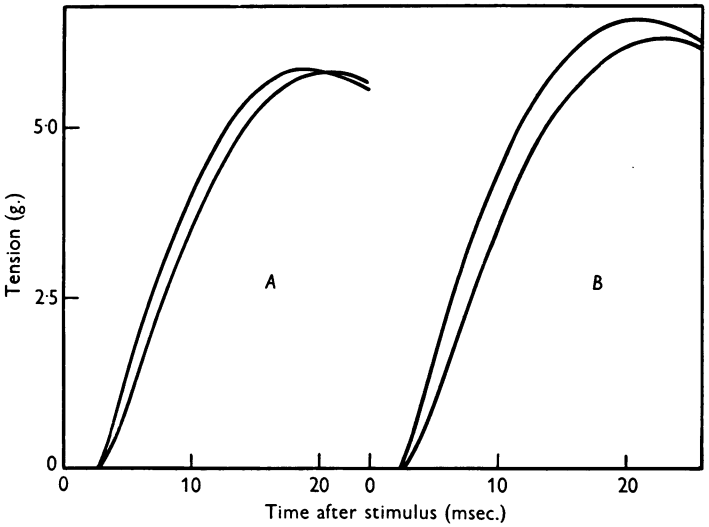

Fig. 2. Rat diaphragm strip 6 mm. in width, mounted on the multielectrode assembly, curarized, equilibrated in oxygenated Tyrode's solution and then stimulated in paraffin. *A*, superimposition of two twitches obtained by 'all-over' and 'one end' stimulation. The 'all-over' trace is on the left and in both traces stimulation is at time zero. *B*, the same, 5 min. after addition of adrenaline (1×10^{-6}) to the bath.

Effect of adrenaline on the duration of the rising phase of the contraction

Using a light torsion wire myograph to record tension, Brown *et al.* (1948) found no consistent change in time from stimulus to peak tension in single twitches of the rat diaphragm after application of adrenaline. The use of piezo-electric crystal or the transducer valve gave us more consistent results.

In seventy-two experiments on thirty-six rats we found that the time from stimulus to peak tension was delayed after adrenaline by 3–20% in sixty-seven instances. Tension and time to peak both increased (Figs. 3 and 5), but not always *pari passu*. In some experiments, in fact, the time to peak was prolonged, although no increase in tension could be observed. This suggests that the two factors are not closely interdependent.

Adrenaline leaves the latent period unchanged. The delay in time to peak occurs then during the contraction phase itself. If this delay was entirely due to slowing of the contraction wave, it would require a much larger slowing than

has been actually observed. In some preliminary experiments (unpublished) Burns & Goffart found that the propagation velocity along the fibres of the cat's gracilis (Brown & Burns, 1949) was slowed by 5–10% when 10 μg. adrenaline is given intra-arterially. Since the propagation velocity in the rat diaphragm is of the order of 3–5 m./sec., a decrease in propagation time of 10% along the fibres could only account for a fraction of a millisecond, whereas the observed delay in time to peak was of the order of 2 msec. Moreover, the delay of the time to peak was of the same order whether the muscle was stimulated through its nerve or at many points after curarization.

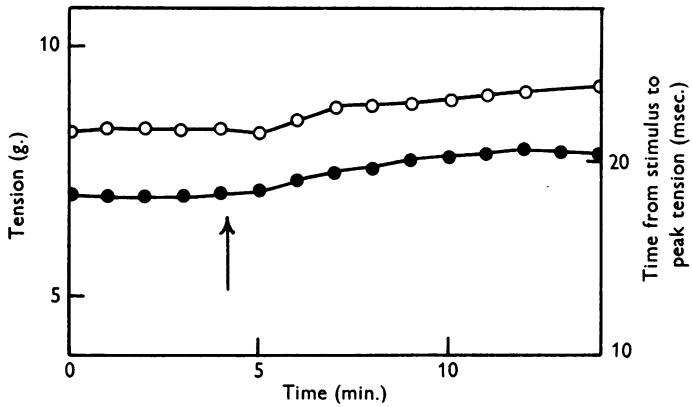

Fig. 3. Rat diaphragm strip, 9 mm. wide, 15 mm. long, weighing 68 mg. stimulated maximally through its nerve entry 10 sec. ●——●, time from stimulus to peak tension; ○——○, peak tension. At arrow 250 μg. adrenaline were added to the 250 ml. bath. Percentage increase in time to peak, 11%. Percentage increase in twitch tension, 9%.

