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THE ELECTRICAL PROPERTIES OF DENERVATED SKELETAL MUSCLE

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When skeletal muscles have been chronically deprived of their motor innervation, their sensitivity to chemical and certain forms of electrical stimulation is enhanced. Thus, denervated mammalian muscle (cat gastrocnemius) becomes one thousand times more excitable to acetylcholine (ACh), administered by close arterial injection (Brown, 1937). Denervated frog muscle is hyperexcitable to ACh by a factor ranging from ten (Brown, 1937—close arterial injection) to several thousands (Kuffler, 1943—isolated sartorius and single fibres), and the threshold to ACh remains 1000 times less at the 'end-plate' region than elsewhere on the muscle (Kuffler, 1943).

The sensitivity to ACh and other chemicals is increased far more than that to electric stimulation. In denervated mammalian muscles the rheobase is generally lowered to about one-fifth of that in the directly stimulated normal muscle (precautions being taken to avoid stimulating intramuscular nerves) (Pollock, Gollseth & Arieff, 1946; De Smedt, 1950*a*). When atrophy develops the situation becomes more complicated because less current would flow through the fibres and more through the outside fluid; this might partially mask the hyperexcitability of the denervated muscle membrane.

The increased excitability to current must be associated with changes in the membrane properties, but there is little quantitative information available on this point. The accommodation of denervated rabbit muscle is reduced (De Smedt, 1950*b*), and in mouse muscle a fall in the resting potential after denervation has been reported (Ware, Bennett & McIntyre, 1954). It seemed desirable to compare more fully the membrane properties of denervated and normal muscle. The 'passive' electrical properties, the resistance, capacity, and time constant of the membrane (Hodgkin & Rushton, 1946; Katz, 1948) are of special interest. Alterations of the electric resistance and permeability of the membrane to ions might affect the resting and action potentials in denervated muscle, and would affect its sensitivity to electric and other forms of stimulation.

In the present investigation the membrane constants, the resting and action potentials, and the sensitivity of the muscle to applied current, as well as to ACh, have been determined in normal and denervated frog muscle. Although some of the signs of denervation develop more markedly and more quickly in mammalian muscle, it was considered an advantage for the present purpose to use the relatively stable, isolated preparations of the frog.

METHODS

Material. Rana temporaria were used throughout the year. The foot muscle, M. extensor longus dig. IV, was used in the experiments with external electrodes and sartorius for the intracellular experiments.

Denervation. The frogs were anaesthetized with 1–2 ml. of an 8% solution of urethane injected intraperitoneally. About 2 cm of the sciatic nerve and all its branches in the thigh were removed through two small incisions. Operated frogs were kept for at least 3 weeks and nearly always for over a month before being used for experiments (cf. Langley, 1908).

Electrical recording apparatus. In all the experiments two cathode followers were used in the input stage, grid current being less than 10^{-11} A. In intracellular experiments connexions were made to the electrode through a junction box kept at cathode potential. A push-pull D.C. amplifier (Copeland, 1952) was connected to an oscillograph and monitor tube.

Membrane constants and electrical thresholds using external electrodes. The method of determining the electrical constants of a non-medullated nerve fibre (Hodgkin & Rushton, 1946) has been applied to the M. ext. long. dig. IV of the frog by Katz (1948). Unless otherwise stated, the methods and symbols are those used by Katz (1948). The electrical threshold was determined using rectangular pulses of approximately 100 msec duration. Starting with very small currents the stimulus was increased until action potentials were initiated. Critical depolarization was taken as the largest depolarization at which action potentials just failed to arise.

In two experiments the conduction velocity was measured by recording with the movable electrode at different distances from the cathode.

The cross-sectional area of the muscle fibres (vol.$_i/l$) and the total surface area of membrane (S) were calculated in the way described by Katz (1948). In two experiments the diameters of all the fibres were measured directly in transverse sections, shrinkage due to histological treatment being corrected for. There was good agreement between the areas measured directly in this way and indirectly by calculation in both denervated and normal muscles.

