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Adaptation of rat extensor digitorum longus to overload and increased activity

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Abstract. Rat extensor digitorum longus (EDL) muscles were overloaded by removal of the synergist tibialis anterior (TA). The weight of the overloaded muscle was increased 15 days after the initial operation and remained higher throughout the period studied (153 days). The times to peak twitch tension and half relaxation remained unaltered, but the twitch and tetanic tensions developed by the overloaded EDL muscles increased. The overloaded EDL muscles became significantly more fatigue resistant. In a separate group of animals the overloaded EDL muscle was also chronically stimulated at 10 Hz. The additional stimulation altered the response of the EDL to overload in that the time to peak twitch tension of the muscle was slightly prolonged. There was no increase in twitch or tetanic tension in spite of the increase in muscle weight, but the electrical stimulation led to a further increase in fatigue resistance above that seen in overloaded muscles. The histochemical and immunocytochemical examination of the muscle revealed that there was a moderate increase in succinate dehydrogenase activity in the muscles overloaded only, but a considerable increase in those overloaded muscles that were also stimulated. There was no obvious change in the number of muscle fibres that reacted with an antibody to slow myosin in either overloaded only or overloaded and stimulated EDL muscles. Thus the addition of continuous activity to overload induced a slowing of contraction and prevented the increase of force usually induced by overload.

Key words: Muscle – Overload – Activity – Adaptation

Introduction

Physiological and biochemical properties as well as molecular characteristics of mammalian skeletal muscle depend on activity [13]. Yet similar types of activity have different effects on homologous muscles of different species of animals. The fast contracting tibialis anterior (TA) and extensor digitorum longus (EDL) muscles of rabbits and cats are converted into slow contracting muscles when stimulated electrically with a pattern of activity resembling that of motoneurons to slow muscles [2, 13, 15]. However, the same pattern of activity when applied to homologous muscles of smaller mammals such as the rat does not change the contractile properties of their muscles [11]. In rabbits, in addition to changes of contractile speed, this low frequency stimulation induces also the expression of slow myosin, but this does not occur in rats [17], even when the EDL or TA muscles are denervated and stimulated [16]. This different response of homologous rat muscles to long-term stimulation may occur either because the muscles in this species are inherently different and are unable to adapt to low frequency stimulation in the same way as rabbit muscles, or it may be due to different environmental conditions, such as hormone levels of the animal or the amount of load they are subjected to while activated.

It is interesting in this context that while chronic stimulation of rat TA or EDL muscles does not induce the appearance of the slow myosin isoform, overloading the rat plantaris and soleus muscles leads to the expression of the slow myosin isoform in a large number of muscle fibres that do not usually contain it [8]. The importance of load for the regulation of myosin expression has also been demonstrated in the tonic anterior latissimus dorsi muscles (ALD) of the chick, where an increase of load leads to a more rapid transition from the slow myosin isoform SM1 to the SM2 isoform [9].

In addition to load, hormones, particularly the thyroid hormones, have been shown to influence myosin expression in stimulated rat skeletal muscle [10]. While low frequency stimulation of the EDL and TA muscles of euthyroid animals fails to induce the expression of slow myosin, in rats with reduced levels of thyroid hormones slow myosin expression occurs in stimulated muscles. These results indicate that the apparent limited adaptive range of rat fast muscles is not an inherent characteristic

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of their muscles, as proposed by Schiaffino et al. [16] but rather a consequence of environmental factors such as higher levels of thyroid hormones in small mammals, in addition to a relatively smaller load bearing function of their muscles.

In this study we attempted to study the effects of increased load on the response of the EDL muscles to chronic low frequency stimulation. In addition the adaptive change of the EDL muscle to increased load alone was also studied.

Preliminary results have been communicated to The Physiological Society [5].

Materials and methods

Changes of the EDL were studied in two different experimental situations. In one group of animals the right EDL muscle was overloaded by removing its agonist TA as described below. In another group of animals, in addition to removing the TA muscle, the EDL was also stimulated via implanted electrodes.

Surgical procedures. Female Wistar rats (6 to 8 weeks old) were anaesthetized with chloralhydrate (45 mg per 100 g body weight, i.p.). Under aseptic conditions, the distal tendon of the TA muscle was sectioned above the retinaculum and the muscle was then separated from the underlying structures by blunt dissection and cut as close as possible to its proximal insertion. Care was taken to stop any bleeding before closing the wound. In some animals following the excision of TA and during the same anaesthesia, the peroneal nerve on the same side was exposed and stimulation electrodes implanted. Two teflon coated wires, insulated except for the tips, were led subcutaneously to the peroneal nerve through an incision at the back of the animal and secured either side of the nerve. A miniature plug attached to the proximal end of the electrodes was secured at the place of the incision at the back where it did not interfere with the movements of the animals and was well tolerated by the rats. Wounds on the leg and back of the animal were closed.

