ELECTRICAL STIMULATION AND DENERVATED MUSCLE

Updated November 22, 2002

Adams L., Carlson B.M., Henderson L., and Goldman D. (1995) Adaptation of nicotinic acetylcholine receptor, myogenin, and MRF4 gene expression to long-term muscle denervation. J. Cell Biol. 131, 1341-1349.
Abstract: Muscle activity alters the expression of functionally distinct nicotinic acetylcholine receptors (nAChR) via regulation of subunit gene expression. Denervation increases the expression of all subunit genes and promotes the expression of embryonic-type (alpha 2 beta delta gamma) nAChRs, while electrical stimulation of denervated muscle prevents this induction. We have discovered that the denervation- induced increases in alpha, beta, gamma, and delta subunit gene expression do not persist in muscles that have been denervated for periods extending beyond a couple of months. However, expression of RNA encoding the epsilon-subunit remains elevated suggesting a return to expression of predominantly adult-type (alpha 2 beta delta epsilon) nAChR in long-term denervated muscles; a finding confirmed by single channel patch-clamp analysis. Since the nAChR subunit genes are regulated by the MyoD family of muscle regulatory factors, and the genes encoding these factors are also induced following short-term muscle denervation, we determined their level of expression in long- term denervated muscle. Although MyoD and myf-5 RNA levels remained elevated, myogenin and MRF4 RNAs were induced only transiently by muscle denervation. Surprisingly, Id-1, a negative regulator of transcription, was gradually induced in denervated muscle with RNA levels peaking about two months after denervation. It is likely that this maintained level of increased Id expression, in conjunction with the returning levels of myogenin and MRF4 expression, account for the reduced level of embryonic receptors in long-term denervated muscle. These changing patterns of gene expression may have important consequences for the ability of muscle to recover function after denervation

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al Amood W.S., Lewis D.M., and Schmalbruch H. (1991) Effects of chronic electrical stimulation on contractile properties of long-term denervated rat skeletal muscle. J. Physiol 441, 243-256.
Abstract: 1. The contractile properties of fast-twitch (extensor digitorum longus or EDL) and slow-twitch (soleus) muscles in the rat were followed for periods of between 4 and 10 months after denervation. The effects of chronic electrical stimulation during the last 3-8 weeks of denervation were investigated. 2. The fall in tetanic tension that follows axotomy ended after about 4 months' denervation. The equilibrium tension was about 0.75% of control tension in EDL and 0.2-0.3% in soleus. 3. The low tension in soleus was due partly to the small diameter of the muscle fibres (atrophy) and partly to their necrosis that resulted in an 8-fold fall in specific tension (the force per unit cross-sectional area). Similar but less extreme changes occurred in EDL. 4. It is speculated that the final level of tension reached by unstimulated denervated muscles is an equilibrium between decrease in force due to atrophy and necrosis and increase due to regeneration. Differences between the final tension levels in soleus and EDL cannot be accounted for quantitatively by

known differences in atrophy alone. Therefore, the rate of necrosis in soleus and of regeneration in EDL may be higher. 5. Chronic stimulation of long-term denervated muscle increased force generation by about 7-fold in EDL and between 20 and 55 times in soleus. The final tension reached was between 4 and 5% of normal in both muscles. Specific tension of fibres was almost completely restored by stimulation and the number of fibres was normal. The failure to recover full tension was largely due to failure to reverse denervation atrophy completely. 6. Twitch contraction and relaxation times were identical in denervated-stimulated soleus and EDL. There was no evidence for dependence on duration of stimulation or tension of the muscle. The normalized maximum rate of rise of tetanic tension remained higher in EDL than soleus

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Abstract: The effect of electrical stimulation on the stability of junctional ACh receptors (AChR) on soleus muscles of Wistar rats was compared to that of denervation and reinnervation. Denervation causes the degradation rate of the slowly degrading AChRs (Rs) at the neuromuscular junction to accelerate and be replaced by rapidly degrading AChRs (Rr), while reinnervation restabilizes the accelerated Rs. Electrical stimulation initiated at the time of denervation prevented the acceleration of the Rs. It could not, however, reverse the effect of denervation if initiated after the AChRs became destabilized, nor could it slow the degradation rate of the Rr. We conclude that electrical stimulation of denervated muscle downregulates the expression of the Rr and prevents the destabilization of Rs

