Comparison Between Animal and Human Studies of Skeletal Muscle Adaptation to Chronic Stimulation

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Functional electrical stimulation (FES) has recently emerged as a clinical tool for treatment of neuromuscular disorders. Chronic muscle stimulation, however, has long been used by basic scientists studying the details of the muscular adaptation process. Biochemical, morphological, and functional changes occur in skeletal muscle secondary to chronic stimulation. Chronic stimulation (12-24 hours per day for six weeks) results in a well-defined progression of changes in which a "fast" muscle becomes a typical "slow" muscle with a large decrease in force-generating capacity. On the other hand, clinical studies of FES have demonstrated muscle strengthening following treatment. An attempt is made to reconcile the results obtained in the two fields.

It has been demonstrated under a variety of conditions that skeletal muscle adapts to the level of use imposed upon it. As a result of this plasticity, the use of functional electrical stimulation (FES) to strengthen skeletal muscle was originally proposed. Several studies suggested that FES might decrease or delay the effects of disuse atrophy. Preliminary studies promoting the use of FES to regain muscle function lost after upper motor neuron lesion have been heralded. Additionally, FES has been reported to reduce postoperative rehabilitation time, aid in the correction of flexion contractures, and improve or augment muscle function. However, because the physiologic basis of FES has yet to be elucidated, there is no general agreement on stimulation parameters, stimulation doses, or stimulation conditions.

In contrast to the recent emergence of FES as a clinical tool, chronic electrical stimulation has long been used to study skeletal muscle adaptation because it induces a repeatable, quantifiable amount of "exercise." The best documented effects of electrical stimulation on skeletal muscle are those observed following chronic, low frequency electrical stimulation of "fast" skeletal muscle using implanted electrode systems. In this setting, a well-defined progression of muscular changes is observed that enables investigation of the mechanism and time course of muscle adaptation to chronic stimulation. In basic studies, however, the stimulation time is extraordinary (12-24 hours/day) compared with that usually possible in the clinics, the electrode systems are usually implanted, and the experimental subjects are stimulated during normal cage activity.

What can be learned from these basic...
science studies and applied to the clinical practice of FES? While it is clear that chronic muscle stimulation using implanted electrodes alters skeletal muscle properties in a well-defined manner, it is still not clear whether this treatment modality, when applied in a clinically relevant manner, actually strengthens muscle or otherwise improves its condition. This paper briefly reviews the basic science literature on muscle stimulation to suggest muscular changes that might be induced by clinical application of FES. Portions of this review were contained in an earlier series on muscle adaptation.26

ANIMAL STUDIES OF CHRONIC MUSCLE STIMULATION

The best documented effects of electrical stimulation on skeletal muscle are those that occur after chronic, low-frequency stimulation of a predominantly "fast" muscle during normal cage activity. In this setting, a well-defined progression of changes is observed in which the muscle first changes its metabolic and then its contractile properties to become a "slow" muscle.43 This has been documented in the rabbit tibialis anterior and extensor digitorum longus,17-20,24,39,40,44-47 the rat extensor digitorum longus,18,29,34 the cat intertransverse,41 and the cat peroneus longus and flexor digitorum longus,1,9 therefore the effects observed are probably not species- or muscle-specific. The fast-to-slow transformation that occurs is detectable by measurement of muscle contractile,1,4,9,19,44,45 ultrastructural,10,24,40 histochemical,4,5,18,29,47 biochemical,5,17,20,24,39,40,44,46,47 and morphological4,5,18,40 properties. In all cases, following transformation the new slow fibers are completely indistinguishable from normal slow skeletal muscle fibers. It is also clear, based on time-series studies10,11 and single-fiber biochemistry,34,47 that the changes that occur result from transformation at the level of the single fiber and not from fast-fiber degeneration with subsequent slow-fiber regeneration.

If low frequency stimulation is applied 24 hours per day, the total transformation process requires only about 30 days. The earliest observed changes occur within a few hours after the onset of stimulation when the sarcoplasmic reticulum (SR) begins to swell.10 Within the next two to 12 days, increases are measured in the volume percent of mitochondria, oxidative enzyme activity, the number of capillaries per square millimeter, total blood flow, and total oxygen consumption, thus reflecting the increased metabolic activity of the muscle.4,10,18,20,40 Histochemically, this is reflected in an increased percentage of Type 2A or fast-oxidative-glycolytic (FOG) fibers at the expense of Type 2B or fast-glycolytic (FG) fibers.18,29 At this point, the width of the Z-band begins to increase toward the wider value observed for normal slow muscle.10 The amount and activity of the calcium transport ATPase decrease and change the particle distribution within the SR bilayer.17,24,29,44,47 This decrease in the amount and activity of the calcium ATPase can be detected physiologically as a prolonged time-to-peak twitch tension and a prolonged relaxation time of a muscle twitch.1,9,19,44 The increase in oxidative enzymes and capillary density is manifested as a decrease in muscle fatigability.19,36,44 Finally, after about four weeks of continuous stimulation, an alteration in the myosin light chain profile is observed whereby the normally fast muscle, containing only light chains LC1f, LC2f, and LC3f, now contains light chains characteristic of slow fibers, i.e., LC1s and LC2s.19,39,46 By this time, muscle fiber cross-sectional area, maximum tetanic tension, and muscle weight have decreased significantly.4,5,18,39 The Z-band is now the full width of that normally observed in a slow fiber, and the density of the T-system is greatly decreased.10 The muscle is now indistinguishable from a normal slow skeletal muscle in every respect.