Intracellular experiments. The method of inserting microelectrodes for recording resting and action potentials was similar to that described by Nastuk & Hodgkin (1950) and Fatt & Katz (1951). To facilitate penetration in muscles where there was considerable atrophy high resistance microelectrodes (up to 23 MΩ) had to be used—which sometimes caused the time constant to reach values as large as 150 μsec. The same electrode, or electrodes of approximately the same resistance, were used for both the denervated and normal muscles of a pair.

In denervated muscle, as in normal, no marked p.d.'s were found along the resting fibre surface, and there are therefore no appreciable differences in resting potential from point to point (see Figs. 8 and 10). To observe action potentials, a brief stimulating pulse was applied to the two compartments of the chamber. For the measurement of threshold a second microelectrode was inserted into the same fibre within about 50 μ of the first; progressively stronger pulses of 50–100 msec duration were applied to the muscle with the internal stimulating electrode as anode. The maximum depolarization at which action potentials just failed to be initiated was taken as the 'critical depolarization'.

The action of ACh on denervated and normal muscle. The methods and apparatus were similar to those described by Fatt (1950), using a fluid meniscus as a moving electrode. In the first few

experiments (on the sartorius) recording was by an ink-writing milliammeter, but in all later experiments on the foot muscle photographic oscilloscope records were taken. The time course of the potential after applying ACh was followed until depolarization was maximal. The threshold concentration of ACh was taken to be the smallest concentration of ACh which initiated action potentials. Prostigmine 10^{-6} (w/v) was used to reduce inconsistencies due to the hydrolysis of ACh by the tissue. Prostigmine 10^{-6} has no depolarizing action on denervated or normal muscle; in two experiments, concentrations of at least 2×10^{-5} prostigmine were necessary to set up a small reversible depolarization of the end-plate region. ACh solutions were freshly made up from ACh chloride (Roche).

Solutions. Ringer solution of the following composition was used throughout: Na^+ 116 mM; K^+ 2 mM; Ca^{2+} 1·8 mM; Cl^- 119 mM; PO_4^{3-} 1 mM; pH 7. Muscles were soaked for at least half an hour before each experiment. The denervated muscle was nearly always examined before the normal control, which was stored in the refrigerator (2° C) until being used (usually on the same day).

RESULTS

Membrane constants

The length constant, λ, was greater in denervated muscle than in normal ($P < 0{\cdot}001$ see Table 1). In denervated muscle the extrapolar potential spreads further and the time course of the rise and fall of potential is slower (Figs. 1 and 2). The mean values of λ were 1·46 and 1·06 mm in denervated and normal muscle respectively; the latter value agrees with that found by Katz (1948) for the normal toe muscle, viz. 1·1 mm.

To measure the time constant, τ, use was made of the fact (Hodgkin & Rushton, 1946) that the time required for half-rise or fall of the electrotonic potential increases linearly with distance, the 'velocity constant' being $2\lambda/\tau$ (see Fig. 3). In every experiment but one τ was greater in the denervated than in the normal muscle; the mean values were 29 and 17 msec respectively. Although the scatter of the results is wide, partly because of inaccuracies of measurement, the difference is highly significant ($P < 0{\cdot}001$).

No significant alterations could be detected in the electrotonic resistance, y, and the parallel value, m, of internal and external resistances of the muscle in denervated muscle. The percentage of extracellular space and the ratio of internal to external resistance of the muscle depend on the amount of surplus fluid surrounding the muscle and the extent of atrophy. Neither of these were significantly altered in denervated muscle ($P > 0{\cdot}25$). Although atrophy did occur in a few muscles, the mean values of S, the total surface area of membrane and $\Sigma\pi\rho^2$, the total cross-sectional area of muscle, were not significantly reduced ($P > 0{\cdot}25$).

In every pair the specific membrane resistance, R_m, was greater in the denervated muscle. The mean value (10,300 Ω.cm^2) was more than double that found in normal muscles (4970 Ω.cm^2); the latter value is in good agreement with the figure of 4300 Ω.cm^2 found in normal toe muscles by Katz (1948).

The specific internal resistance of myoplasm, R_i, and the membrane capacity, C_m, were not significantly altered in denervated muscles ($P > 0{\cdot}25$).

The scatter of values of R_i was wide in both denervated and normal muscles (Table 1). The mean values of both R_i and C_m in denervated muscle are within the normal range found by Katz (1948).

