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Plasticity in Mammalian Skeletal Muscle [and Discussion]

A. J. Buller, R. Pope, G. Melvill Jones and D. M. Lewis

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Plasticity in mammalian skeletal muscle

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While it has been recognized for many years that different limb muscles belonging to the same mammal may have markedly differing contractile characteristics, it is only comparatively recently that it has been demonstrated that these differences depend upon the motor innervation. By appropriately changing the peripheral nerve innervating a mammalian skeletal muscle, it is possible to change dramatically the contractile behaviour of the reinnervated muscle.

The manner by which the motor innervation determines the nature of a muscle fibre's contractile machinery is not completely understood, but it appears that the number and pattern of motor nerve impulses reaching the muscle play an important role. The biochemical changes occurring within muscle fibres whose contractile properties have been modified by altered motor innervation include the synthesis of different contractile proteins.

Introduction

By the year 1958 J. C. Eccles and his associates had accumulated a very considerable volume of data on the pattern of monosynaptic connections established with anterior horn cells by the afferent nerve fibres entering the lumbar segments of the cat's spinal cord. In that year Eccles designed a series of experiments to examine the extent to which the normal monosynaptic connections could be modified by operative procedures performed on newborn kittens. Within 24 h of birth aseptic operations were performed on each of the animal's two hind limbs. On both sides the nerves innervating two muscles having antagonistic actions across the ankle joints were completely cut across. On the side which was to act as a control the proximal and distal cut ends of each nerve were sutured together so that normal reinnervation of the two muscles could occur. On the experimental side the distal end of one cut nerve was sutured to the proximal end of the other cut nerve, and vice versa, so that cross-reinnervation of the two muscles took place. The kittens were allowed to recover from the anaesthetic and left to lead normal lives, insofar as that was possible within the confines of an animal house, for periods of between six and twelve months.

One of us (A.J.B.) had the good fortune to be present when the first of the terminal experiments was undertaken in Canberra in 1958. The cat, then some 10 months old, was prepared for microelectrode recording from the anterior horn cells of those motor axons which had been cut across during the earlier aseptic operation. Various peripheral nerves in the lower limbs were sectioned and their central cut ends prepared for stimulation in the manner described by Eccles, Eccles & Lundberg (1957). A lengthy experiment ensued during which many anterior horn cells were examined but it became increasingly apparent that in the particular animal under study, no obvious differences existed between the spinal monosynaptic connections on the experimental side and those on the control side. As the experiment drew to an unexciting conclusion J. C. Eccles (Rose Eccles was also present) remarked that we had better confirm that the muscles which had been acutely denervated at the time of the aseptic operation

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had become satisfactorily reinnervated. He picked up a pair of stimulating electrodes and applied them successively to the distal ends of the cut motor nerves. On the control side the muscle contractions, observed with the naked eye following single shocks to the motor nerve, appeared perfectly normal, but on the experimental side the twitch contractions were not at all as expected. Unintentionally Eccles had designed an experiment that demonstrated the marked plasticity of mammalian skeletal muscle.

In order to understand the significance of Eccles's observation, and to appreciate his remarkable perceptiveness as an experimenter, it is necessary to recall that the limb muscles of many laboratory mammals including the cat and the rat, may be divided into two groups, the fast-twitch muscles and the slow-twitch muscles. Measured isometrically the twitch contraction of a fast-twitch muscle in an adult cat has a time to peak (the time from the start of the isometric contraction to the instant of peak tension development) of 20–25 ms, and a half relaxation time (the time from the instant of peak tension development until the tension has fallen to half its peak value) of 17–19 ms. For a cat slow-twitch muscle the time to peak is 65–75 ms and the half relaxation time 80–90 ms. These differences between the twitch contractions of fast-twitch and slow-twitch muscles are sufficiently great to be appreciated by the experienced eye. In designing his cross-reinnervation experiments Eccles had, by chance, used one fast-twitch muscle and one slow-twitch muscle in each limb. His earlier studies of the isometric responses of mammalian skeletal muscles (Cooper & Eccles 1930) had provided Eccles with the experience to spot that the cross-reinnervated muscles had an inappropriate speed of contraction, the normally fast-twitch muscle having a longer and the normally slow-twitch muscle a shorter contraction time than was normal. Eccles immediately appreciated the significance of his unexpected observation, and his first series of cross-reinnervated cats were used to study the changes in isometric responses of the reinnervated muscles (Buller, Eccles & Eccles 1960).