Askmark H. and Wistrand P.J. (1992) Leakage of carbonic anhydrase III from normal and denervated rat skeletal muscle following contractile activity. Muscle Nerve 15, 643-647.
Abstract: Skeletal muscle extracellular carbonic anhydrase III was investigated in anesthetized rats by a microdialysis technique. A small dialysis probe was inserted into the tibialis anterior (TA) muscle and perfused continuously. Perfusates were collected before and during muscle contraction, induced by electrical stimulation of the muscle or of the sciatic nerve. In the perfusate of resting normal and denervated muscle, the concentration of CA III was 10 to 12 ng/mL, as measured by a radioimmunosorbent technique. During contractile activity, the concentrations of CA III increased markedly in the normal and denervated muscle. A TA muscle suspended in physiological saline behaved similarly, even though the leakage before and during contraction was higher than in vivo. The results show that skeletal muscle leaks CA III both in vivo and in vitro, a leakage which was markedly increased by contractile activity. The microdialysis technique should also be useful in humans to study the efflux of various proteins from different kinds of diseased or fatigued muscles

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Abstract: Isomyosin analyses by biochemical, immunochemical, and histochemical investigations have been carried out in five sheep following unilateral recurrent laryngeal nerve paralysis and direct functional electrostimulation of the denervated cricoarytenoid posterior muscle. Myosin light chains were identified by two-dimensional gel electrophoresis. Myosin heavy chains were analyzed by one-dimensional SDS-polyacrylamide gel electrophoresis. Slow myosin heavy chain was identified by orthogonal peptide mapping and immunochemistry. The stimulation effect at cellular level was determined using adenosine triphosphatase (ATPase) histochemistry. A dramatic increase of the type 1 fiber area (slow, fatigue-resistant fibers) could be seen after many weeks of an increasing regime of low-frequency direct electrical stimulation. Biochemically, the amount of slow myosin was always higher than in normal muscles. Some muscles were transformed almost completely to the slow type. At the time they were studied and with the methods employed, the expression of embryonic isomyosin was not observed. In conclusion, after numerous weeks of maintained functional activity, elicited by direct electrostimulation, the denervated muscle regionally showed areas of hypertrophy or at least lack of atrophy of slow myofibers without major signs of muscle damage

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Abstract: The study was conducted to determine if daily electrical stimulation of denervated muscle, initiated the day following crush denervation and continued for 8 weeks (i.e., 5 weeks after presumptive reinnervation), would influence denervation-associated alterations in muscle size and in situ contractile properties of rat gastrocnemius. A stimulation protocol of brief, strong, isometric contractions was designed to maximize the beneficial effects as described by previous authors. By 8 weeks after crush, unstimulated muscles were still significantly lighter in wet weight, were tetanically weaker, and showed slower isometric contractile responses in situ than controls. Denervated muscles which had been stimulated daily were heavier and tetanically stronger (the latter not different from controls) than those in the nonstimulated group. Muscle weights from groups of animals killed at 2 or 4 weeks after nerve crush indicated the major benefit of stimulation occurred during this initial 4-week period. In situ fatigue properties were unaffected by denervation or stimulation. A protocol of electrical stimulation-evoked strong contractions, initiated soon after denervation and continued after reinnervation, was effective in attenuating the strength-related, but not speed-related, changes in neuromuscular function resulting from denervation. These latter changes are presumably the result of loss of "neurotrophic influence" and/or continuous low-tension muscle activity lost as a result of denervation

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Abstract: The standardized programme of electrical stimulation was applied to the control and denervation atrophied muscle of dog, Canis domesticus and the pattern of changes in the carbohydrate metabolism was analysed in the control (C), denervated control (DC), control stimulated (CS) and denervated stimulated (DS) gastrocnemius muscles. The programme of electrical stimulation of the control muscle has elevated glycogenolysis, glycolysis and increased the level of operation of TCA cycle with decreased mobilization of carbohydrates into hexose monophosphate pathway, indicating the setting in of trained condition. Sciatectomy, on the other hand, lowered the level of operation of glycogenolysis and decreased the utilization of carbohydrates through hexose-mono and di-phosphate pathways and TCA cycle. The programme of electrical stimulation applied to the denervated muscle has restored the utilization of carbohydrates through hexose mono and diphosphate pathways and oxidative metabolism indicating the applicability of this programme of electrical stimulation in the treatment of muscular atrophy