TABLE 1. Membrane constants and thresholds of normal (N) and denervated (D) muscle. ΔV is the critical depolarization after correcting for interelectrode shunting; I_{cD}/I_{cN} is the ratio of the estimated value of I_c (from $\Delta V/\sqrt{[r_m.r_i]}$) of denervated to normal muscle; 'ACh' is the threshold concentration of ACh.

Days denerv-ated	Muscle	Temp. °C	λ mm	τ msec.	R_i Ω.cm	R_m Ω.cm²	C_m μF/cm²	ΔV mV	I_{cD}/I_{cN}	'ACh'
117	N	21	1·77	20	450	6,850	2·92	27·7	0·37	$7·5 \times 10^{-7}$
	D	19	1·80	30·5	263	7,250	4·20	8·4	—	$7·5 \times 10^{-9}$
67	N	18	1·29	21·5	210	4,050	5·30	31·4	0·10	—
	D	16	1·75	25	158	6,560	3·82	3·1	—	5×10^{-9}
169	N	17	1·02	17·2	306	5,450	3·17	33·0	0·27	1×10^{-6}
	D	18	1·99	37·2	126	10,100	3·68	15·3	—	8×10^{-9}
23	N	17	0·76	11	—	—	—	—	—	2×10^{-6}
	D	16	1·82	19·6	325	13,200	1·27	23·6	—	2×10^{-8}
27	N	19	1·08	11·6	299	3,850	3·02	24·0	0·64	$7·5 \times 10^{-7}$
	D	17	1·32	20·3	417	6,730	3·80	17·8	—	1×10^{-8}
31	N	19	0·79	9·5	172	1,710	5·56	22·0	0·42	5×10^{-7}
	D	16	0·99	16·7	515	5,530	3·01	28·3	—	$7·5 \times 10^{-9}$
45	D	20	2·08	40·5	—	—	—	—	—	$2·5 \times 10^{-9}$
47	N	19	0·80	21·1	442	3,230	6·54	36·2	0·03	5×10^{-7}
	D	18	1·47	20·2	176	7,320	2·76	6·6	—	—
51	N	18	0·74	9·0	180	1,500	5·97	12·8	0·34	$2·5 \times 10^{-7}$
	D	17	1·04	28·7	285	5,760	4·96	12·6	—	5×10^{-9}
36	N	18	1·31	33	366	9,900	3·34	35·0	0·30	1×10^{-6}
	D	17	1·49	47·7	405	16,400	2·91	19·3	—	8×10^{-9}
21	N	19	0·98	17·2	405	5,140	3·34	33·1	0·30	4×10^{-7}
	D	19	1·06	21·3	412	7,250	2·94	12·1	—	1×10^{-8}
41*	N	19	1·13	21·2	334	6,360	3·33	29·4	0·22	1×10^{-6}
	D	17	1·72	46·5	435	20,000	2·33	12·6	—	$7·5 \times 10^{-9}$
33	N	19	1·36	20·9	370	9,080	2·33	43·4	0·21	4×10^{-7}
	D	18	1·68	28·5	331	12,750	2·24	11·9	—	6×10^{-9}
37	N	21	0·72	10·0	425	2,540	3·94	38·8	0·06	—
	D	21	1·25	27·4	720	15,000	1·83	9·5	—	—
Mean values	N	19	1·06	17·2	328	4,970	4·1	30·6	0·27	8×10^{-7}
	D	18	1·46	29·3	350	10,300	3·1	13·9		8×10^{-9}

* Figs. 1, 2 and 3 were obtained from this pair of muscles.

It seemed possible that the conduction velocity, which depends on the membrane properties and fibre diameter, might be altered in denervated muscle. In two experiments no consistent differences were found between the paired muscles, the average velocity being 1·4 m/sec in the denervated and 1·6 m/sec in the normal.

Since the denervated muscle was always examined before the normal, an experiment was made on a pair of normal foot muscles to check whether the observed differences of λ, τ and R_m could be due to the effect of different storage times on normal muscle. In this pair of muscles the respective values for λ were 1·3 and 1·4 mm, for τ were 29 and 39 msec, and for R_m were 8,400

and 9,600 Ω.cm²; the second figure refers to the stored muscle, which gave the slightly larger values of λ, τ and R_m.