Although the central theme of this paper will be the changes which may be produced in mammalian skeletal muscle by alterations of its motor innervation, it would be inappropriate to leave this backward glance into physiological history without mentioning that Eccles subsequently returned to study the plasticity of monosynaptic connections onto anterior horn cells. By using the nerves to two fast-twitch muscles which had antagonistic actions across the ankle joint, it was demonstrated that cross-reinnervation could produce a significant increase in the number of 'aberrant' monosynaptic connections. However, the results suggested that after birth there remained only a small degree of plasticity within the cat spinal cord (Eccles, Eccles & Magni 1960).

Eccles's initial observation on the influence exerted by the motor innervation on mammalian skeletal muscle raised two questions. First, what part of the contractile machinery within the muscle fibres was altered by cross-reinnervation, and secondly, how did the motor innervation bring its influence to bear. These questions will be dealt with in turn.

Contractile changes following cross-reinnervation

The early studies of the contractile characteristics of cat self-reinnervated and cross-reinnervated fast-twitch and slow-twitch muscles were undertaken using only isometric recording (Buller *et al.* 1960; Buller & Lewis 1965). Using this technique it was unambiguously demonstrated that the twitch time to peak of cat fast-twitch muscle reinnervated by the nerve that had formerly supplied the soleus muscle (a slow-twitch muscle) was greatly slowed, the

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time to peak values obtained being comparable to those observed in normal or self-reinnervated soleus muscles. In contrast the soleus muscle of the cat reinnervated by the nerve that had formerly supplied the flexor digitorum longus muscle (a small fast-twitch muscle) invariably had its time to peak shortened, but never to such low values as were observed in normal or self-reinnervated fast-twitch muscle. Thus it appeared that there was some asymmetry in the contractile changes which could be produced in muscle by cross-reinnervation. The results obtained were similar whether the aseptic operation was performed on new-born kittens or adult cats. Furthermore, other characteristic differences in the behaviour of normal mammalian fast-twitch and slow-twitch skeletal muscle, such as the transient effect of a short tetanus upon the size of a subsequent twitch response (Brown & Euler 1938), and the effect upon the twitch size of a 10 °C fall of muscle temperature (Buller, Ranatunga & Smith 1968), were also noted to alter asymmetrically following cross-reinnervation. Fast-twitch muscle reinnervated by the former nerve to soleus showed a complete transformation in its behaviour both to a brief tetanus and to a fall of temperature, whilst the soleus muscle reinnervated by the former nerve to flexor digitorum longus (FDL) showed either no change in behaviour to either test, or a modest reduction in the magnitude of the change characteristic of normal or self-reinnervated slow-twitch muscle.

In 1964 Russell Close, working in Eccles's department at Canberra, published the first detailed description of the contraction characteristics of mammalian muscle using after-loaded isotonic recording (Close 1964). He demonstrated two major differences between the force-velocity relationships of adult rat hind-limb fast-twitch and slow-twitch skeletal muscle. First the maximum shortening velocity (which he expressed in terms of micrometres per second per sarcomere) of fast-twitch muscle was approximately 2.5 times greater that of slow-twitch muscle, and second, the downward convexity of the force-velocity curve of fast-twitch muscle was less than that of slow-twitch muscle. Since Close used the Hill equation to fit his experimental data (Hill 1938), the greater downward convexities of the slow-twitch muscle force velocity curves were associated with smaller values for the ratio of a/P_0. These smaller ratios are probably related to the greater efficiency of slow-twitch muscle (Woledge 1968; Gibbs & Gibson 1972; Wendt & Gibbs 1973).