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Abstract: Denervated extensor digitorum longus muscles of Wistar rats were electrically stimulated in vivo for 4 days (2h per day) after peroneal nerve crush 1 cm from the muscle. Isometric contractile properties and endplate ultrastructure were measured on days 11 and 18. On day 11, the time to peak (116% of control) and 1/2-relaxation time (136% of control) for the twitch tensions of stimulated muscles measured in vivo were significantly less than those (127% and 157% of controls, respectively) of non-stimulated muscles. Peak twitch and tetanic tensions were not significantly different. The postsynaptic area of endplates for stimulated muscles were closer in size to controls than those for the non-stimulated ones. On day 18, no difference was found in the contractile responses between stimulated and non-stimulated groups. Similarly, the postsynaptic areas were the same for both groups. These results demonstrate that denervated muscle stimulated electrically for 4 days prior to reinnervation can preserve the structure of the endplate as well as accelerate recovery of normal function in reinnervated muscle fibers after 11 days of denervation

Eberstein A. and Eberstein S. (1996) Electrical stimulation of denervated muscle: is it worthwhile? Med. Sci. Sports Exerc. 28, 1463-1469.
Abstract: Research conducted over the past 25 years has demonstrated that muscle activity, not neurotrophic substances, is the most important factor in the regulation of specific physiological and biochemical properties of muscle fibers. Application of this knowledge has led to considerable experimentation with chronic electrical stimulation

as a possible clinical tool for the treatment of denervated muscles. Evidence accumulated from animal studies has indicated that direct electrical stimulation of denervated muscles can to a large extent substitute for innervation and preserve or restore the normal properties of the muscles. Appropriate stimulation parameters were critical for a successful intervention, and the best results were obtained when the stimulation pattern resembled the firing pattern of the normal motoneuron. Thus, fast muscles required intermittent, brief, high frequency stimulation and slow muscles needed continuous, low frequency stimulation. For human denervated muscles, critical questions still remain to be resolved before electrical stimulation will yield the optimum benefit. Research must be performed in human subjects to define the appropriate stimulation parameters the stimulation current, and the type and placement of electrodes

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Goldberg A.L., Etlinger J.D., Goldspink D.F., and Jablecki C. (1975) Mechanism of work-induced hypertrophy of skeletal muscle. Med. Sci. Sports 7, 185-198.
Abstract: Skeletal muscle can undergo rapid growth in response to a sudden increase in work load. For example, the rat soleus muscle increases in weight by 40% within six days after the tendon of the synergistic gastrocnemius is sectioned. Such growth of the overworked muscle involves an enlargement of muscle fibers and occasional longitudinal splitting. Hypertrophy leads to greater maximal tension development, although decreased contraction time and reduced contractility have also been reported. Unlike normal developmental growth, work-induced hypertrophy can be induced in hypophysectomized or diabetic animals. This process thus appears independent of growth hormone and insulin as well as testosterone and thyroid hormones. Hypertrophy of the soleus can also be induced in fasting animals, in which there is a generalized muscle wasting. Thus muscular activity takes precedence over endocrine influences on muscle size. The increase in muscle weight reflects an increase in protein, especially sarcoplasmic protein, and results from greater protein synthesis and reduced protein breakdown. Within several hours after operation, the hypertrophying soleus shows more rapid uptake of certain amino acids and synthesis of phosphatidyl-inositol. By 8 hours, protein synthesis is enhanced. RNA synthesis also increases, and hypertrophy can be prevented with actinomycin D. Nuclear DNA synthesis also increases on the second day after operation and leads to a greater DNA content. The significance of the increased RNA and DNA synthesis is not clear, since most of it occurs in interstitial and satellite

cells. The proliferation of the non-muscle cells seems linked to the growth of the muscle fibers; in addition, factors causing muscle atrophy (e.g. denervation) decrease DNA synthesis by such cells. In order to define more precisely the early events in hypertrophy, the effects of contractile activity were studied in rat muscles in vitro. Electrical stimulation enhanced active transport of certain amino acids within an hour, and the magnitude of this effect depended on the amount of contractile activity. Stimulation or passive stretch of the soleus or diaphragm also retarded protein degradation. Presumably these effects of mechanical activity contribute to the changes occuring during hypertrophy in vivo. However, under the same conditions, or even after more prolonged stimulation, no change in rates of protein synthesis was detected. These findings with passive tension in vitro are particularly interesting, since passive stretch has been reported to retard atrophy or to induce hypertrophy of denervated muscle in vivo. It is suggested that increased tension development (either passive or active) is the critical event in initiating compensatory growth