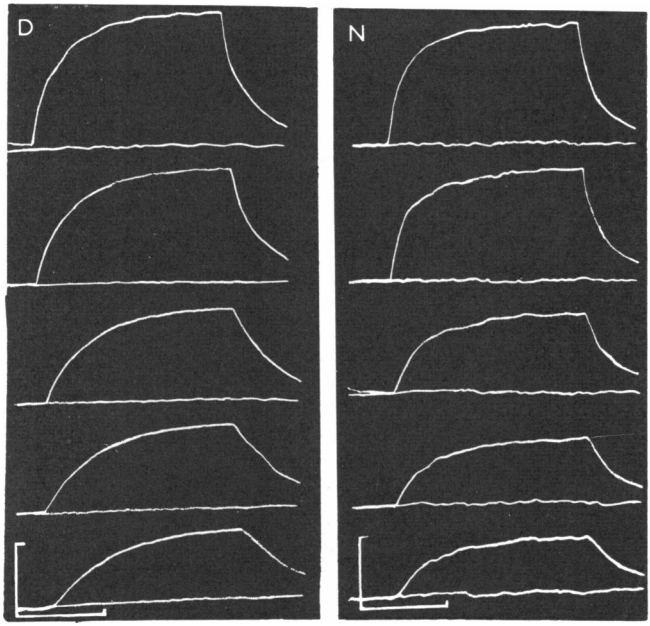

Fig. 1. Extrapolar potentials at distances of (from above downwards) 0, 0·2, 0·6, 0·8 and 1·0 mm from the anode with rectangular current pulses, in a denervated (D, 41 days) and a normal muscle (N). Calibration: 1·5 mV and 50 msec. This pair of muscles is identified by an asterisk in Table 1. The records have been retouched.

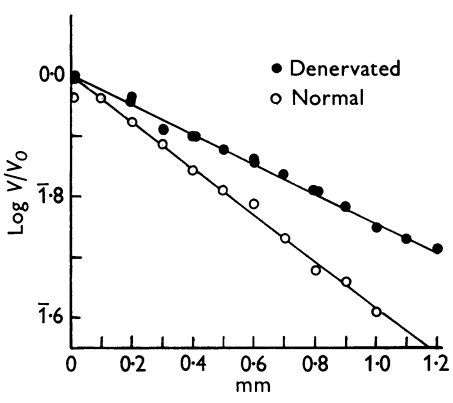

Fig. 2.

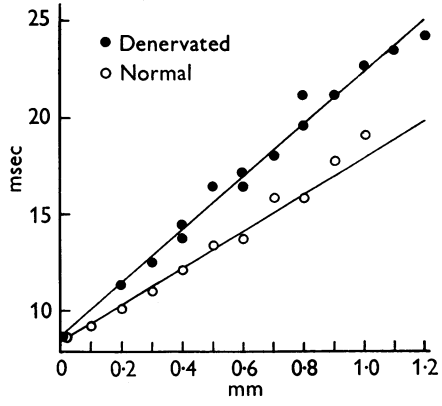

Fig. 3.

Fig. 2. Log of extrapolar potential plotted against distance in mm from anode in a denervated (41 days) and a normal muscle. Same muscles as for Fig. 1.

Fig. 3. Mean of times for half-rise and fall of extrapolar potential (msec) plotted against distance (mm) from the anode (same muscles as in Figs. 1 and 2).

Resting and action potentials

The measurements were carried out on eight pairs of muscles. The criteria for successful penetration of any denervated or normal fibre were that the insertion, as observed on the oscillograph, should be abrupt and that the potential should fall instantly and be maintained. If these conditions were fulfilled, all fibres were accepted irrespective of the size of the resting or action potential.

The resting potential was not altered in denervated fibres. The mean value was 85 mV (S.E. of mean $\pm 0{\cdot}5$ mV), in 311 denervated fibres, and 85 mV (S.E. $\pm 0{\cdot}9$ mV) in 118 normal fibres. The statistical scatter was also similar in denervated and normal fibres (see Fig. 4). Some very low resting potentials occurred in both normal and denervated muscles. The sixteen denervated values below 70 mV (Fig. 4) occurred in the first experiments; thereafter low resting potentials were encountered only rarely.