Close followed his study of the isotonic characteristics of normal muscles with an examination of the influence of self-reinnervation and cross-reinnervation on the force-velocity curves of rat fast-twitch and slow-twitch muscles (Close 1965, 1969). In parallel with the findings of those who had used isometric recording and cat muscles, Close found that self-reinnervation produced no change in the dynamic responses of either type of muscle, but that cross-reinnervation produced marked changes. However, in apparent contrast with the findings of the earlier isometric studies, Close demonstrated symmetrical changes in the force-velocity curves following cross-reinnervation of fast-twitch and slow-twitch muscle. It therefore appeared that there was a conflict between the results obtained from the cat and those obtained from the rat. In retrospect it is remarkable that it took so long to attribute the apparent difference between the cat and the rat to the different nerves which were being used for cross-reinnervation. In the cat Buller and his successive colleagues had used the soleus as the slow-twitch muscle and the flexor digitorum longus muscle as the fast-twitch muscle. The choice of slow-twitch muscle was determined by anatomical constraints, and since similar constraints occurred in the rat as in the cat Close and his successive colleagues also used the soleus muscle as their slow-twitch muscle. However, in both species, the choice of a suitable fast-twitch muscle was greater. In the

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cat the flexor digitorum longus was chosen because, in a normal animal, the two muscles (soleus and FDL) produce very similar maximum tetanic tensions, and are therefore instrumentally convenient. In the rat, the extensor digitorum longus (EDL) was chosen, apparently because it provided the maximum separation of the two nerve unions following cross-reinnervation. The maximum tetanic tension produced by the rat EDL is considerably greater than that produced in the same animal by the soleus muscle. Subsequent experiments in both Bristol and Canberra (Buller & Kean 1973; Luff 1974, 1975) have clearly illustrated that the degree of conversion of cross-reinnervated slow-twitch muscle is determined by the particular fast-twitch nerve that is used. Thus in the cat an effectively complete transformation of soleus to muscle of the fast-twitch type may be achieved by cross-reinnervation with either the nerve which previously innervated the large flexor hallucis longus (FHL) or the nerve to the extensor digitorum longus muscle, while in the rat incomplete transformation of the soleus muscle results from its cross-reinnervation with the nerve which previously innervated the flexor digitorum longus. A full explanation for the differing degrees of conversion exerted by various motor nerves when used to cross-reinnervate slow-twitch muscle is not yet available, but it may be related to the ease with which individual muscle fibres are reinnervated by different single motor nerve fibres (Hoh 1975).

Biochemical changes following cross-reinnervation

Pari passu with studies of the isometric and isotonic contraction characteristics of mammalian muscle there has been increasing interest in the biochemical differences between fast-twitch and slow-twitch muscle. A considerable number of histochemical studies have been undertaken by a variety of workers. For example, differences in phosphorylase and succinic dehydrogenase concentrations between normal fast-twitch and slow-twitch muscle have been demonstrated, as have alterations in the histochemical profile of muscle following cross-reinnervation, but these results will not be considered in detail. However, reference must be made to the biochemical changes in the contractile proteins which accompany (and presumably account for) the contractile changes following cross-reinnervation. The pivotal concept in much of this work has been the hypothesis, first proposed by Bárány (1967), that the ATPase activity of myosin is the rate limiting step which determines a muscle's maximum shortening velocity. This certainly appears to be true for cat and rat skeletal muscles. Furthermore, the changes in maximum shortening velocity following cross-reinnervation in both the cat and the rat mirror the measured changes in ATPase activity (Buller, Mommaerts & Seraydarian 1969; Bárány & Close 1971). More recent studies of the contractile proteins following cross-reinnervation have also demonstrated reciprocal changes in the myosin light chains (Weeds, Trentham, Kean & Buller 1974) and the polymorphic form of troponin I, but not of tropomyosin or troponin C (Amphlett *et al.* 1975). It certainly appears that the motor innervation determines the characteristics of at least some of the contractile proteins in skeletal muscle, and that it is the changes in these proteins following cross-reinnervation which produces the alterations in the isometric and isotonic contractions.