A number of conclusions can be formed based on this well-established time-course of
transformation: (1) muscle metabolic enzymes, capillaries, SR, and T-system are much more easily altered than contractile proteins and (2) while chronic stimulation does increase muscle endurance capacity, it is not an effective means for strengthening normal muscle. In fact, most studies report a 50%–80% decrease in tetanic tension following chronic stimulation. The effect of stimulation on denervated or tenotomized muscle is much more promising in terms of its clinical applicability. Several weeks of denervation decreases muscle weight and maximum tetanic tension by 30%–40%. Stimulation of muscle following denervation attenuates the decrease in weight and maximum tetanic tension so that the net loss may only be 10%–20%.6,27,28

HUMAN STUDIES OF CHRONIC MUSCLE STIMULATION

The best studied effects of FES in humans are those obtained by isometric stimulation of quadriceps muscles at about 30° of flexion. The treatment usually consists of relatively high frequency stimulation (37–2000 Hz) for less than one hour per day for five to 28 weeks. Muscle forces reached during the treatment periods are reported to be equal to 50%–100% of a subject's maximum voluntary contraction (MVC). Following the treatment period, joint torque,7,13,16,22,25,30–32,36,42 joint range of motion,2,33 and muscle fiber diameters33 have been measured.

Electrical stimulation training in humans results in a moderate amount of muscle strengthening relative to immobilization or inactivity, but no increase relative to voluntary contraction or normal activity. Electrical stimulation superimposed upon voluntary contraction does not strengthen muscle more than either treatment alone.7,30,52 In the case of severely atrophic muscle (as with denervated animal muscle), muscle strength is clearly increased by transcutaneous FES. As in animal studies, transcutaneous FES increases muscle oxidative capacity as evidenced by an increased histochemical succinate dehydrogenase staining intensity33 and decreased muscle fatigability.36 An increase in the passive range of motion has also been observed.2 Interestingly, cases demonstrating increased voluntary motor function secondary to FES treatment (or traditional physical therapy) are mentioned in the literature2,50 although the basis for these observations remains to be elucidated.

COMPARISON BETWEEN ANIMAL AND HUMAN STUDIES

An apparent contradiction exists between animal and human studies. Why do most human studies generally demonstrate muscle strengthening with FES while basic studies show weakening and/or fiber type transformation? The three major differences between most animal and human studies presented to date are that (1) chronic animal FES is usually accomplished using implanted electrode systems while most human muscle is stimulated transcutaneously (cf. References 33 and 36); (2) the stimulation doses in animal studies have been ten to 100 times greater than the doses used in human studies; and (3) human muscle has been stimulated isometrically while animal limbs were allowed to move freely.

First, the difference is probably not related to the implantation of electrodes. It has been shown that because motor nerves have a lower threshold to activation than muscle fibers during electrical activation of a whole muscle, the nerves are first depolarized causing depolarization of the muscle fibers.21 If a subject is curarized (thus blocking neuromuscular transmission), activation thresholds for muscle contraction increase by an order of magnitude. One study has demonstrated no difference in muscle histochemical appearance after chronic stimulation with ei-
ther transcutaneous or implanted electrodes.\textsuperscript{41} Second, increased stimulation dose causes decreased muscle force in basic studies; therefore, that human stimulation doses are much lower than animal doses is probably not responsible for the different degrees of strengthening noted. The difference probably lies in the conditions of stimulation (i.e., isometric vs. free moving). Muscle strengthening depends, to a large degree, on the stress imposed on the muscle. Sprinting exercise, in which fibers are allowed to shorten upon full activation, results in less strengthening than weight-lifting, in which the fibers remain more nearly isometric or even contract eccentrically.\textsuperscript{8} The change in maximum force that occurs as a function of shortening velocity is given by the classic force–velocity equation. For example, if a muscle is stimulated isometrically at 10 Hz, the force developed is equivalent to about 30% of its maximum tetanic tension ($P_0$). Now, if the same muscle is allowed to shorten at a velocity equal to only 10% of its maximum shortening velocity (easily obtainable under physiologic conditions), the force developed is only about 18% $P_0$. Thus, to the extent that muscle stress results in muscle strengthening, the stimulating conditions will influence the results of electrical stimulation training.

In order to reconcile the disparity of animal and human research on FES, future research in FES application to muscle rehabilitation requires an examination of the physiologic basis for the muscular response to transcutaneous stimulation. In order to utilize the available literature on muscle plasticity, experiments must be designed such that direct muscle treatment force is well-defined. Experimental parameters measured must be related to muscle force generating capacity (e.g., isometric torque, muscle fiber diameters) and not simply muscle bulk (e.g., limb volume or circumference). In order to make valid comparisons with the basic science literature, it may be necessary to distinguish between FES treatment of fast and slow normal or atrophied muscle under well-defined conditions. As a result of such studies, FES may be applied to a variety of clinical problems, with underlying fundamental work available to justify the various procedures.

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