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Abstract: Injury of afferent motor axons or pathological loss of motoneurones from the spinal cord causes the remaining axons within a muscle to sprout and to reinnervate the denervated muscle fibres. Sprouting occurs at two sites along intramuscular axons, at nodes of Ranvier (nodal sprouting) and at the neuromuscular junction (terminal sprouting). Terminal sprouting is also produced by treatment with botulinum toxin and by other agents that render muscle inactive. The muscle probably provides a signal for terminal sprouting as restoration of muscle activity by direct electrical stimulation prevents sprouting. Such a signal might be a local change on the muscle fibre surface or a 'soluble' sprouting factor, although the failure to induce terminal sprouting in one muscle by denervating adjacent muscles argues against the latter hypothesis. I now report that rabbit antisera against a 56,000 (56K)-molecular weight protein secreted by denervated rat muscle suppress botulinum toxin-induced terminal sprouting in the mouse gluteus muscle. An immune response against this protein has also been detected in serum of patients with amyotrophic lateral sclerosis (ALS), a disease in which loss of motoneurones from the spinal cord is not accompanied by the degree of sprouting and reinnervation seen in other motoneurone diseases

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Abstract: Electrical stimulation has been widely employed for the treatment of peripheral nerve lesion, however, its effects are not well known. Effects of electrical stimulation on denervated muscles were studied by measuring the weight of anterior crural muscles and the diameter of muscle fibers of the extensor digitorum longus muscle of the rat. The muscle fibers were classified by myofibrillar ATPase reaction. The denervated muscle showed loss of weight, a marked decrease in diameter of type 1 fibers and a small increase in diameter of type 2 fibers. Electrical stimulation suppressed weight loss of the denervated muscles. Electrical stimulation with high frequency cycle, like phasic motoneuron discharges, significantly suppressed the increase in diameter of type 2 muscle fibers. Electrical stimulation with low frequency cycle, like tonic motoneuron discharge, significantly suppressed the decrease in diameter of type 1 muscle fibers

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Abstract: 1. During the differentiation of skeletal muscle, there is a synchronized expression of a number of muscle-specific proteins including the acetylcholine-gated ion channel (AChR). Another muscle- specific ion channel, responsible for chloride conductance, was shown to be expressed in an anticoordinate fashion to AChR. An organ culture system for rat lumbrical muscles was developed to manipulate the expression of these two ion channels. 2. Denervation induced a change in expression of both channels that was mimicked in culture and reversed by direct electrical stimulation. 3. The time course of the disappearance of both channels was similar and started immediately after denervation (chloride conductance) or stimulation (AChR). The time course of the appearance of AChR was delayed several days after denervation and culture but chloride conductance increased immediately upon stimulation. 4. The loss of chloride conductance in muscle cultured in cycloheximide exhibited first-order kinetics, providing an estimate of the half-life (2.3 days) for the chloride conductance channel. This resembled the disappearance of chloride conductance in normal medium, suggesting that synthesis of this channel ceases following denervation. The decrease in chloride conductance characteristic of denervated muscle was not halted by cycloheximide. 5. Changes in chloride conductance presumably alter the intracellular concentration of chloride. The possibility that chloride might regulate the expression of AChRs in skeletal muscle was tested by altering the intracellular concentration of chloride in muscles maintained in organ culture. 6. Denervated muscles, whose intracellular concentration of chloride is elevated, were cultured in medium containing 9 mM-chloride (low-Cl- medium). AChR expression was reduced by either low-Cl- medium or electrical stimulation. Together, low-Cl- medium and electrical stimulation reduced expression more than either treatment alone. 7. The loss of AChRs in low-Cl- medium was blocked when muscle fibrillation was halted by TTX. 8. When chloride conductance was blocked by 9AC (9- anthracene carboxylic acid) intracellular chloride was elevated to the levels seen in denervated muscle. The elevated levels of chloride did not prevent the reduction in AChR expression induced by electrical stimulation. 9. The uncoupling of AChR expression and the intracellular concentration of chloride showed that they were not rigidly linked. Chloride affects the expression of AChR indirectly, by altering the activity of muscle cells