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The nature of the neural influence

If it is indeed the alterations in the contractile proteins which produce the changes in a muscle's mechanical response following cross-reinnervation how does the motor innervation bring about the biochemical changes? In their first paper on cross-reinnervation Buller *et al.* (1960) suggested two possible explanations. First, that the frequency of nerve impulses reaching a muscle, or their aggregate number over a period of time, might be the determinant factor.

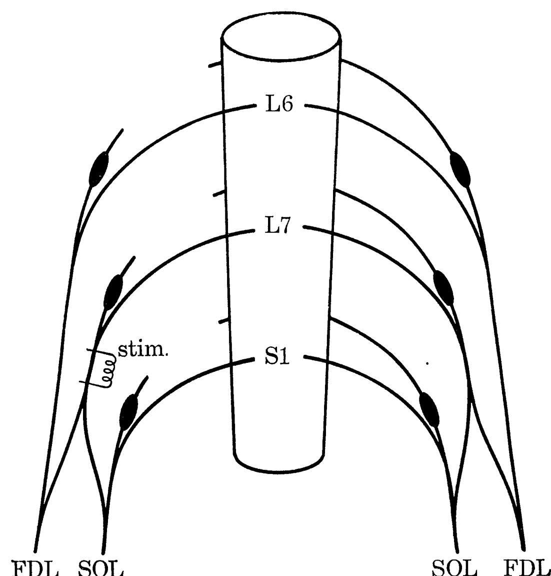

Figure 1. Diagram illustrating the experimental arrangement for chronic stimulation. L6, L7, S1 indicate the spinal lumbar and sacra segments. Stim. indicates the position of the stimulating electrodes. FDL indicates the nerve to the flexor digitorum longus (fast-twitch) muscle and SOL indicates the nerve to the soleus (slow-twitch) muscle.

Secondly, that some trophic substance or substances were involved, and that the continuous release of such material from the motor nerve endings onto the muscle fibres determined the latter's biochemical behaviour. While conceding that the first explanation was the simpler, it was discarded in favour of the second, primarily because the frequency of nerve impulses reaching both types of muscle was known to vary markedly over any 24 h period. In retrospect this reasoning may be seen to be fallacious since the variability of impulse frequency in any nerve fibre will be effectively averaged by the turnover time of the contractile proteins, but this was not appreciated in 1960. Notwithstanding an expressed preference for the trophic hypothesis (Buller *et al.* 1960) Eccles, Eccles & Kozak (1962) sought changes in the isometric twitch time of cat fast-twitch muscles following percutaneous stimulation of their motor nerves at a frequency of 10 Hz for 2–10 min every 24 h over periods of 8 weeks. The results were equivocal, and it was left to Gerta Vrbová and her collaborators (Vrbová 1966; Salmons & Vrbová 1969; Pette, Smith, Staudte & Vrbová 1973) to demonstrate with successively increasing clarity that the isometrically recorded time to peak of mammalian fast-twitch muscle could be increased to values normally found in slow-twitch muscle by chronic stimulation at a frequency of 10 Hz. It is also now known that the slowing of the twitch response is associated with a decreased ATPase activity and a change in the light chains of the muscle myosin (Streter, Gergely, Salmons &

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Romanul 1973). It was therefore of interest to look for changes in the force velocity relationship of chronically stimulated fast-twitch muscle.

The experimental arrangement used by us is illustrated in figure 1. Intradural resection of the dorsal roots of spinal lumbar segments 6 and 7 and sacral segment 1 was performed under aseptic conditions. Stimulating electrodes were placed on the mixed L7 root and connected to a 10 Hz stimulator mounted on the cat's back. The animal was then allowed to recover from the anaesthetic. In every animal 2 days were allowed to elapse before the stimulator was switched on.