Preparation of the electrodes. The electrodes used for stimulation consisted of a pair of teflon coated stainless steel wires protected in silicone tubing. The insulation was removed from both ends. One end was attached to a miniaturised silicone coated plug and the other exposed end was shaped into a loop and prepared for implantation in the leg.

Stimulation. As soon as the progress of the wound healing permitted, the animals were connected to a programmable constant current stimulator (COMPEX, Medicompex SA, Ecublens, Switzerland) through the implanted plug. The leads between animals and stimulator were protected by a light soft metal spring in a manner that allowed the animals to move freely during the stimulation. Pulses of 0.2 ms of alternating polarity were used. The current intensity was adapted individually in order to obtain strong but still comfortable contractions of the overloaded EDL. The muscles were stimulated at 10 Hz, 8 h a day, 5–6 days a week as long as the implanted stimulation system remained functional.

Assessment of contractile properties and fatigue resistance. The animals were anaesthetized with chloralhydrate as above and contractile properties as well as fatigue resistance of both experimental as well as contralateral control EDL were recorded in situ: the distal tendon of both EDL muscles was dissected and prepared for attachment to an isometric force tranducer. The sciatic nerve was sectioned and the common peroneal nerve was dissected in the popliteal fossea. The leg was secured by pins to a rigid steel plate. The tendons of the EDL muscles were then attached to a force transducer and isometric contractions were elicited by stimulating the common peroneal nerves.

The length of the muscle was adjusted so as to produce maximal tension during a single twitch contraction. Tetanic contractions were elicited by stimulating the nerve for 600–800 ms at 40, 60, 80 and 100 Hz. After completion of these recordings the fatigue resistance of the muscle was tested. The muscles were stimulated at 40 Hz for 250 ms every second. A fatigue "index" was calculated by dividing the force developed after 3 min of stimulation by that developed during the first contraction of the test.

Histochemistry and immunohistochemistry. Following the tension recordings, control and experimental EDL muscles were removed from the animal under a terminal chloralhydrate anaesthesia and frozen in melting isopentane. Transverse cryostat sections were collected and processed for succinate dehydrogenase (SDH) [12]. Immunohistochemistry was performed using a specific antibody against slow myosin [4]. The total number of slow myosin positive fibres per muscle was counted in experimental and control EDL on camera lucida drawings.

Statistics. The level of significance of differences between means was determined using 2-tailed *t*-tests for paired or unpaired data as appropriate and indicated in the text. A difference was considered significant if $P \leq 0.05$.

Results

Effect of overload on contractile properties and muscle weight of EDL

Contractile properties and muscle weight of overloaded EDL were determined 12–153 days after the removal of its agonist TA. The contractile properties of the EDL muscles of 19 animals were assessed. In 8 additional animals it was impossible for technical reasons to complete the experiments, but muscle weight and histochemistry were established. Thus, muscle weight of 27 pairs of EDL could be determined.

Records of tension recordings from an overloaded EDL and its control are shown in Fig. 1. In this and many other experiments the overloaded EDL was slightly faster contracting than its control. The maximal twitch tension (Fig. 1 c) as well as the maximal tetanic tension (Fig. 1 d) were higher compared to the control side.

The ratio of operated over contralateral control side of muscle weight and time to peak tension of each indi-

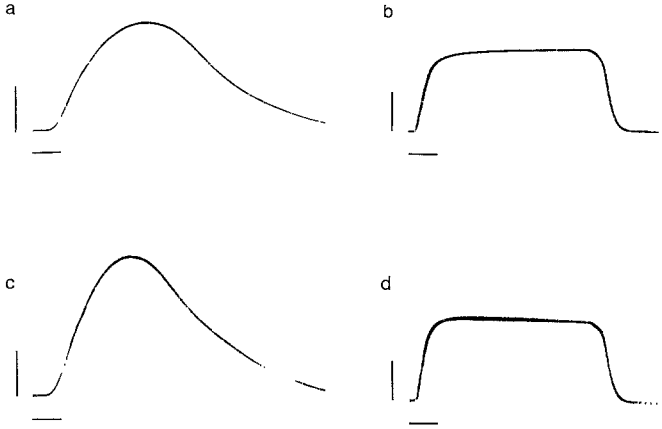
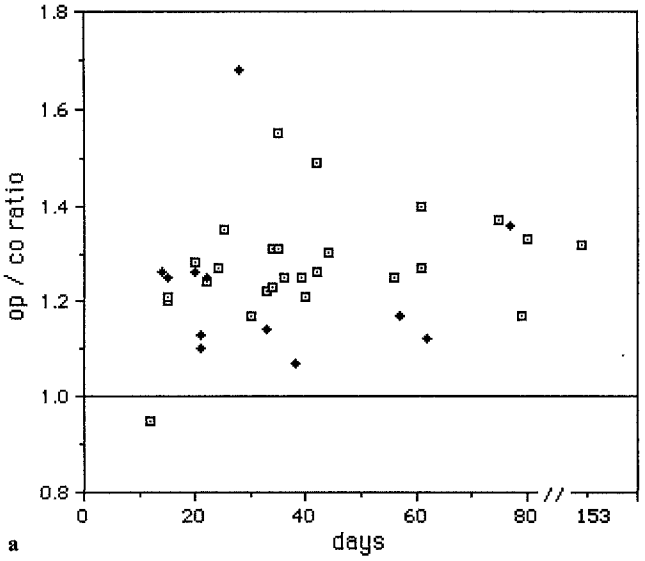