A single maximal twitch of this curarized muscle was difficult to achieve: as the stimulating current was progressively increased, more and more fibres were stimulated and the peak tension rose; but on increasing the current beyond that required to give a tension equal to that produced by a single maximal shock to the nerve, the peak tension continued to rise steadily. The explanation seems to be that when the current was sufficient to cause all the fibres to discharge, some were on the point of discharging repetitively. When repetitive responses occurred, the time to peak, which had been steadily decreasing, now began to increase. However, when adrenaline was added to the bath submaximal, maximal and supramaximal twitches showed about the same percentage potentiation and this potentiation was always accompanied by an increase in time to peak. These findings exclude the hypothesis that adrenaline acts by recruitments of more fibres, because recruitment tends to reduce the time to peak. The adrenaline effect is not due to repetitive firing either because the action potentials recorded by Brown *et al.* (1948) never showed any sign of repetition.

The absence of a close relation between the increase in time to peak and the mechanical tension attained by the muscle suggests that another factor comes into play.

Rate of rise of tension and velocity of contraction

The early stage of tension development was examined by using a three times faster time base and higher gain than those we normally employed to display the contraction on the C.R.O. The rate of rise of tension in the control twitches, taken at 1 min. intervals before the addition of adrenaline, did not vary: after adrenaline the tension usually developed more slowly. Fig. 4*A* shows the first third of the rising phase before and at the tenth minute after the addition of adrenaline. The complete contraction curve can be seen in Fig. 5, which shows that the curve of the potentiated twitch does not cross the control twitch curve until the latter is approaching its peak.

This decrease in the rate of rise is due at least in part to the slowing of the propagation of the contraction wave along the muscle fibre, but because direct 'all-over' stimulation in the curarized muscle also gives a slowing in the development of tension (Fig. 4*B*), we think that some other factor such as slowing of the contractile process itself is involved.

We tried to gain information on this point by measuring the maximum velocity of shortening in isotonic twitches under low load. In these circumstances the effect of the series elastic component is eliminated and the velocity of shortening reflects the properties of the contractile substance proper. Accurate measurements were not possible because of the difficulties of fitting tangents to a curve, but the suggestion was that adrenaline slightly decreased the velocity of shortening.

In a few instances, however, the potentiation of the maximal twitch by adrenaline was accompanied by a quicker rate of onset of tension, similar to that reproduced in Fig. 6.

In the twitch, therefore, adrenaline causes an increase in the contraction time, generally accompanied by some slight decrease in the rate of development of tension.

Twitch potentiation by potassium chloride and caffeine

Addition of potassium chloride in an amount sufficient to treble the external potassium ion concentration (0·5 ml. of 20% KCl to a 250 ml. bath) regularly caused an increase of maximal twitch tension. The time-course of the potentiation differed according to the method of addition of the potassium chloride: if the solution was injected close to the suspended muscle the greatest potentiation occurred within 30 sec. This time course is similar to that observed in muscle with normal circulation when the solution is given by close arterial injection. When the solution was added to the bath at its periphery and free mixture allowed, the twitch increased gradually and reached its maximum in 5–10 min.

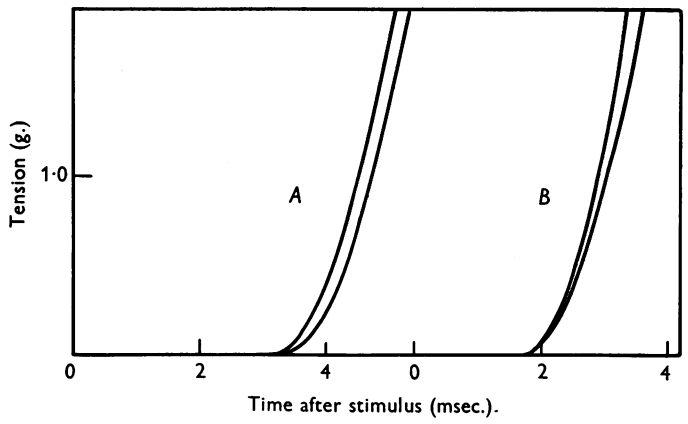

Fig. 4. Same muscle as in Fig. 5, at higher amplification and quicker time base. *A*, superimposed traces of the beginning of the tension rise. *B*, the same as in *A*, after curarization. In *A* and *B* the curve on the left is before adrenaline, that to the right 10 min. after adrenaline was added to the bath.