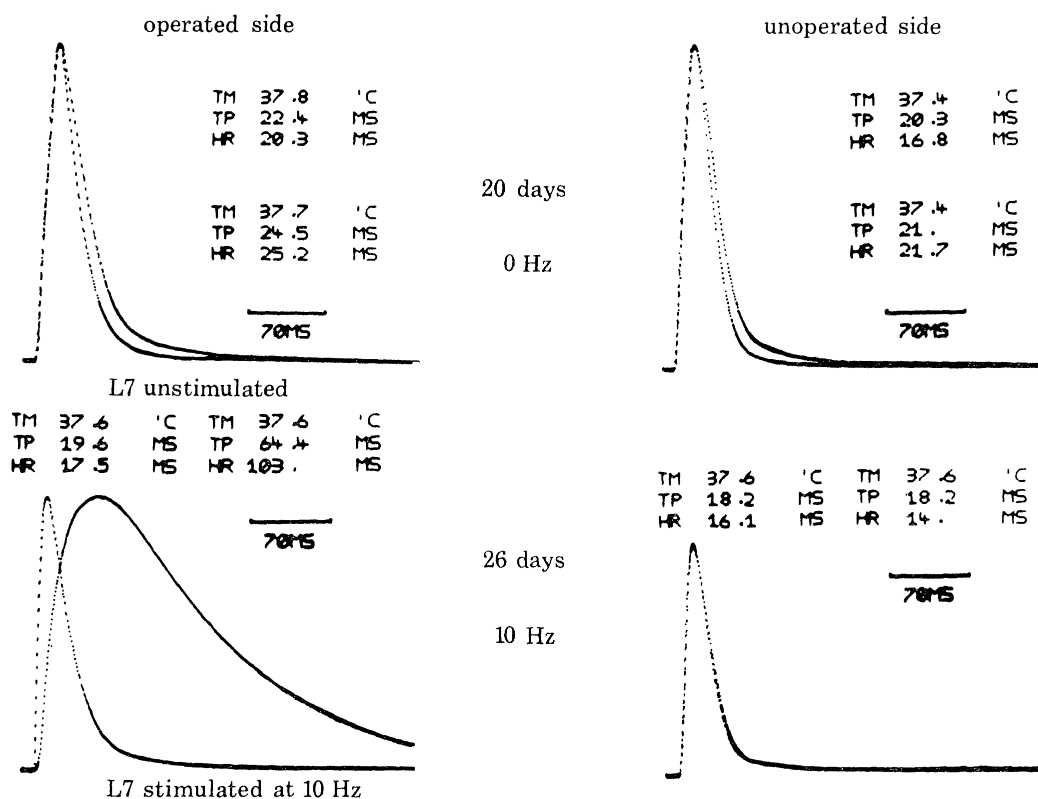

Figure 2. Each of the four pairs of responses illustrates the superimposed maximal isometric twitch contractions obtained following separate stimulation of the L6 and L7 ventral roots. The records on the left were obtained from the operated (deafferentated side), those on the right from the control side. In the upper left hand pair of records the L7 root was not stimulated (although electrodes had been placed on the nerve). In the lower left hand pair of records the L7 root had been stimulated at 10 Hz. The alphanumeric displays show, for each twitch, the muscle temperature (TM measured in °C), the time to peak and time of half relaxation (TP, TR each measured in ms). The dotted nature of the traces is due to the sampling time of the computer. For explanation see text.

In the cat the motor nerve supply to the FDL muscle is provided from the ventral roots of lumbar segments 6 and 7. Although there is considerable animal to animal variation in the proportion of the muscle innervated by each of the two roots, in a single animal there is remarkable similarity between the pattern of innervation on the right and left hand side. Without chronic stimulation previous work had shown that for periods up to 8 weeks after unilateral L6, L7 and S1 deafferentation (the longest intervals examined) there were no detectable differences between the isometric or isotonic contraction characteristics of the FDL muscle on the

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operated side and those on the normal side (Al-Amood 1973). This remains true whether, at the terminal experiment, the muscle is activated by stimulation of the L6 root, stimulation of the L7 root or stimulation of the muscle's motor nerve. The present experimental arrangement allowed prolonged stimulation of those motor units within the FDL muscle which were innervated via the L7 ventral root, and, at the terminal experiment, a comparison to be made of their contractile behaviour and the behaviour of the motor units within the same muscle which were innervated via the unstimulated L6 root. Also the responses obtained from the FDL muscle on the deafferented side could be compared with those obtained from the FDL muscle on the normal side.