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Abstract: The treatment of peripheral neuropathies should be aimed at maintaining the range of motion of the joints, re-educating the patient in skilled activities and optimizing the recovery of strength. Many techniques have been described to substitute for, to strengthen and to improve the function of residual innervated muscle; however, not all of these techniques are of unquestioned value. Specifically, electrical stimulation does not appear to enhance reinnervation of totally denervated muscle. Similarly, overstretching weakened muscle may impair the use of paretic muscle. Because overwork may damage partially denervated muscle, brief isometric or isotonic contractions may be more beneficial for increasing strength than a program of habitual exhausting activities

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Abstract: Inactivation of skeletal muscle by denervation increases motoneurone survival activity in extracts of skeletal muscle. The present investigation shows that electrical stimulation of denervated muscle decreases motoneurone survival activity in extracts of these muscles. The result suggests that motoneurone survival is dependent on a factor(s) in muscle whose synthesis and/or release is regulated by muscle contraction

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Abstract: The regulation of the number of extrajunctional acetylcholine (ACh) receptors was assayed by 125I-labelled alpha-bungarotoxin binding sites in denervated rat diaphragm muscle in culture. Sustained K depolarization does not eliminate extrajunctional ACh receptors. In fact, muscle cultured in high-K medium (normal Cl) for 3 days exhibits a greater binding capacity than controls. Under conditions in which the intracellular Cl concentration is unaltered (high-K-low-Cl medium) this effect of high-K medium on the number of extra-junctional ACh receptors is blocked. The number of extrajunctional receptors increases 24-48 h after exposure to high-K-normal Cl medium, similar to the time course of the initial appearance of extrajunctional receptors in the denervated diaphragm muscle in vivo or in organ culture in normal media. High-K-normal Cl medium did not alter the rate of receptor degradation. Electrical stimulation of denervated muscle strips cultured in low-Ca medium containing D-600 eliminated extrajunctional receptors as efficiently as stimulation of muscles in control medium. Electrical stimulation did not reduce the extrajunctional ACh receptor population in glycerol-treated uncoupled muscles to the same extent as in untreated muscles. The extrajunctional ACh receptor content of denervated muscle cultured for 3 days in 2 and 5 mM-caffeine was reduced by about half respectively. Denervated muscle cultured in 0.3 mM-caffeine did not differ from control denervated muscle. Other agents which may alter intracellular cyclic nucleotide levels: dibutyryl cyclic GMP, dibutyryl cyclic AMP, papaverine, and sodium nitroprusside, did not mimic the effect of caffeine or electrical stimulation in lowering the levels of extrajunctional ACh receptors. We conclude that intracellular Ca release from the sarcoplasmic reticulum is necessary for the elimination of extrajunctional ACh receptors in denervated muscle. The levels of intracellular Cl also influence the population of extrajunctional receptors. Conditions which lead to higher levels of intracellular Cl result in greater rates of synthesis of ACh receptors

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Abstract: The use of electrical stimulation for denervated muscles is still considered to be a controversial issue by many rehabilitation facilities and medical professionals because prior clinical experience has shown that treating denervated muscle tissue using exponential current over a long time period constitutes an impossible task. Despite this fact, we managed to evoke tetanic contractions in denervated muscle using a long duration stimulation with anatomically shaped electrodes and sufficiently high amplitudes. The pulse amplitudes, which were being used for this purpose, exceeded by far the MED-GV and EC regulations (300 mJ/impulse). For this reason, an application has recently been submitted to have the EC regulations changed accordingly. It takes a tetanic contraction to achieve the desired muscle fiber tension, constituting a hypertrophic stimulus. It is also an appropriate means of exercise, which is capable of creating the metabolic and structural conditions needed (e.g, increased mitochondrial volume and capillary density) to obtain satisfactory muscle performance. With patients suffering from a complete spinal cord injury at level