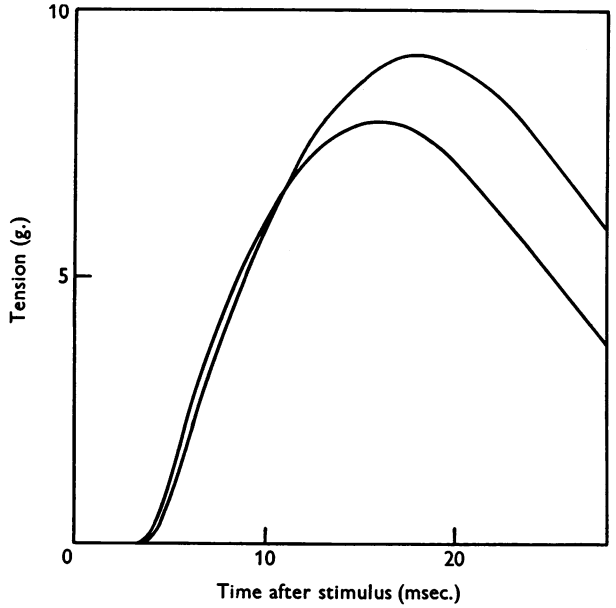

Fig. 5. Rat diaphragm strip, 9 mm. wide, 14 mm. long, weighing 87·8 mg. stimulated through its nerve every 10 sec. Two twitches superimposed, before and 6 min. after addition of adrenaline (1×10^{-6}).

In twenty-four of twenty-five experiments on ten rats, using either method of administration, potassium chloride caused an increase in twitch which was associated with a prolongation of the contraction time of 3–18%. The prolongation of contraction, however, as in the experiments with adrenaline, did not run parallel with the increase in tension, and, indeed, in the exceptional experiment, there was an increase in tension and no change in contraction time.

The rate of onset of tension showed three different types of change: (*a*) it was diminished as in the majority of the adrenaline experiments; (*b*) it increased for the first few minutes of the potentiation of the twitch and then became slower (Fig. 6); and (*c*) it was greater than in the controls throughout the potentiation period. Table 1 illustrates conditions (*a*) and (*c*) and it will be noted that the potentiated twitch tension is greater when the rise in tension is quicker and the contraction time only moderately prolonged. We are uncertain of the conditions which control this variation in the rate of onset of tension: different results can be obtained consecutively on the same preparation (Table 1) and these differences do not depend on the way in which the potassium chloride is added to the bath. They do not depend on the mode of stimulation whether applied through the nerve or directly at many points simultaneously. Although we know that adrenaline does not act on the muscle by liberation of potassium from the fibres (Goffart & Perry, 1951) the similarities in the changes they both produce in the muscle twitch are striking. That they are not at all specific is shown by what was found in experiments where the potentiation by caffeine was investigated. The increase in maximal twitch tension induced by caffeine (1×10^{-4}) is generally accompanied by a prolongation of the contraction time. This is in keeping with the results of Huidobro & Amenabar (1945), who showed that caffeine injection turns an unfused tetanus into a fused one. The same decrease in the rate of rise of tension as those described for potassium chloride, and incidentally for adrenaline, were observed.