The action potential was not altered in size in denervated fibres; the membrane potential was reversed to the same extent as in normal muscle (Figs. 5 and 6), the magnitude of this reversal being 25 mV in 118 denervated fibres and 24 mV in 72 normal fibres. These values are smaller than those reported by previous workers (Nastuk & Hodgkin, 1950; Fatt & Katz, 1951). The explanation is probably that the results were not selected. Most of the action potentials of small magnitude occurred in those fibres with low resting potentials in the first experiments. If the action potentials obtained from the first two experiments are omitted, the mean values for the reversed potential become 30 mV for the denervated muscles and 27 mV for the normal. Another factor tending to reduce action potential size was the use of high resistance microelectrodes.

Electrical thresholds using external electrodes

The mean value of the critical depolarization was reduced by half in denervated muscle (Table 1 and Fig. 7), and the mean value of the threshold current was reduced by two-thirds (Fig. 7). These reductions in threshold were not significantly altered if interelectrode shorting was corrected for, using the factor $(1+r_i/r_o)$ (cf. Katz, 1948). The increased sensitivity of the denervated muscle to current is clearly due to two factors: (*a*) the higher membrane resistance, r_m, which means that less current is needed to produce a given depolarization, the current being proportional to $1/\sqrt{r_m}$ (cf. Fatt & Katz, 1951), and (*b*) the fact that a smaller depolarization, ΔV, is required to set up a propagated spike.

For a muscle in a large volume of fluid (as is the case in intracellular experiments or *in situ*) the current flowing through the fibre at threshold, I_c, is proportional to $\Delta V/\sqrt{(r_m r_i)}$ and when estimated in this way can be compared with

the results of intracellular experiments (see below); the mean value of I_c in denervated muscle was reduced to 0·27 of the normal (Table 1).

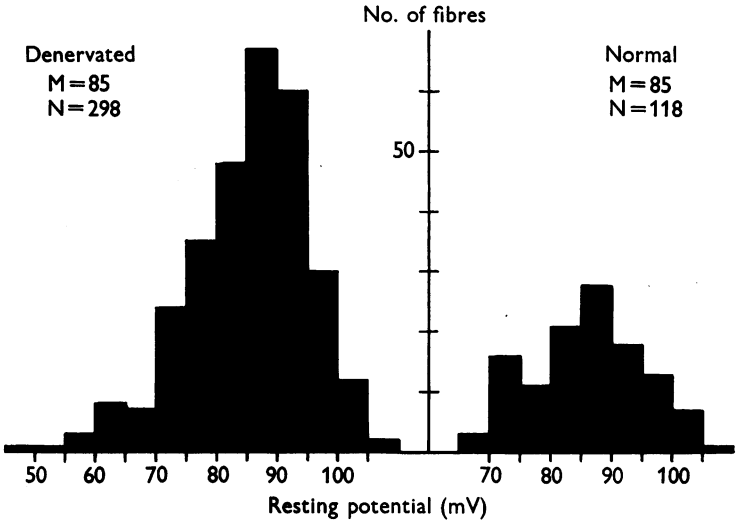

Fig. 4. Histograms of resting potentials in denervated and normal muscles. Abscissa, resting potential in mV; ordinate, number of fibres. M = mean resting potential, N = total numbers of fibres.

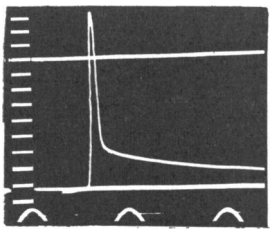

Fig. 5.

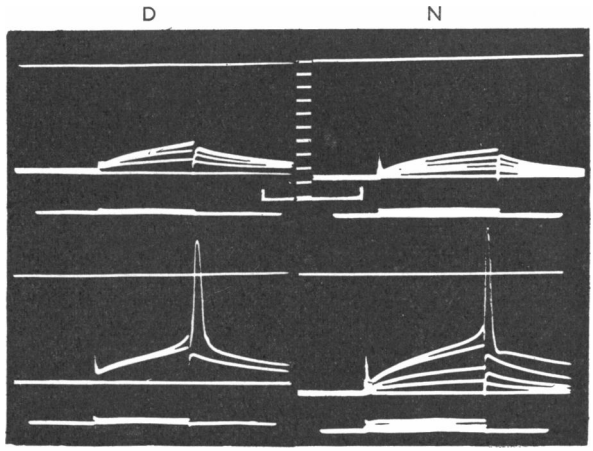

Fig. 6.