Fig. 1 a–d. Effect of 35 days of overload on EDL maximal twitch tension and maximal tetanus. The *traces* represent maximal twitch tension (**a, c**) and maximal tetanus at 100 Hz (**b, d**) recorded from an overloaded EDL (**c, d**) and its control (**a, b**). *Horizontal bars* indicate 10 ms in *traces* **a** and **c**, 100 ms in *traces* **b** and **d**. *Vertical bars* represent 25 g in *traces* **a** and **c**, 100 g in *traces* **b** and **d**. Twitch and tetanus of the overloaded muscle show an increased speed and force of contraction



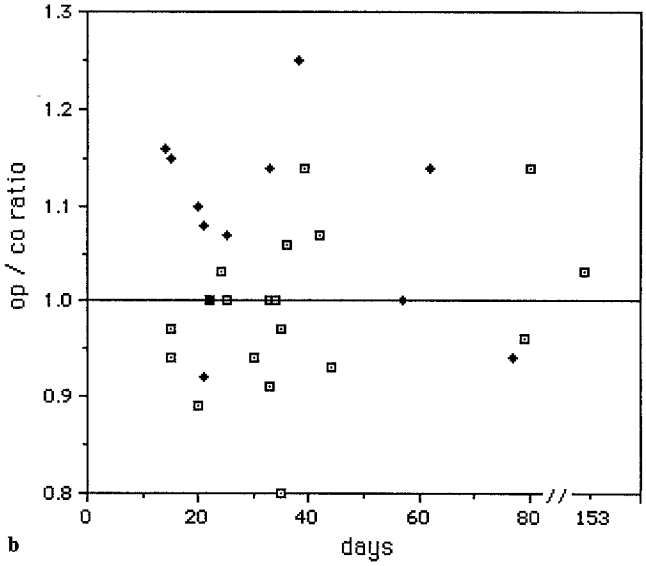


Fig. 2. Effect of overload and overload combined with low frequency stimulation on **a** muscle weight and **b** time to peak contraction of EDL. The weight and time to peak contraction of each experimental EDL (*op*) is expressed as a ratio of the contralateral control (*co*) muscle and plotted against the duration of the overload (days). □, Values obtained from EDL muscle overloaded only; ◆, Overloaded stimulated muscles. Stimulation started 6±1 days (mean±SEM) after the beginning of the overload. An increase in muscle weight is already present 2–3 weeks after overload and remained so thereafter over the whole period studied. In both groups the increase in muscle weight was similar. In the overloaded and stimulated EDL the time to peak contraction was already increased after 10 days of stimulation (2 weeks of overload) and remained so thereafter

vidual experiment are shown as a scatter diagram in Figs. 2a and b. An increase in muscle weight was already present 15–20 days after the beginning of the overload and there was no further increase if the overload was prolonged. As the quantitative changes shown in Fig. 2 seem to be similar for periods of overload between 14 and 61 days, the individual results from overloaded EDL examined during this time interval were pooled and the mean values±standard error are shown in Table 1. Although the time to peak twitch tension was decreased by up to 7 ms in many experiments, there was no significant decrease of the mean value compared to the control muscles. Maximal twitch and tetanic tensions increased less than muscle weight, so that tension development per mg of muscle tissue decreased by 10% and 11% for maximal twitch tension and maximal tetanus respectively.