DISCUSSION

When it had been established that the main action of adrenaline on the mammalian nerve-muscle preparation was upon the muscle itself (Brown *et al.* 1948) the question of the effects of changes in ionic balance inside and outside the fibres became important. It was shown that an excess of K^+ in the fluid surrounding the muscle impaired the potentiating action of adrenaline on single maximal twitches (Goffart & Brown, 1947), and that K^+ depletion of the inside of the muscle could even reverse the effect (Goffart, 1947). The hypothesis that adrenaline might act by liberation of potassium ions from the muscle—a process which is known to increase the twitch tension (Brown & Euler, 1938)—was however abandoned when it was observed that adrenaline decreased the loss of K^+ ions from muscle (Goffart & Perry, 1951) and increased

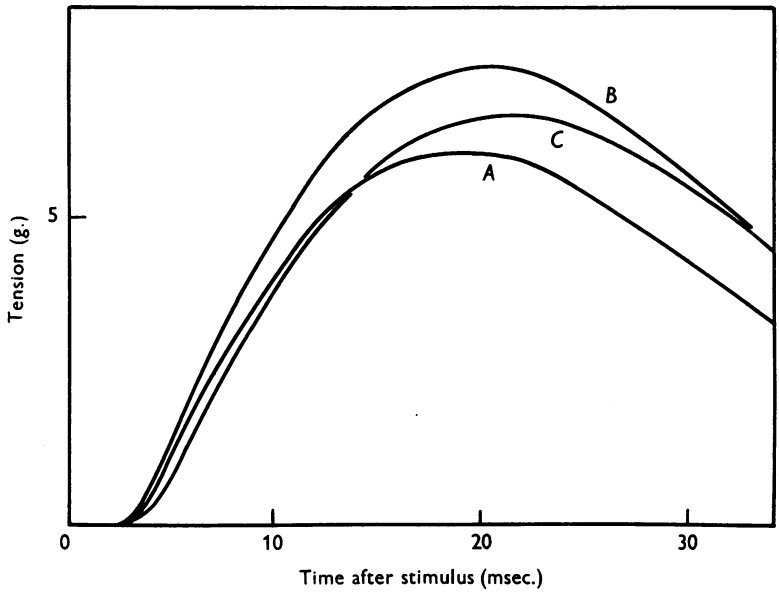

Fig. 6. Rat diaphragm strip, 11 mm. wide, 18 mm. long, weighing 89·0 mg. stimulated directly every 10 sec. at many points simultaneously, after curarization. Three twitches superimposed: *A*, before addition of potassium chloride; *B*, 30 sec. after injection of 0·5 ml. 20% potassium chloride near the muscle in a 250 ml. bath; *C*, 3 min. after *B*.

TABLE 1. Effect of increased potassium concentration on maximum tension and time to peak in a twitch

Date (1951)	Stimulation	Increase in tension (%)	Increase in time to peak (%)
Group A. Rate of onset of tension decreased after trebling the concentration of KCl in the Tyrode			
31 July	Indirect	25·6	17·6
26 July	Indirect	19·0	13·6
26 July	Indirect	16·0	14·1
23 July	Indirect	14·1	9·1
20 July	Direct	13·9	11·5
27 July	Direct	10·1	5·8
27 July	Direct	6·0	4·4
Mean		14·9	10·9
Group B. Rate of onset of tension increased after trebling the concentration of KCl in the Tyrode			
13 Aug.	Direct	39·1	5·0
23 July	Indirect	38·4	9·0
31 July	Indirect	32·3	6·6
31 July	Direct	30·0	8·2
1 Aug.	Direct	28·5	7·0
10 Aug.	Direct	24·3	2·6
27 July	Direct	8·5	0
Mean		28·7	5·5

the demarcation potential (Brown *et al.* 1950). This increase is contrary to the effect of potassium which reduces the demarcation potential.

In this paper we have tried to find out why adrenaline increases the maximal twitch tension and yet slightly decreases the maximal force that a muscle can exert in a fused tetanus.

Brown *et al.* (1948) suggested that the widening of the muscle action potential produced by adrenaline might be due to a slowing of transmission of the muscle impulse. Goffart (1950) thought that this slowing might be responsible for an increase in twitch tension, because it was a factor common to the potentiation produced by potassium, post-tetanic potentiation (Burns & Goffart, 1949, unpublished) and cooling (Brown *et al.* 1948; Walker, 1949). But, although a slowing of the contraction wave, with the consequent slowing of the development of tension, would increase the contraction time it is difficult to see how more tension could be developed in the single twitch. Moreover, when the propagation time is greatly reduced by stimulating the muscle at many points, the potentiating effect of adrenaline is still obtained. So this factor is certainly not an important one in the potentiating action of adrenaline, and if anything, it works in the opposite direction.