Fig. 5. Resting and action potential from a denervated fibre (28 days). Time, 20 msec; voltage calibration in 10 mV steps. Retouched.

Fig. 6. Subthreshold (upper records) and threshold (lower records) stimulation of denervated (D, 28 days) and normal (N) muscles. Intracellular electrodes for stimulation and recording. Current monitored across 100 kΩ, under each record. Calibration, 10 mV steps and 20 msec. Spikes retouched.

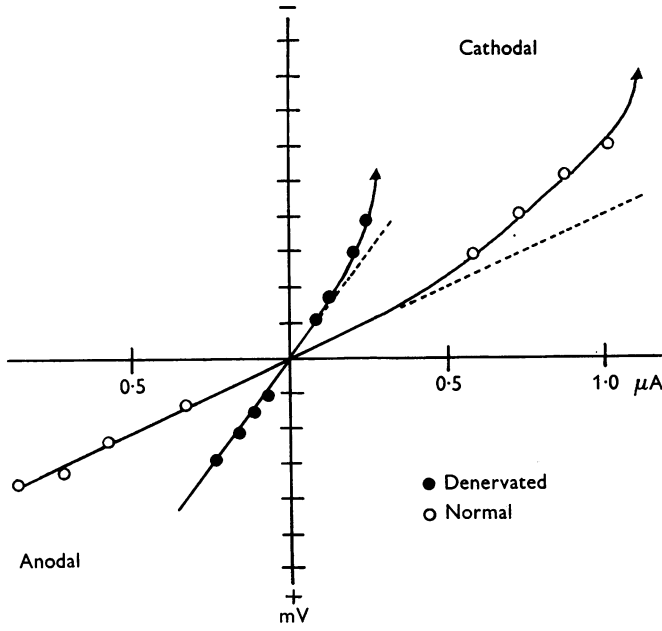

Fig. 7. Determination of threshold. Graph of current strength (μA—abscissae) against potential at anode and cathode (mV—ordinates) in denervated (41 days) and normal muscle.

Electrical thresholds using intracellular electrodes

The critical current, I_c, was reduced by about one-third in denervated fibres; the mean values were $6{\cdot}7 \times 10^{-8}$ A in seventy-three denervated fibres and $9{\cdot}6 \times 10^{-8}$ A in forty-three normal fibres (see Fig. 6). Statistically this difference was highly significant ($P < 0{\cdot}005$). If the minimum instead of the mean values are compared, I_c is reduced by three-quarters in the denervated fibres.

The critical depolarization was also reduced; in the seventy-three denervated fibres it was 31 mV, compared to 36 mV in the normal fibres ($P < 0{\cdot}005$, S.E. of means $\pm 0{\cdot}6$ and $\pm 0{\cdot}9$ mV respectively). Comparing the minimum values, ΔV was reduced by about one-third in the denervated fibre (18 mV compared to 29 mV).

The insertion of a second microelectrode to within about 50μ of the first usually produced a fall of several millivolts in the resting potential, which also affects the measurement of threshold. The fall in resting potential reduces the critical depolarization, but does not affect the level of critical membrane potential (i.e. the p.d. across the membrane at which excitation occurs) (cf. Fatt & Katz, 1951). The latter is therefore a measurement which is relatively unaltered by a fall in resting potential. The level of the critical membrane potential was 47 mV in the denervated and 38 mV in the normal fibres.

The action of acetylcholine

ACh in concentrations of 10^{-9} (w/v) produced a just visible depolarization of the 'end-plate' region in denervated muscles. Increasing the concentration (up to a limit of about 5×10^{-7}) caused progressively greater depolarization of the 'end-plate' region (Fig. 8); depolarization persisted without declining for at least 15 min in the presence of prostigmine. In normal muscles, at least 5×10^{-8} ACh is required for a just observable depolarization of the 'end-plate' region. In five muscle pairs, the denervated muscle was more sensitive to ACh by a factor of 50 to 100, using a given depolarization as the index (Fig. 9).

