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Plasticity in Skeletal, Cardiac, and Smooth Muscle
Historical Perspectives: Plasticity of mammalian skeletal muscle

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Pette, Dirk. Historical Perspectives: Plasticity of mammalian skeletal muscle. *J Appl Physiol* 90: 1119–1124, 2001.—More than 40 years ago, the nerve cross-union experiment of Buller, Eccles, and Eccles provided compelling evidence for the essential role of innervation in determining the properties of mammalian skeletal muscle fibers. Moreover, this experiment revealed that terminally differentiated muscle fibers are not inalterable but are highly versatile entities capable of changing their phenotype from fast to slow or slow to fast. With the use of various experimental models, numerous studies have since confirmed and extended the notion of muscle plasticity. Together, these studies demonstrated that motoneuron-specific impulse patterns, neuromuscular activity, and mechanical loading play important roles in both the maintenance and transition of muscle fiber phenotypes. Depending on the type, intensity, and duration of changes in any of these factors, muscle fibers adjust their phenotype to meet the altered functional demands. Fiber-type transitions resulting from multiple qualitative and quantitative changes in gene expression occur sequentially in a regular order within a spectrum of pure and hybrid fiber types.

chronic low-frequency stimulation; cross-reinnervation; exercise training; muscle fiber transformation; neuromuscular activity

"PLASTICITY OF MUSCLE" was the title of an international symposium at the University of Konstanz in 1979 (73). This symposium attempted to summarize the current knowledge on muscle ontogeny; the multiplicity of muscle fibers; their structural, functional, metabolic, and molecular heterogeneity; and, above all, their malleability by modulation of neural input, usage, and hormones. As such, the presentations exemplified the change of paradigm of muscle phenotype that essentially originated from the nerve cross-union experiments performed by Buller, Eccles, and Eccles on cats (15). Their findings demonstrated that when the slow-twitch soleus muscle became reinnervated by nerve fibers normally supplying the fast-twitch flexor digitorum longus muscle contractile speed increased and when the fast-twitch muscle was reinnervated with the soleus nerve it became slower contracting. These results established that motor nerves exert a phenotypic influence on the muscles they innervate. This malleability of muscle fibers inspired John Eccles to use the term "plasticity" in the title of his first report on these experiments (30). Plasticity, a commonly used term in neurophysiology, was thus applied to muscle physiology, signaling that the terminally differentiated muscle fiber is not a fixed unit but represents a highly versatile entity. Moreover, these findings provided for the first time evidence as to how the matching between the requirements of motoneurons and muscle properties is established, especially with regard to muscle differentiation, specialization, and adaptation.

NERVE CROSS-UNION: A KEY TO MUSCLE PLASTICITY

Many studies have since confirmed the molding influence of fast- and slow-type motor nerves on the contractile properties of adult skeletal muscles (18, 24) and have shown that nerve cross-union leads to alterations in the composition and properties of nearly all functional elements of the muscle fiber.

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An important prerequisite to the understanding that the neurally induced transformation of muscle encompasses, in addition to altered contractile properties, qualitative and quantitative changes in the molecular properties of nearly all elements of the muscle fiber was the increasing knowledge of myofibrillar protein isoforms and their distribution in specific fiber types (for review, see Ref. 75). Furthermore, the elucidation of the plasticity phenomenon at both the cellular and molecular levels was enhanced by the availability of appropriate analytical methods. Thus the combination of enzyme histochemistry with measurements of contractile properties in defined motor units (19, 23, 25) was fundamental for the identification of fast and slow muscle fiber types and their delineation by histochemical methods (8, 13, 44). The application of these methods to cross-reinnervated muscles revealed pronounced changes in fiber-type distribution (see, for example, Refs. 29, 45, 60, 82, 101). Bárány's (6) observation that a relationship exists between contractile velocity and actin-activated myosin-ATPase activity made it possible to assign the neurally induced changes in contraction speed to altered myosin properties (see, for example, Refs. 7 and 17). New methods in analytical protein chemistry indicated that these changes corresponded to altered myosin isoform profiles (see, for example, Refs. 50, 58, 87, 97). Analyses on cross-reinnervated muscles detected alterations in the pattern of thin-filament regulatory proteins (1, 47). Changes in Ca^{2+} uptake and Ca^{2+}-ATPase of the sarcoplasmic reticulum and related proteins explained the altered relaxation properties of cross-reinnervated muscles (66, 69, 70, 88). Finally, enzyme activity measurements revealed that fast- and slow-twitch muscles respond to nerve cross-union with a thorough rearrangement of their enzyme activity patterns related to energy supply (38, 59, 80).