Hill (1950) pointed out that the true internal physical change which occurs when a muscle is stimulated is abrupt and reaches its full extent at the end of the latent period. The external manifestation of this activity—the muscle twitch—is however a more gradual process: tendons have to be stretched before the muscle can develop tension, and it takes time for this to be done. By the time the rat diaphragm muscle at 37° C. has reached its maximal tension in a single twitch the active state has fallen to about one-seventh of its initial value, as can be deduced from the figure of 7·3 for the tetanus/twitch ratio. Fig. 7 of Hill (1949*b*) gives a representation of these events in a frog sartorius at 0° C., where the muscle constants are, of course, different from those described here: a contraction time of 300 msec. is to be compared with 20 msec. for the rat diaphragm at 37° C. and the tetanus/twitch ratio is 1·75. It is to be noted that the tension curve in the twitch crosses the activity curve at the time when maximum tension is developed. Our Fig. 7 is a tentative adaptation of Hill's Fig. 7 (1949*b*) to rat muscle.

On this basis, the decrease in the rate of shortening of the contractile component might be responsible for the slower onset of tension which is observed in a twitch during the action of adrenaline and for the longer contraction time. But although the slowed tension curve would meet the activity curve at a later time, there would be a reduction in the tension developed at this time.

Because adrenaline causes a rise in the twitch tension, associated with an increase in the time to peak, we put forward the argument that adrenaline delays the decay of the active state, shifting the activity curve to the right (Fig. 7). The tension curve thus meets the activity curve at a later time and at

a higher level. An increase in contraction time can, of course, be caused other than by a prolongation of the active state. For example, if, as described above, the rising phase is slowed and there is no change in the active state, the time to peak will increase but the tension will be less. However, when the contraction time *and* the twitch tension increase, the most plausible explanation is that the active state has been prolonged. In a few experiments when, after the

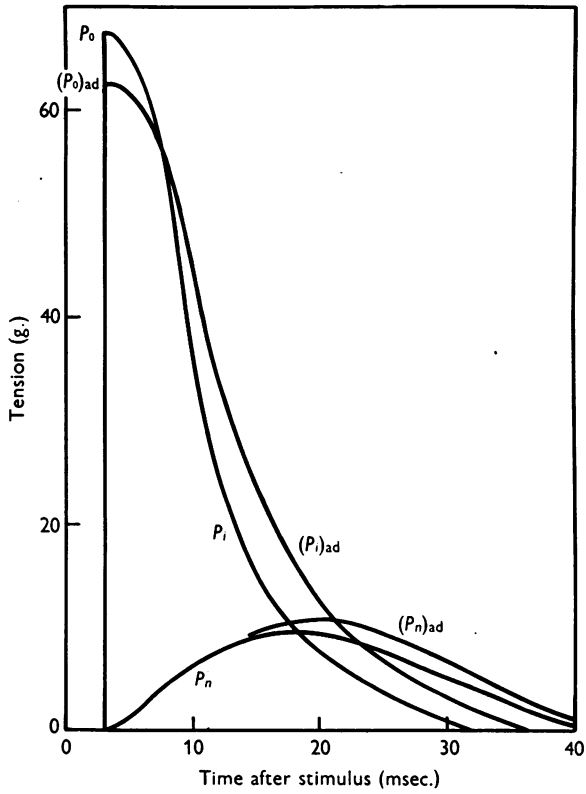

Fig. 7. Diagram of mechanical changes during twitch of rat diaphragm strip at 37° C. P_0, maximal tetanic tension; (P_0)ad, maximal tetanic tension after adrenaline. P_i, inherent activity at any moment; (P_i)ad, the same after adrenaline; P_n, maximal twitch before adrenaline. (P_n)ad, maximal twitch after adrenaline.

application of adrenaline, the time to peak increased but the tension was unaltered, it is possible to account for this by the action of two opposing factors such as the slowing of the rising phase and the prolongation of the active state.

In some instances adrenaline increases the twitch tension with only a trivial increase in contraction time—or even none at all—and with a quicker rate of onset of tension. The peak twitch tension is conditioned both by the rate of rise and the activity curve, so if more tension is produced and the time to peak

is unchanged it implies that, at a given time, more activity is available, i.e. that the active state has been prolonged.