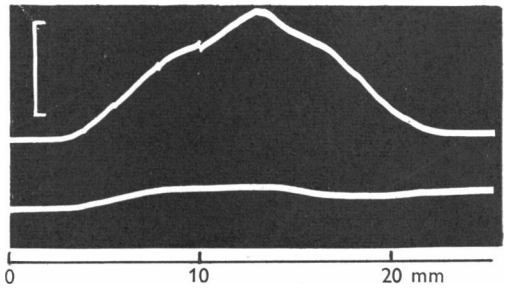

Fig. 8. The distribution of potential in a foot muscle denervated 24 days previously. The abscissa is the distance in mm from the electrode at the proximal end of the muscle. Negativity with respect to this electrode is indicated upwards. The lower record is the distribution of potential with the muscle in Ringer solution; the upper record is the potential distribution in Ringer containing ACh 10^{-8}. Breaks in this record are due to action potentials. Calibration: 5·0 mV.

The threshold concentration of ACh at which spikes arose was measured on thirteen denervated and twelve normal foot muscles; the mean values were 8×10^{-9} and 8×10^{-7} respectively (see Table 1). The depolarization produced by a threshold concentration of ACh was reduced in denervated muscles to about one-half of the normal value (see Fig. 10). Threshold concentrations of ACh depolarize only the 'end-plate' region of denervated and normal muscle; the proximal 'end-plate free' region of the foot muscle or sartorius is depolarized only if much higher concentrations of ACh are applied. In two experiments the muscles were mounted with the proximal end at the bottom of the bath, and the distal end in contact with the upper electrode. Fluid containing ACh was run upwards into the bath until it reached the proximal end of the muscle; this region was depolarized only by concentrations of about 10^{-3} ACh in denervated muscle and more than 10^{-2} in normal muscle.

The thresholds to electrical and ACh stimulation, and the membrane constants were not further affected by prolonging the period of denervation beyond 3 weeks, by which time fully hyperexcitability had been attained (Table 1).

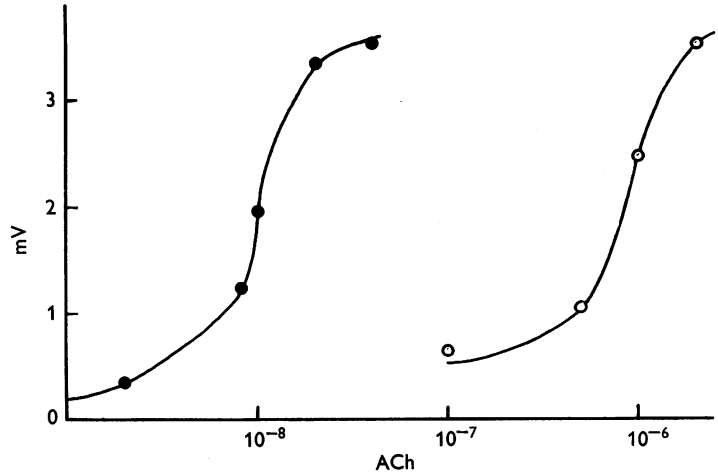

Fig. 9. Response curve of denervated (●—●, 33 days) and normal (○—○) foot muscle to ACh. Abscissae: log concentration of ACh. Ordinates: mV depolarization at region of maximal sensitivity.

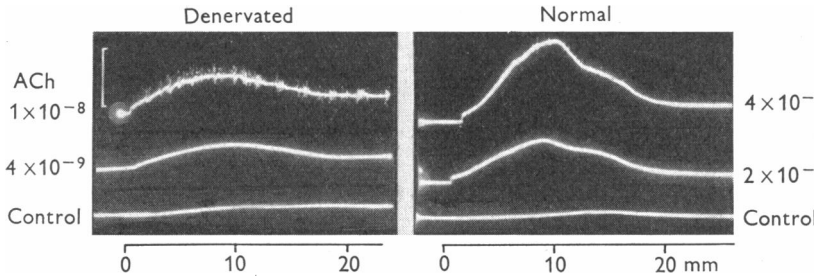

Fig. 10. Threshold to ACh of denervated (33 days) and normal muscle. Ordinates and abscissae same as in Fig. 8. 10^{-8} ACh is above threshold for the denervated muscle—there are many action potentials on the record. 4×10^{-7} is first threshold for the normal muscle. The maximum depolarization at threshold was 4 mV in the denervated and 7 mV in the normal. Calibration 5·0 mV.