Table 1. Effect of overload only on contractile properties and weight of EDL

Parameter	Group		*p* value
	Control EDL	Overloaded EDL	
Time to peak tension	34.8 ±1.8 ms	33.9 ±1.7 ms	0.282
Half relaxation time	36.6±2.6 ms	37.8±2.4 ms	0.590
Maximal twitch tension	49.6±3.6 g	56.0±3.7 g	0.034
Maximal tetanic contraction	187.5±9.2 g	208.6±7.5 g	0.015
Muscle weight	126.4±4.2 mg	161.6±4.8 mg	<0.001
Maximal twitch tension per mg muscle	0.40±0.03 g	0.35±0.02 g	0.039
Tetanic tension per mg muscle	1.52±0.08 g	1.30±0.03 g	0.007

Duration of overload between 15 and 61 days (see text). All values are means±SE. The *P* values refer to a 2-tailed *t*-test for paired data ($n = 16$ for all means except muscle weight where $n = 22$). There is a significant increase in maximal twitch tension, maximal tetanic contraction and muscle weight. The speed of contraction and relaxation remain unchanged. Note also the significant decrease of maximal twitch tension and maximum tetanic contraction per mg muscle

Effect of overload and long-term low frequency stimulation on contractile properties and muscle weight of EDL

Twelve rats had their right EDL overloaded as described above and had their overloaded muscles stimulated at 10 Hz for 10–70 days. Stimulation was started as soon as the wound healed resulting in a delay of 6±1 days (mean±SEM) between the beginning of the overload and the stimulation. The tension recordings obtained from one of the experiments are shown in Fig. 3. The time to peak tension of the overloaded and stimulated EDL was longer when compared to that of the contralateral control side. The twitch and tetanic tensions were occasionally reduced in the experimental muscle and Fig. 3 shows an example from an experiment where this was the case. The ratio of operated over contralateral control side of muscle weight and time to peak contraction of each individual experiment are shown on the scatter diagrams in Figs. 2a and b.

The first 3 muscles, overloaded for 14, 15, and 20 days and stimulated for 10, 11 and 15 days respectively, already show an increase of the time to peak tension of the stimulated muscle compared to its contralateral control. The slowing of the twitch occurred therefore quite early and did not change over periods of stimulation up to at least 58 days (62 days of overload). An increase in muscle weight was also present and could be seen already after 10–15 days of stimulation (14–20 days of overload).

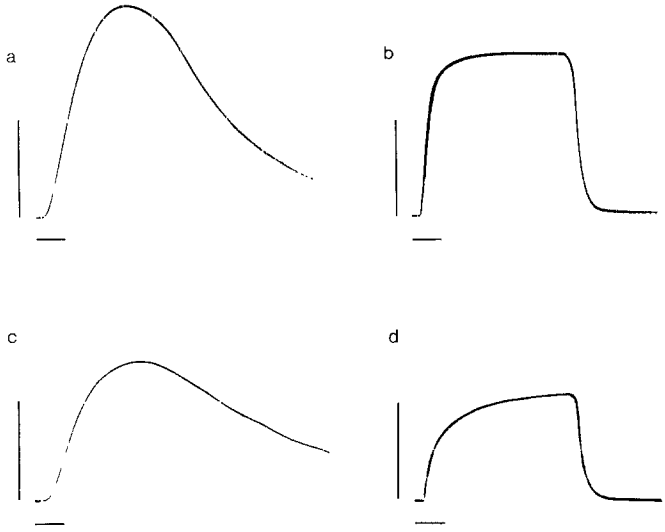


Fig. 3a–d. Effect of 14 days of overload combined with electrical stimulation for 10 days on maximal twitch tension and maximal tetanus of EDL. The *traces* show twitch tension (**a, c**) and maximal tetanus at 100 Hz (**b, d**) recorded from an overloaded and stimulated EDL (**c, d**) and its control (**a, b**). *Horizontal bars* indicate 10 ms in *traces* **a** and **c**, 100 ms in *traces* **b** and **d**. *Vertical bars* represent 25 g in *traces* **a** and **c**, 100 g in *traces* **b** and **d**. Twitch and tetanus of the overloaded stimulated muscle have a decreased speed and force of contraction

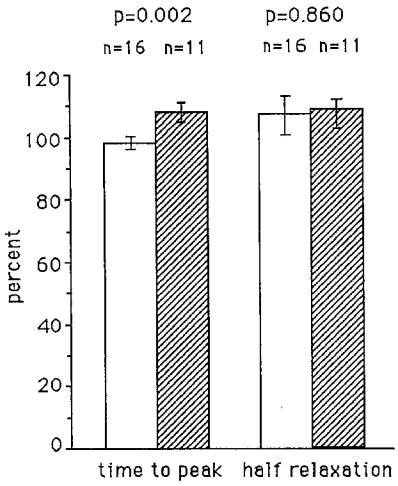


Fig. 4. Comparison of the speed of contraction and relaxation of overloaded only and overloaded, stimulated EDL. The time to peak tension and the half relaxation times were expressed as a percentage of the control side. The same data pools as for Tables 1 and 2 were used. The mean percentage ± SE are given for overloaded only (*plain columns*) and overloaded, stimulated (*shaded columns*) EDL. *n* is the number of experiments. The significance of the difference between the two groups is given by the *P* value of a 2-tailed *t*-test for unpaired data. There is a significant increase of the time to peak tension if low frequency stimulation was added to the overload, whereas overload alone does not affect the contractile speed