Nerve cross-union experiments have thus unambiguously demonstrated the determining influence of innervation on muscle phenotypes and proven that terminally differentiated skeletal muscle is a highly versatile tissue. Subsequently, this notion has been extended by results from other experimental models utilizing various methods, for example, changes in neuromuscular activity, mechanical loading, or altered motoneuron impulse patterns (for reviews, see Refs. 10, 36, 37, 76–78).

MUSCLE ADAPTATION TO EXERCISE TRAINING

At approximately the same time when major efforts were undertaken to investigate neurally induced muscle transformation, reports appeared on metabolic adaptations of muscle in response to exercise training (see, for example, Refs. 31, 39, 40, 51, 52). These and numerous other studies clearly demonstrated the capability of mammalian skeletal muscle to adapt to sustained performance by qualitative and quantitative changes in fuel supply and catabolism, especially with regard to elevated capacities of aerobic-oxidative metabolic pathways (for reviews, see Refs. 10, 53, 84).

Exercise training also appears to induce transitions in myosin isoforms and myosin-based fiber types. In most cases, however, transitions are limited to the fast fiber subtypes and thus consist of fast to less fast transitions (2, 42). However, increased training intensities and/or duration may force transitions to slow fiber types with corresponding changes in myosin (5, 41, 54, 56, 65).

ALTERED NEUROMUSCULAR ACTIVITY BY CHRONIC ELECTRICAL STIMULATION

Chronic low-frequency stimulation (CLFS) was originally applied to test the hypothesis that motoneuron-specific impulse patterns have an impact on the contractile speed of mammalian skeletal muscles (83, 96). The observation that a tonic stimulus pattern, which mimics the impulse pattern of a slow motoneuron, has a slowing effect on contraction and relaxation times of fast-twitch muscles initiated an ever increasing number of investigations on CLFS-induced fast-to-slow muscle transformation (for reviews, see Refs. 76 and 78).

In addition to the CLFS-induced fast-to-slow transitions, experiments that used direct stimulation of denervated fast and slow muscles in rats revealed that motoneuron-specific stimulus patterns are capable of maintaining and converting muscle fiber phenotypes (3, 43, 63, 64).

CLFS was used as a powerful tool for investigating the effects of enhanced neuromuscular activity on muscle fiber phenotypes. The advantage of this experimental model is that all motor units of the target muscle are activated by the same impulse pattern under standardized and reproducible conditions. In contrast to training studies in which habituation to increased activity is necessary, high levels of activity can be immediately imposed on the target muscle using CLFS. Adaptive responses can thus be followed from the onset of stimulation until they reach their maximum. Furthermore, CLFS attains much higher levels of activity over time than any exercise regimen, thus challenging the muscle to its full adaptive potential. In view of these advantages, it is not surprising that CLFS continues to be used as an experimental model for the study of muscle plasticity.

Initial studies on rabbit muscles showed that CLFS converts fast-twitch fatigable muscles into slower, less fatigable muscles and that this time-dependent process encompasses changes in functional, metabolic, and molecular properties. The slowing of the time courses of contraction and relaxation results from exchanges of fast with slow myofibrillar protein isoforms (14, 62) and fast-to-slow isoform transitions of sarcoplasmic reticulum and functionally related proteins (71). CLFS-induced fatigue resistance primarily results from an increase in the capacity of aerobic-oxidative pathways for energy supply, elevated levels of sarcolemmal fuel and metabolite transporters (9, 34, 49, 68), and enhanced capillarization and perfusion (55, 86). These changes display dose-response relationships

and follow specific time courses, (see, for example, Refs. 32, 33, 48, 57, 62, 67, 71, 81, 85, 92).