Figure 2 shows the isometric twitch responses obtained from the FDL muscles of two animals. The two upper illustrations were obtained from an animal in which stimulating electrodes were placed on the left L7 root but stimuli were applied only for a few seconds (to confirm the adequacy of the stimulating circuit) on each of the second, ninth, sixteenth and twentieth day after deafferentation. This animal, together with one other similarly treated save that it was left for 40 days after deafferentation, acted as controls for the presence of stimulating electrodes in contact with the L7 root. The upper illustrations of figure 2 show, on the left, two superimposed twitches obtained from FDL on maximal stimulation of first the left L6 root and then the L7 root, and, on the right, the superimposed twitches of FDL obtained following stimulation of the L6 root and then the L7 root on the animal's right (normal) side. In all four illustrations of figure 2 the two twitch amplitudes have been made to coincide by adjustment of the amplifier gain in order to make comparison of the time to peak values easier. It is apparent from the two upper pictures that, in the absence of chronic stimulation, the isometric time to peak of that part of FDL muscle innervated by the L6 root is very similar to that of the part innervated by L7, and that the two times to peak recorded on the deafferented side (left) are similar to those recorded on the normal side (right).

The lower pair of illustrations, taken from an animal in which the left L7 root had been stimulated at 10 Hz for 26 days, confirm the results of Vrbová and her colleagues. On the animal's left side (left hand picture) stimulation of the L6 root results in a normal fast-twitch response, but a single stimulus applied to L7 root results in a twitch response resembling that normally obtained from a slow-twitch muscle. The lower right hand section of figure 2 demonstrates that on the right side of the same animal stimulation of the L6 and L7 roots produced twitch responses with identical times to peak.

Figure 3 demonstrates the changes in time to peak (above) and half relaxation time (below) with different durations of chronic stimulation. In both the upper and lower illustrations the filled circles indicate the value obtained at the terminal experiment on stimulating the L7 root, and the open circles the value obtained following stimulation of the L6 root. The two filled squares at 20 and 40 days indicate the values obtained following stimulation of the L7 root of animals which had effective stimulating electrodes on that root, but in which 10 Hz chronic stimulation had not been applied. It is apparent that the changes in the value of both the time to peak and half relaxation time take time to develop, but there is a suggestion that complete conversion from the values expected from fast-twitch muscle to values similar to those normally occurring in slow-twitch muscle may occur within 4–5 weeks. It is certainly true that after four weeks the twitch response of the chronically stimulated part of the FDL muscle exhibits behaviour following a short tetanus or a fall temperature of 10 °C which exactly mimics the characteristics of normal slow-twitch muscle.

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Figures 4 and 5 illustrate the force-velocity data obtained from some of the animals whose isometric data is given in figure 3. On the left of figure 4 the hatched area completely encloses the seven force-velocity curves constructed from the isotonic data obtained from seven L6 roots on the deafferented side. On the right of figure 4 are illustrated the two fitted force-velocity curves (Hill 1938) obtained from the two unstimulated L7 roots on the deafferented side. All nine force-velocity curves of figure 4 fall within the range found for a large sample of FDL force-velocity curves from normal animals (Buller, Kean & Ranatunga, unpublished), both in respect of maximum velocity of shortening and curvature.