DISCUSSION

The main alteration which has been found in the membrane constants of denervated muscle is an increase in the membrane resistance. A possible explanation of this would be a lowering of the potassium conductivity of the membrane. Harris & Nicholls (1953) have found that the uptake of tracer K per unit weight is reduced in denervated muscles. A reduction in potassium permeability alone would tend to reduce the resting potential, yet no change was observed in the resting potential of the denervated fibres. Using the equation of Hodgkin & Katz (1946), it can be calculated that halving the potassium permeability would reduce the resting potential by 7% (6 mV in

this case) which is far greater than the standard errors of the mean (0·5 and 0·9 mV in denervated and normal fibres respectively). It is possible that there are changes in the permeability or intracellular activity of other ions beside potassium, which compensate for the effect of the reduced potassium flux.

The increase in membrane resistance accounts partly for the increased sensitivity of denervated muscle to electric current—less current is required for a given depolarization. The reduction in critical depolarization causes a further lowering of threshold. Since the membrane current is proportional to $1/\sqrt{r_m}$, one would expect a reduction of I_c by approximately 30% in a muscle whose membrane resistance was doubled. With intracellular recording I_c was reduced by about 30% and the critical depolarization by only one-seventh in an average denervated fibre. With external electrodes, however, far greater reductions in current and depolarization were found. This is probably because the most excitable fibres of a muscle are selected in the 'external' measurement of threshold (see Methods) and the fibres of denervated muscle appear to have a wider scatter of excitability than those of normal muscle. There is better agreement between the results of external and intracellular recording, if the values found for the most excitable fibres in denervated and normal muscle are compared.

These results confirm the previously reported reduction in rheobase but do not account for the apparent *decrease* in sensitivity to currents of short duration observed in denervated muscles *in situ*, where the chronaxie is increased (Pollock *et al.* 1946; De Smedt, 1950*a*). Possibly the membrane capacity is increased in denervated mammalian muscle; alternatively the decreased sensitivity *in situ* may arise from atrophy of the fibres and consequently increased shunting.

The increase in membrane resistance and reduction in critical depolarization cannot account for the increase in sensitivity to ACh, which is of a greater order of magnitude. Thus fifty times less ACh is necessary for a given depolarization of denervated muscle and one hundred times less ACh will produce action potentials. The way in which a smaller amount of ACh is able to produce a given depolarization in denervated muscle is still not understood.

SUMMARY

1. The electrical properties of denervated and normal frog muscle have been compared. The membrane constants (measured on the M. extensor longus. dig. IV, cf. Katz, 1948) are altered by denervation. The length constant, λ, is increased and the membrane resistance, R_m, is doubled. With the membrane capacity unchanged, this gives rise to an increased time constant.

2. The resting and action potentials measured by intracellular electrodes are not changed after denervation. In 311 fibres from denervated sartorius muscles, the mean resting potential was $85 \pm 0{\cdot}5$ mV (S.E.) and in 118 normal

fibres the mean was $85 \pm 0{\cdot}8$ mV. The reversed p.d. during the action potential was 30 mV in denervated fibres and 27 mV in normal fibres.

3. The minimum current required to stimulate is reduced by about one-third in an average denervated fibre, although there is greater reduction in the threshold of the most excitable fibres. In addition, there is a reduction in the critical depolarization at which action potentials are initiated, which, with the increase in R_m, explains the increase in sensitivity to electrical stimulation.

4. The increase in sensitivity to ACh is many times too great to be accounted for by these measurements. The threshold concentration of ACh which produces action potentials is reduced by a factor of one hundred; the depolarization with threshold concentrations is restricted to a region corresponding to that of the 'end-plates' in normal muscle.

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