DECREASED NEUROMUSCULAR ACTIVITY

The observation that the slow-twitch soleus muscle becomes faster after tenotomy (16, 95) had a great impact on research related to muscle plasticity. Besides initiating experiments to counteract this effect by CLFS (83), it provided a model for the study of muscle plasticity under conditions of reduced neuromuscular activity by mechanical unloading. Independent experimental models, especially unloading by hindlimb suspension or microgravity, have recently become fashionable. Decreased neuromuscular activity elicits transitions from slower to faster phenotypes, both in slow-twitch and fast-twitch muscles, although the degree of the changes may vary (4, 11, 21, 27, 28, 35, 61, 72, 91, 94).

PURE AND HYBRID FIBER TYPES AND FIBER-TYPE TRANSITIONS

Single-fiber studies have allowed the elucidation of *1*) the metabolic heterogeneity and *2*) the adaptive potential of skeletal muscle fibers (see, for example, Refs. 22 and 74). Immunohistochemical studies with antibodies against specific myosins and microelectrophoretic separation of myosin heavy chain (MHC) isoforms in single fiber fragments have led to the delineation of "pure" and "hybrid" fiber types (75). Pure fiber types, for example, type IIB, type IID/X, type IIA, and type I, express MHC IIb, MHC IId/x, MHC IIa, and MHC Iβ, respectively, whereas hybrid fibers express more than one MHC isoform. The percentage of hybrid fibers greatly increases in transforming muscles, for example, up to 60% in fast-to-slow transforming rabbit muscle (89), thus emphasizing their transitory nature.

Time course studies on fast-twitch muscles of rat and rabbit exposed to CLFS indicate that fast-to-slow conversion encompasses sequential MHC isoform exchanges in the direction of MHC IIb to MHC IId/x to MHC IIa to MHC Iβ, corresponding to fiber-type transitions from type IIB to type IID/X to type IIA to type I. This is complemented by hybrid fibers, which, according to their coexisting MHC isoform patterns (MHC IIb + MHC IId/x, MHC IId/x + MHC IIa, MHC IIa + MHC Iβ) bridge the gaps between the pure fiber types (26, 89).

It is remarkable that the proposed sequence of fast-to-slow fiber-type transitions follows a gradual decrease in tension cost (12) and ATP phosphorylation potential in the same direction (26). Fast-to-slow fiber transitions thus seem to follow an energetically and functionally defined "next-neighbor rule" (76, 77).

Sequential fiber-type transitions, although in the opposite direction, have also been deduced from sequential changes in MHC composition and single-fiber studies on unweighted rat soleus muscle (90, 91). In light of recently published research, further work, however, will be needed to confirm the proposed sequence of transitions in MHC isoforms and fiber types. Studies on slow-to-fast transforming rat soleus muscle have observed atypical fibers with "non-nearest-neighbor" combinations of MHC isoforms (it should be noted, however, that most hybrid fibers did display next-neighbor combinations) (20, 93).

It is tempting to combine the data from fast-to-slow and slow-to-fast transforming muscles in a general scheme of reversible transitions in MHC isoform expression, namely, MHC IIb ⟷ MHC IId/x ⟷ MHC IIa ⟷ MHC Iβ (77). According to this scheme, fiber-type transitions occur in a stepwise manner, encompassing up- and downregulations of MHC isoforms in a gradual sequence. Moreover, depending on their position in the MHC isoform spectrum, some fibers have the ability to transform in either direction. Fiber-type-specific options for transforming in the fast or slow direction could explain species-specific (57, 85) and muscle-specific differences in response to altered functional demands.

Finally, the functionally and energetically determined alignment of the MHC isoforms explains the existence of hybrid fibers with next-neighbor combinations not only in transforming but also in muscles under "steady-state" conditions (79, 98–100). Coexpression of functionally similar MHC isoforms in next-neighbor combinations may thus serve to optimally adjust muscle fibers to their function. The observation that pure muscle fibers, defined by their lone MHC protein complement, display coexpressed MHC isoforms at the mRNA level points to the impact of post-transcriptional regulation in the control of muscle fiber phenotypes. It also points to the "readiness" of the muscle fiber to rapidly adapt to altered functional demands. In this sense, muscle fibers may be regarded as dynamic structures, a notion expressed in a pioneering paper 30 years ago (46).

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