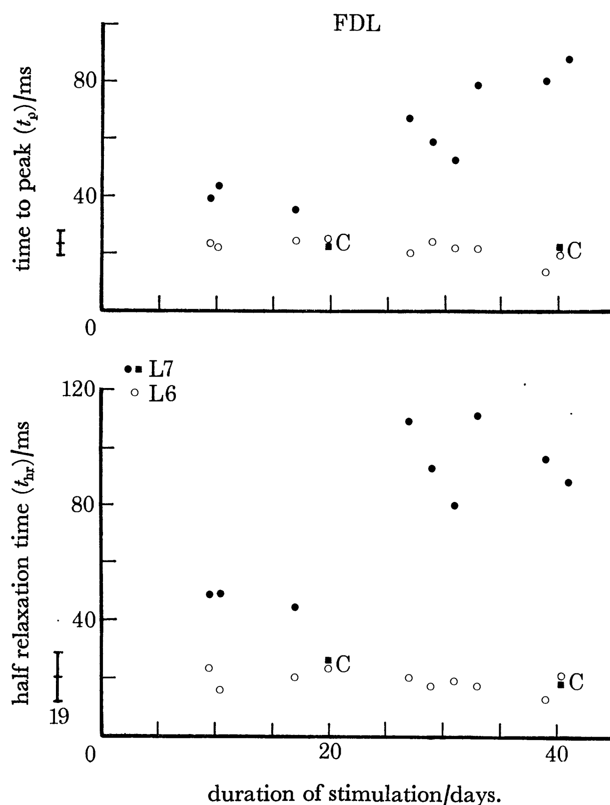

FIGURE 3. The time to peak (upper graph) and half relaxation time (lower graph) obtained from the FDL muscle following stimulation of the L7 (●, ▪) and L6 (○) ventral roots, plotted against days after deafferentation. The L7 root had been chronically stimulated at 10 Hz in all animals, save the two controls (▪C). The vertical bars outside the two ordinates give the range of values obtained in 19 unilaterally deafferented but unstimulated animals in which stimulating electrodes were not implanted on the L7 root.

Figure 5 illustrates the force-velocity data obtained from seven chronically stimulated L7 ventral roots. On the left, the hatched area completely encloses all the fitted force-velocity curves obtained from animals stimulated for durations ranging from 10 to 41 days. On the right are the two Hill curves fitted to the data obtained from L7 roots that had undergone stimulation for 33 and 41 days (isotonic data was not obtained on a cat stimulated for 39 days, and for which isometric data is included in figure 3). While the left-hand part of figure 4 includes curves which fall within the range of both normal fast-twitch and normal slow-twitch muscle (and some which are alien to both normal ranges), the two curves shown on the right-hand side of figure 4 illustrate both the low maximum velocity of shortening and the greater downward

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convexity (low values of a/P_0) which are characteristic of normal cat soleus muscle (Buller, Kean & Ranatunga, unpublished data).

If the results of the isometric and isotonic experiments are pooled there can be little doubt that the prolonged imposition of a 10 Hz pattern of stimulation on normal cat fast-twitch muscle causes that muscle to change its contractile properties so that they become very similar to those characteristic of normal cat slow-twitch muscle. However, there remain one or two anomalous findings, for example the twitch/tetanus ratio of chronically stimulated fast-twitch muscle is high compared with that of normal slow-twitch muscle, but such discrepancies may be the result either of the use of an inappropriate frequency of chronic stimulation, or to some associated trophic effect.

It is of considerable interest that recently two reports have appeared which illustrate that rat slow-twitch muscle may be caused to assume the isometric characteristics of rat fast-twitch muscle by means other than cross-reinnervation. In the first of these reports Lømo, Westgaard

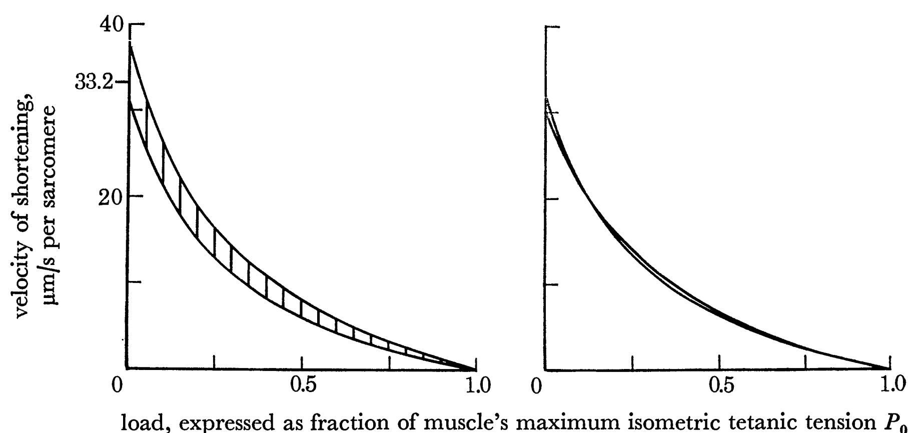

FIGURE 4. Force–velocity data from FDL muscles. On the left: the results obtained following stimulation of seven L6 roots on the deafferented side (interval after deafferentation ranged from 10–41 days). $a/P_0 = 0.343$. On the right: the Hill curves for two unstimulated L7 roots obtained 20 and 40 days after deafferentation. $a/P_0 = 0.369$.