As for the muscles overloaded only the results obtained over a period of 10–58 days of stimulation (overload of 14–62 days) were pooled and the mean values ± standard error of results are shown in Table 2. There was a small but significant increase of the time to peak tension and half relaxation time, but other parameters such as maximal twitch and tetanic tension were not significantly different from control muscles. The muscle weight increased by 22% and therefore the tension development per mg tissue decreased by 20% for both twitch and tetanus.

Table 2. Effect of overload and long-term low frequency (10 Hz) electrical stimulation on the contractile properties and weight of EDL

Parameter	Group		*p* value
	Control EDL	Overloaded and stimulated EDL	
Time to peak tension	30.6 ± 1.9 ms	33.1 ± 1.4 ms	0.019
Half relaxation time	29.3 ± 2.1 ms	31.9 ± 2.4 ms	0.033
Maximal twitch tension	53.3 ± 2.8 g	50.8 ± 2.6 g	0.304
Maximal tetanic contraction	192.0 ± 8.0 g	185.6 ± 11.6 g	0.622
Muscle weight	123.5 ± 4.4 ms	150.3 ± 7.3 mg	0.002
Maximal twitch tension per mg muscle	0.43 ± 0.02 g	0.34 ± 0.01 g	0.005
Maximal tetanic contraction per mg muscle	1.59 ± 0.06 g	1.27 ± 0.11 g	0.009

The experimental muscles were stimulated for periods between 10 and 58 days (overloaded for 14–62 days, see text). All values are means ± SE. The *P* value refers to a 2-tailed *t*-test for paired data ($n = 11$, except for maximal tetanic contraction and maximal tetanic contraction per mg muscle where $n = 10$). The time to peak tension of the overloaded and stimulated EDL is significantly increased as are half relaxation time and muscle weight. Maximal twitch tension and maximal tetanic contraction remain unchanged. Note also the significant decrease of force output per mg muscle

Comparison of effects of overload and overload and stimulation on contractile speeds and force

In order to compare directly changes induced by overload alone and those by overload and low frequency stimulation, the various parameters measured were normalised and expressed as a percentage of the contralateral control muscle. The same data shown in Tables 1 and 2 (period of overload between 14 and 63 days) were used. These values were then compared for the overloaded only EDL and overloaded stimulated EDL.

The stimulated overloaded muscles had a significantly prolonged time to peak twitch tension as compared to the EDL overloaded only as shown in Fig. 4. There was

Table 3. Effect of overload and overload combined with low frequency electrical stimulation on the fatigue resistance index of EDL

Group	*n*	Fatigue resistance index	
		Control side	Experimental side
Overloaded EDL	15	0.234 ± 0.026	0.452 ± 0.034*
Overloaded and stimulated EDL	10	0.278 ± 0.033	0.578 ± 0.068*

The fatigue resistance index was calculated as described in Methods. The values given are means ± SE. *, Significantly different from the control side, $P < 0.001$ (2-tailed *t*-test for paired data). Overload alone increases the fatigue resistance significantly. If combined with electrical stimulation the increase in fatigue resistance is bigger, but the additional increase of the fatigue resistance is not significant ($P = 0.178$, 2-tailed *t*-test for unpaired data)

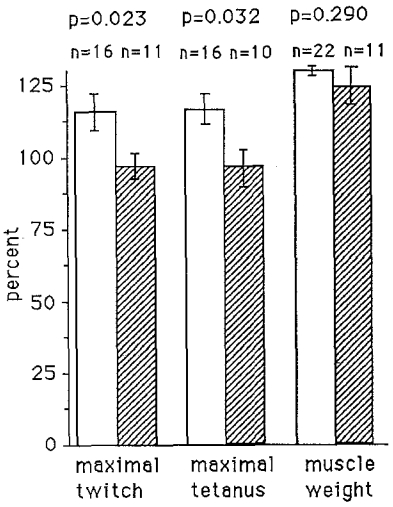


Fig. 5. Comparison of force of contraction and muscle weight of overloaded only and overloaded, stimulated EDL. The force of the maximal twitch and the maximal tetanus as well as the muscle weight were expressed as a percentage of the control side. The same data pools as for Tables 1 and 2 were used. The mean percentage ± SE are given for overloaded only (*plain columns*) as well as overloaded and stimulated (*shaded columns*) EDL. *n* is the number of experiments. The significance of the differences observed between the two groups is given by the *P* value of a 2-tailed *t*-test for unpaired data. Low frequency stimulation significantly prevents the increase in muscle force brought about by overload only, whereas the same increase in muscle weight is seen in both groups

no difference in their speed of relaxation. Moreover Fig. 5 illustrates that low frequency electrical stimulation prevents the increase in maximal twitch and maximal tetanic tension brought about by the overload while muscle weights increased to a similar extent in both groups.