D12/L1, having motor and sensory loss in both lower extremities, we were able to train denervated muscle using long- duration stimulation, evoking single muscle contractions at first, soon followed by tetanic contractions against gravity. To increase the efficacy of this functional electrical stimulation (FES) strengthening program, we used ankle weights. With daily FES training over a period of 1-2 years, denervated muscle was exercised until it produced torques between 16 and 38 Nm in the m. quadriceps. With that muscle force, it is possible to stand up from a sitting position in parallel bars. Our results show that denervated muscle in humans is indeed trainable and can perform functional activities with FES. Furthermore, this method of stimulation can assist in decubitus prevention and significantly improve the mobility of paraplegics

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Mihelin M., Trontelj J.V., and Stalberg E. (1991) Muscle fiber recovery functions studied with double pulse stimulation. Muscle Nerve 14, 739-747.
Abstract: Direct electrical stimulation with paired pulses at varied intervals was used to study the propagation velocity and action potential amplitude recovery functions (VRF and ARF) of single muscle fibers. Following a subnormal period with slowed conduction, most of the muscle fibers tested in healthy subjects showed a period of supernormal propagation velocity starting at 3 to 12 ms, with a peak between about 5 and 15 ms, a mean increase of 7%, and an approximately logarithmic decay toward 1 second. The onset of supernormality was earlier in muscle fibers from patients with muscular dystrophy and significantly delayed in those from denervated muscles. Denervated muscle fibers also had a significantly longer refractory period

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Abstract: The efficacy of electrical stimulation on a chronically denervated muscle depends on stimulus parameters, which have an important influence on the development of atrophy. Stimulus frequency and/or total activity are particularly responsible for the development of some histological, biochemical and contractile features. The present study in 18 rabbits deals with a recently developed electrical

stimulus, which had proved effective in maintaining muscle force following denervation. This current has (1) unusual long bidirectional rectangular impulses (20 ms) and (2) a frequency of 25 Hz, which is between the frequencies of

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Abstract: The influence of muscular contraction on the oxidative enzymes and the diameters of muscle fibers was investigated. Soleus muscles of guinea pigs were denervated for four weeks. The denervated fibers showed a reduction in the intensity of staining for beta-hydroxybutyrate dehydrogenase, cytochrome oxidase, succinate dehydrogenase, and NADH- dependent tetrazolium reductase. Denervation also resulted in a decrease in fiber diameter. Denervated soleus muscles were electrically stimulated to contract over a four-week period at a frequency normally received by slow contracting muscles. Electrical stimulation caused the stain intensity of histochemical reactions for oxidative enzymes to appear to be normal or greater than normal in 90% of the denervated fibers. Stimulation also caused 69% of the denervated fibers to be of normal or greater than normal size. The results demonstrate that contraction of denervated muscle by electrical stimulation prevents the loss of oxidative enzymes and the atrophy associated with denervation

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Abstract: This experimental study investigated the effects of continuous electrical stimulation on denervated muscle. The canine peroneal nerve was severed and repaired microsurgically, and the denervated extensor muscle group of the leg was stimulated continuously with an implantable electrode and pulse generator. EMG study, muscle force measurement, muscle weight measurement, histology, and histochemistry were performed to study the effect at eight weeks after the operation. Continuous electrical stimulation (pulse frequency 130 pps, burst rate approximately 1 train/min) was effective in decreasing muscle atrophy and in improving muscle force. These findings may have broader clinical applications

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Nix W.A., Reichmann H., and Schroder M.J. (1985) Influence of direct low frequency stimulation on contractile properties of denervated fast-twitch rabbit muscle. Pflugers Arch. 405, 141-147.
Abstract: A continuous electrical 8 Hz impulse pattern imposed directly via implanted electrodes on denervated fast twitch muscle induced changes in its contractile characteristics. Compared with non-stimulated denervated muscle, stimulated muscle showed slowing of contraction time and improved fatigue resistance. The reaction for succinic dehydrogenase was more intense in the denervated stimulated muscle, indicating an increased capacity of oxidative enzymes. The rate of atrophy was not influenced by stimulation. The 8 Hz frequency pattern is the mediator for these changes in the characteristics of denervated muscles. It demonstrates a

comparable effect on innervated muscle. The contralateral normal innervated muscle was also influenced by the electrical stimulation. Contraction time as well as twitch tension were increased. This finding is important when using the normal muscle as intraindividual control