The above arguments are by nature indirect, and we attempted to measure the activity curve directly by applying quick stretches to the muscle in the way described by Hill (1949*b*). We failed in this, because the rat muscle is so quick that it was difficult to stretch it in a time which was small compared with its contraction time: the problems involved in stretching a rapid muscle have been discussed recently by Hill (1951*a*).

More evidence could be obtained by analysis of the heat produced by muscles treated by adrenaline; if the active state were prolonged the muscle would maintain tension more economically, and its maintenance heat during a tetanus would be less than in an untreated muscle. However, since the treated muscle is observed to relax more slowly, in that at any given time during the relaxation phase the tension in the treated muscle was greater than in the untreated, it would be strange if this greater economy were not found and there was little point in embarking on myothermic experiments requiring great care, delicate control, and much time. Certainly the effect of previous activity (e.g. a tetanus) which so strongly resembles the effect of adrenaline—increase in time to peak and twitch tension—has been shown to increase the economy of maintaining tension (Hill, 1931).

The effect of adrenaline may be compared with the effects of other means by which the single maximal twitch can be increased: e.g. cooling, addition of potassium, caffeine, a previous tetanus or high pressure. K^+ ions and caffeine increase the contraction time in most cases. Table 1 shows that, with K^+, the increase in the contraction time is no index of the increase in twitch tension and that the rate of onset of tension may be slower or quicker. When slower, the contraction time is the more affected: when quicker, the tension. A little study of Fig. 7 will show that this effect of a variable rate of rise of tension is that which is expected if K^+ ions cause similar changes in the activity curve to those described for adrenaline.

The rate of rise of tension and the rate of decay of the active state do seem to be separable processes. For example, a previous tetanus or cooling causes a marked decrease in the rate of decay of the active state, but whereas a tetanus has no effect on the rate of rise of tension (Abbott, unpublished), cooling greatly reduces it. In the case of cooling it is because the decay activity is the more affected that the twitch is potentiated (Hill, 1951*a*). The effect of adrenaline therefore lies between those of a tetanus and cooling in that there is only a slight decrease in the rate of onset of tension. A change in rate of rise of tension is a complicating factor in the argument since contraction time and peak twitch tension may no longer increase together (e.g. Table 1). But as long as one of them increases and the other at least does not decrease, one must assume that the active state is prolonged.

Cooling (Hill, 1951*b*), potassium (Aubert & de Loof, 1948), like adrenaline, slightly reduce the maximal tetanic tension; caffeine (Huidobro & Amenabar 1945), application of high pressure (Cattell & Edwards, 1928), close arterial injection of potassium chloride into a mammalian muscle or a previous tetanus do not affect the maximal force a muscle can exert. But all of them, caffeine (Huidobro & Amenabar, 1945), potassium (Walker, 1948), cooling Brown *et al.* 1948; Walker, 1949) and high pressure (Brown, 1936) increase the maximal twitch tension and prolong the time to peak. We suggest therefore that there may be a common factor underlying these increases of the maximal single twitch, a prolongation of the active state.

SUMMARY

1. The action of adrenaline on some mechanical properties of mammalian muscle has been investigated.

2. Close arterial injection of adrenaline into the cat's tibialis anterior, increases the maximal twitch tension, but slightly decreases the maximal tetanic tension.

3. Isolated rat diaphragm strips develop a force of 1·62 kg./sq. cm. and have a tetanus/twitch ratio of about 7.

4. Adrenaline (1×10^{-6}) augments the maximal twitch tension recorded in strictly isometric conditions by 5–20%, and this is associated with an increase in the contraction time and with a slowing of the rate of rise in tension. This can be observed whether the muscle is stimulated directly or through its nerve.

5. Increase in tension produced by an excess of K^+ ions or caffeine (1×10^{-4}) is associated with a longer contraction time, but the rate of onset of tension varies greatly.

6. The slowing of the propagated contraction wave along the muscle fibre, induced by adrenaline, is not an important factor in the potentiation process.

7. It is concluded that adrenaline increases the maximal twitch by prolonging the active state of the stimulated muscle.

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