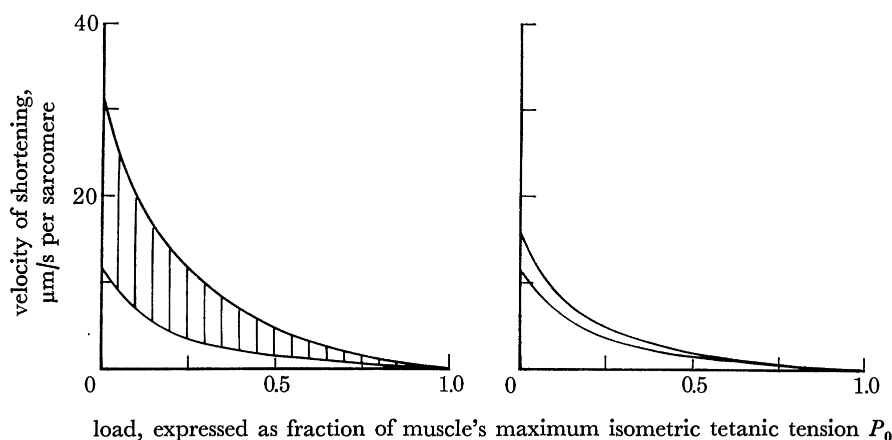

FIGURE 5. Force–velocity data from FDL muscles. On the left: the results obtained following stimulation of seven L7 roots which had been chronically stimulated at 10 Hz following deafferentation (interval after deafferentation ranged from 10 to 41 days). On the right: the Hill curves for two L7 roots that had undergone chronic stimulation at 10 Hz for 33 and 41 days. The mean value for the ratio a/P_0 is 0.176 for both graphs.

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& Dalh (1974) stimulated denervated rat soleus muscles for 3–6 weeks with brief trains of stimuli at 100 Hz. In the second series of experiments Hoh & Dunlop (1975) observed the transformation of the isometric contractions of rat soleus muscle towards those characteristic of fast-twitch muscle 6–11 weeks after transection of the lower thoracic cord at 4 weeks of age. They attributed the changes to an inferred alteration in the pattern of activation of the soleus muscle.

Conclusion

It is now incontroversial that the pattern of nerve impulses reaching a muscle has a profound influence upon the contractile properties of that muscle. It is also clear that mammalian muscle exhibits marked plasticity and, even in adult life, may be modified as a result of prolonged altered activation. The pattern of motor nerve impulses appears to exert its influence on muscle by determining the nature of the protein synthesis within the individual muscle cells. It is possibly this concept, namely that the protein synthesis of a post-synaptic cell may be markedly influenced by the pattern of impulses reaching the surface of that cell, which may prove of general interest to this discussion meeting on plasticity in the nervous system.

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Discussion

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Presumably the innervation of successfully adapted cross-innervated muscles would be called upon to generate new patterns of neural activity to match their new function in movement control. Is there any evidence that changes occur in (1) their fully adapted patterns of neural activity and (2) patterns of reflex response, for example to peripheral or vestibular stimulation?

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There is other evidence that nerves may be affected by cross-innervation. If soleus nerve is cut and then allowed to reinnervate its own muscle, the mean conduction velocity of the α motor axons above the site of section is less than normal, as would be expected. However if soleus nerve is allowed to cross reinnervate a fast muscle (FDL), there is no reduction in the mean motor axon conduction velocity. The conduction velocity of FDL axons is the same whether they reinnervated FDL or soleus.