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Abstract: Electrical stimulation was applied daily for 20 minutes to denervated rabbit extensor digitorum longus muscle. One group was stimulated with short tetani, another with 1-Hz frequency, using isometric contractions for both. Tetanic stimulation induced severe fibrosis and is harmful to denervated muscle. One Hertz stimulation retarded denervation-induced fatigue and atrophy, as well as slowing of contraction time

Nix W.A. (1989) [The plasticity of motor units in change of the activity pattern by electric stimulation--electrostimulation and its possible clinical applications]. Fortschr. Neurol. Psychiatr. 57, 94-106.
Abstract: Motoneuron and muscle fibers interact on the motor unit level, whereby discharge characteristics from the neuron imposed on the muscle seem to play a major role. Within the unit all muscle fibers are biochemically homogeneous and display a high degree of plasticity under different functional demands. To distinguish the existing different units rationals are listed that classify the units by physiological and histochemical parameters. Furthermore the review summarizes the available knowledge on the importance of activity patterns--as a biological principle--involved in the control of phenotypic expression of innervated and denervated muscle. The sequelae are shown of electrical stimulation on innervated and denervated animal muscles. In extent to these findings the consequences are discussed for stimulation procedures that can be imposed on normal and diseased human muscles as a therapeutic tool

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Abstract: The influence of low frequency (8-10 Hz) electrical stimulation on denervated fast-twitch muscle from rabbit was investigated. Prolonged direct stimulation of denervated muscle resulted in higher oxidative enzyme activities.

Furthermore, single fibre analyses for succinate dehydrogenase showed a more uniform distribution of activity in stimulated-denervated muscle when compared to normal muscle. As was also the case following stimulation of innervated muscle, glycolytic enzymes were decreased in activity and the LDH-isozyme pattern was also shifted towards heart type. No change of the myosin light chain pattern could be observed after 56 days of stimulation

Rothstein J. and Berlinger N.T. (1986) Electronic reanimation of facial paralysis--a feasibility study. Otolaryngol. Head Neck Surg. 94, 82-85.
Abstract: We set out to adapt the concept of functional electrical stimulation to the reanimation of the paralyzed face. In the New Zealand white rabbit model we studied the strength-duration curves of both innervated and denervated facial muscles. We next studied the electromyographic signals corresponding to different strengths of contraction of innervated facial muscles. With Teflon-coated stainless steel electrodes implanted at opposite ends of the denervated muscle groups under study, bipolar stimulation yielded useful mimetic function that was modifiable by varying the voltage output and the rate of pulse generation. We demonstrated that an electronic circuit can indeed respond to the voltage generated within a functioning facial muscle, and then reproducibly trigger a corresponding graphic signal in synchrony with the mimetic function. The next step will be to adapt an electronic circuit that will deliver a predetermined electrical current to a denervated facial muscle in response to a determined generated voltage in the contralateral corresponding innervated facial muscle

Salerno G.M., Bleicher J.N., and McBride D.M. (1991) Restoration of paralyzed orbicularis oculi muscle function by controlled electrical current. J. Invest Surg. 4, 445-456.
Abstract: A canine model of facial nerve paralysis was studied to apply controlled electrical current to the peripherally denervated orbicularis oculi muscle, in the attempt to effectively restore the absent function of this denervated muscle. After unilateral facial nerve neurotmesis was performed in eight dogs, the denervated orbicularis oculi muscles of four dogs were electrically stimulated for 75 postoperative days (40 min/day). Denervated and normal orbicularis oculi muscles were electrophysiologically studied and compared with the Student t test. During the study period, minimum closure of denervated treated orbicularis oculi muscles was evoked with average stimulus strength (80-ms duration) of 1.61 +/- 0.22 log mA x ms, not significantly different from that of denervated nontreated or normal orbicularis oculi muscles. From days 10 through 30 only, maximum closure of denervated treated orbicularis oculi muscles was achieved with mean pulse strength (80-ms duration) of 2.37 +/- 0.09 log mA x ms, significantly lower (P less than .01) than that evoking the same type of contraction from denervated nontreated muscles (80-ms duration, mean 2.83 +/- 0.10 log mA x ms). In addition, denervated treated muscle pulse strength eliciting maximum contraction was not significantly different from that of normal orbicularis oculi muscles during the same period. This finding was not observed, however, from day 40 through the end of the study. This investigation demonstrates (1) the transient reversal of denervation changes of paralyzed orbicularis oculi muscle by daily electrical stimulation, and (2) the feasibility of restoring orbicularis oculi muscle function by controlled electrical current