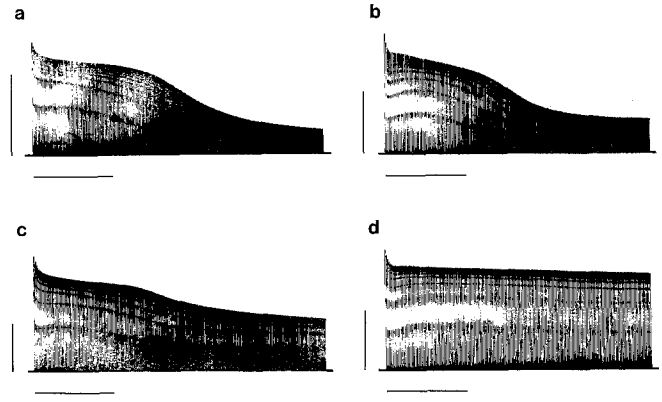


Fig. 6a–d. Effect of overload alone and overload associated with low frequency electrical stimulation on the fatigue resistance of EDL. The fatigue resistance was tested by stimulating the muscles for 250 ms every second at 40 Hz. *Panels* **a** and **b** are control muscles to **c** and **d** respectively. *Horizontal bars* represent 1 min, *vertical bars* 100 g force. In **c** the EDL was overloaded for 44 days whereas in *d* the muscle was overloaded for 20 days and stimulated for 15 days. **c** Overload alone clearly increases the fatigue resistance, but not to the same extent as if low frequency stimulation is associated (**d**). Note the much higher initial tetanus of the overloaded EDL in **c** compaired to the control muscle (**a**, different force *scale*) whereas the overloaded stimulated muscle **d** produces about the same force as its control **b**

Effect of overload and overload combined with low frequency electrical stimulation on the fatigue resistance of EDL

The values of the fatigue resistance of overloaded only and overloaded and stimulated EDL are given in Table 3. Overload alone significantly increased the resistance to fatigue. Stimulation increased the fatigue resistance further but this further increase was not significant. Recordings are shown in Fig. 6, of a fatigue test from experiments on an animal that had its EDL overloaded (Fig. 6a, c) and an animal that in addition to overload had its EDL muscle also stimulated (Fig. 6b, d). As illustrated in Fig. 6, while there is some decrease of tension in the muscles overloaded only there is hardly any change in the tension produced by the overloaded and stimulated EDL (Fig. 6d).

Histochemical examination of the muscles was also carried out. Inspection of the slides revealed that in the muscles overloaded only there appears to be a slight increase in the intensity of the reaction of SDH within some muscle fibres (Fig. 7b). When the overload was combined with low frequency stimulation a dramatic transformation of the muscle took place resulting in an increase in SDH staining in all muscle fibres (Fig. 7d).

Effect of overload and overload combined with low frequency electrical stimulation on the total number of slow myosin positive fibres of EDL

There is no difference in the number of slow myosin positive fibres in either overloaded only or overloaded and stimulated EDL (Fig. 8, Table 4).

Discussion

The present results show that continuous low frequency electrical stimulation modifies the outcome of the effect of overloading a rat fast muscle. The rat EDL muscle, after removal of its synergists, was able to adapt to a greater functional demand by hypertrophy, increased force output and fatigue resistance. In spite of these clear indications of adaptive changes there was no alteration of the time course of contraction or relaxation. Although some previous reports indicated that such changes do take place in the rabbit flexor digitorum longus [18] or rat plantaris [3] our present results could not detect such changes in rat EDL muscle. This is consistent with earlier results of Binkhorst et al. [1] in overloaded rat plantaris. In the present experiments the overloaded muscles showed a tendency to become faster contracting. Thus the overload produced very specific changes of some, but not other, muscle characteristics. The specificity of these changes is probably associated with the particular functions that such an overloaded muscle has to carry out in its new situation. In addition to increased stretch during locomotor activity [6] a general increase in overall activity of the muscle may also contribute to the development of some of the observed changes. It was therefore surprising that in our present experiment a further increase in activity cancelled some of the changes induced by the