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Abstract: A portable lightweight stimulator for small animals is described. It delivers pulse trains of high intensity and is convenient for denervated muscle studies. It does not cause discomfort and does not restrict activity

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Abstract: Denervated muscle fibres were stimulated electrically with needle electrodes introduced close to a recording single fibre electrode. The denervated muscle fibre could be driven with rates up to 100 Hz. The jitter was large at threshold but low at suprathreshold stimulus strength. There was evidence of discrete low threshold sites along the denervated muscle fibre, seen as stepwise latency change on smoothly changing stimulus strength, hepatic activation from other fibres and also as extra-discharges originating from such sites

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Abstract: Serum carbohydrate metabolism was analysed in control, control stimulated, denervation atrophied and denervation stimulated dogs, Canis domesticus. The muscular training has resulted in the hypoglycemia through the mobilization of glucose into both hexose mono- and diphosphate pathways. The denervation atrophy, on the contrary, resulted in hyperglycemia because of exactly opposite changes in the carbohydrate metabolism in the serum and also possibly due to the lack of uptake by the muscle. The training programme of electrical stimulation applied to this denervated muscle has wiped off the hyperglycemia. The importance of muscular work in modulating the serum carbohydrate metabolism was indicated

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Abstract: Clinical results obtained from electrical stimulation of muscle, nerve, spinal cord, cerebellum, and cerebrum are surveyed. Some more data are presented from our own experience with stimulating denervated muscle and cerebellum. Mechanisms which might be responsible for its clinical effects on the muscle, synapse, or nervous system are discussed

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Abstract: Functional recovery following motor nerve injury and repair is directly related to the degree of muscle atrophy that takes place during the period of nerve

regeneration. The extent of this muscle atrophy is related to a number of factors including the accuracy of nerve repair; the distance through which the nerve must regenerate; the age of the patient; and the type of nerve injury and other associated tendon and soft tissue and bony damage. Atrophy of muscle that is always associated with nerve injury is a combination of disuse and degeneration. Our hypothesis proposed the following question: "Would continuous electrical stimulation of the denervated muscle during the period of nerve regeneration maintain the integrity of the muscle fibers and hence their potential functional capacity?" We have completed a series of animal studies (rabbit and canine models) in our laboratory using a completely implantable system to provide continuous muscle stimulation following nerve injury and microsurgical repair. In several different experiments, the nerves under study were cut and repaired at 4 and 12 cm from the muscles to study the effects of short- and long-term recovery. In all experiments, a beneficial effect was demonstrated with improved morphology and functional capacity of the reinnervated stimulated muscles when compared with nonstimulated controls. In addition, electrical stimulation using this implantable system could be applied for extended periods without evidence of discomfort in the experimental animals

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Abstract: Functional electrical stimulation (FES) of the posterior cricoarytenoid (PCA) muscle to produce vocal fold abduction offers an alternative approach to current surgical therapies for bilateral vocal fold paralysis. The purpose of this study was to characterize the application of FES to chronically denervated PCA muscles. Specific goals were to develop a stimulus delivery system for the PCA muscle, determine a practical means of implantation, and identify stimulus parameters effective in activating chronically denervated muscle. Seventeen dogs were implanted with planar electrode arrays 3 months after unilateral recurrent laryngeal nerve resection. A nail-bed electrode array allowed discrete activation of the PCA muscle and gave the greatest abductions, with minimal charge dissipation. Muscle mapping revealed hot-spot regions on the PCA muscle surface, in which stimulation produced maximum abduction. A conservative stimulus paradigm effective in activating chronically denervated muscle was a 1- second pulse train of 2-millisecond-duration pulses, delivered at a tetanizing frequency of 30 Hz and an amplitude of 4 to 14 mA