Table 4. Total number of slow myosin heavy chain positive fibres in individual muscles of overloaded only and overloaded and stimulated EDL

Overloaded EDL			Overloaded and stimulated EDL			
Duration of overload (days)	Control side	Experimental side	Duration of overload (days)	Duration of stimulation (days)	Control side	Experimental side
15	81	78	20	15	198	209
35	145	70	21	14	158	151
44	189	201	33	25	215	255
			38	25	125	119
Means ± SEM	138 ± 32	116 ± 43			174 ± 20	184 ± 30

There is no increase in the number of slow myosin positive fibres in either overloaded or overloaded and stimulated EDL

overload, in particular the increase in force output of the muscle. Interestingly, although the force output did not increase, the overloaded stimulated muscle did undergo hypertrophy so that the force per unit weight was less in these muscles than in unoperated control EDL muscles. In addition the chronic electrical stimulation of the overloaded muscle induced a change of the time course of contraction in that the time to peak tension was slightly prolonged. This has not been seen in muscles that have been stimulated without an overload [11], or when the muscles were overloaded but not simulated. The present results therefore clearly show that different functional demands induce specific changes in muscle properties and these are induced either by increased neuromuscular activity, or by a change in the biomechanical conditions under which the muscle is operating. The two stimuli can sometimes be additive, as in the case of muscle fatigue, where overload alone did increase the muscle's fatigue resistance, and this was further augmented by added electrical stimulation.

The present results do not allow us to elucidate the mechanisms that lead to these changes in muscle properties, either after overload alone, or in combination simulation. Nevertheless, certain indications as to what may be causing particular changes are evident from some of our results. The increase in fatigue resistance seen in overloaded muscles is probably caused by an increased capillary density, which was clearly noticeable on inspection of cross-sections stained for alkaline phosphatase. On the other hand the changes in oxidative enzymes appear to be

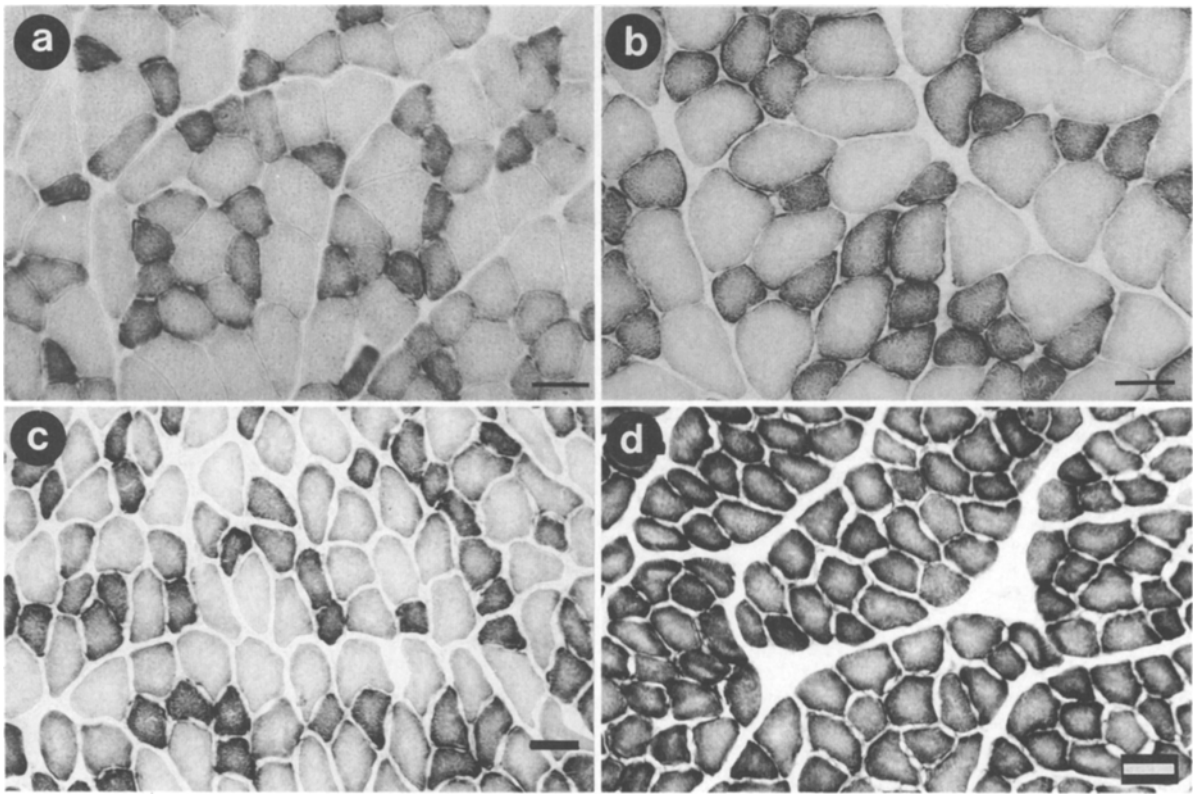


Fig. 7. Effect of overload and overload with low frequency electrical stimulation on succinate dehydrogenase activity (SDH) of EDL. The SDH activity was visualized histochemically. **a** and **c** are control muscles to **b** and **d** respectively. In **b** the EDL was overloaded for 44 days. In **d** the EDL was overloaded for 62 days and stimulated for 58 days. Overload alone hardly changes the metabolic muscle fibre pattern, whereas a homogeneously SDH positive muscle results if low frequency electrical stimulation is associated. *Bars* represent 0.05 mm

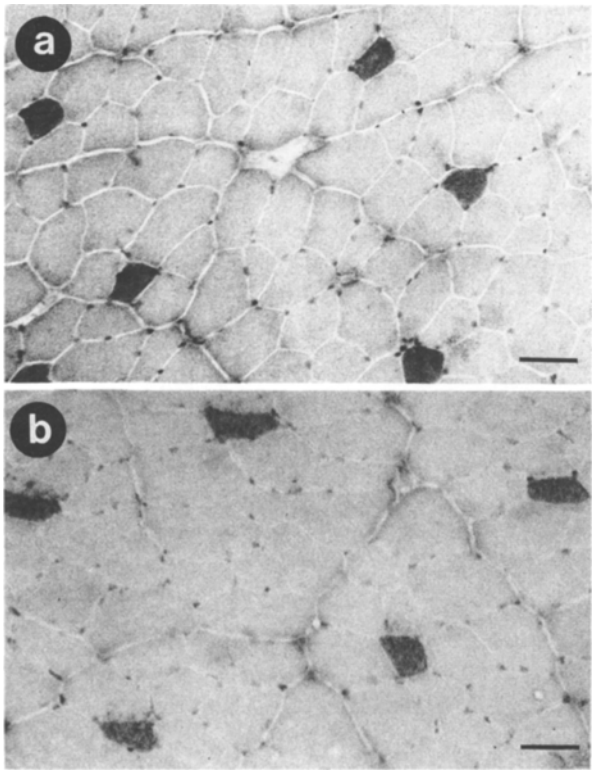


Fig. 8a, b. Effect of overload combined with low frequency electrical stimulation on slow myosin heavy chain expression in EDL. **a** Control muscle, **b** experimental muscle overloaded for 77 days and stimulated for 70 days. There is no obvious difference in the proportion of slow myosin positive and negative fibres, although slow myosin positive muscle fibres are hypertrophied in the experimental muscle. Bars represent 0.05 mm

only slight considering the large change in fatigue resistance. Examples where fatigue resistance is dissociated from changes in oxidative enzymes have been reported in previous studies in chronically stimulated muscles [7] and our results are consistent with those reports. It is however possible that the increase in capillary density can lead only to a limited improvement of the muscles fatigue ability, and that to increase the fatigue resistance beyond this point, (as induced by low frequency stimulation) the increase of oxidative enzymes may be necessary. It may be that the usually accepted association of increased oxidative capacity of the muscle with an increase of fatigue resistance is apparent only in these extreme situations.

Unlike in rabbit fast muscles the time course of contraction of rat EDL muscles is not altered by low frequency electrical stimulation, and neither does overload on its own affect this parameter of muscle function. Yet the combination of the two conditions does lead to an increase in the time to peak contraction. This increase is unlikely to be due to a change in the myosin molecule, for it occurs very quickly within 10 days after commencement of the stimulation, which is not long enough for this transition to occur, since earlier experiments have shown no increase in slow myosin expression in rat fast muscles stimulated for up to 56 days [17]. Moreover, when muscle fibres were reacted for the presence of slow myosin heavy chains, there was no increase in the number of fibres that contained this molecule in either experimental situation. The slowing of the contraction is therefore more likely to be due to a change other than that of the myosin. Finally, it is unclear why the stimulation prevents the increase in force output seen after overload only, though it could be that replacing contractile machinery with mitochondria as seen in rabbits [14] may be responsible for this. The overloaded and stimulated EDL seems to give priority to the adaptation to activity over the adaption to overload.

In conclusion the present results show that the muscle has the potential to adapt in a highly specific way to various challenges, and that this may be of great practical importance when attempting to modify muscle function during exercise or in patients that suffer from neuromuscular disorders and require either muscle strengthening, or modifications of their fatiguability.

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