Plasticity in Skeletal, Cardiac, and Smooth Muscle
Invited Review: Plasticity and energetic demands of contraction in skeletal and cardiac muscle

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Sieck, Gary C., and Michael Regnier. Invited Review: Plasticity and energetic demands of contraction in skeletal and cardiac muscle. J Appl Physiol 90: 1158–1164, 2001.—Numerous studies have explored the energetic properties of skeletal and cardiac muscle fibers. In this mini-review, we specifically explore the interactions between actin and myosin during cross-bridge cycling and provide a conceptual framework for the chemomechanical transduction that drives muscle fiber energetic demands. Because the myosin heavy chain (MHC) is the site of ATP hydrolysis and actin binding, we focus on the mechanical and energetic properties of different MHC isoforms. Based on the conceptual framework that is provided, we discuss possible sites where muscle remodeling may impact the energetic demands of contraction in skeletal and cardiac muscle.

cross-bridge cycling; actomyosin ATPase; myosin heavy chain; muscle fiber mechanical properties; muscle remodeling

Muscles are a major source of energy consumption and heat generation, and much of our daily activities are directed at meeting this energy demand. At rest, overall muscle ATP consumption is relatively low; however, during activation, force generation, and shortening, there is a dramatic increase in energy demand. Not surprisingly, there has been a longstanding interest in the mechanisms that underlie energy consumption by muscle. This mini-review cannot comprehensively cover the vast literature related to the multiple facets of muscle plasticity and energy consumption. Instead, we will focus on sarcomeric interactions between thin and thick filaments (i.e., actomyosin cross-bridge cycling) and provide a conceptual framework by which to explore the impact of plasticity on the energetic demands of contraction in skeletal and cardiac muscle.

As will be discussed, any plasticity or remodeling of thin and thick filament structure can have marked effects on the muscle energetic demand. Such remodeling can take the form of changes in the expression of contractile and thin filament regulatory proteins. Remodeling can also involve changes in myofilament protein density or loading conditions. For the most part, the key players in muscle energy consumption are the same for skeletal and cardiac muscle. However, across muscles (e.g., fast vs. slow skeletal fibers and cardiac myocytes), there are interesting and important differences in contractile performance and regulation related to differences in contractile protein isoform expression. Therefore, muscle is an ideal model system for studying how dynamic protein-protein interactions lead to cellular function and for exploring the factors controlling (coordinated) protein expression.

The Myosin Molecular Motor

Myosin is ubiquitously expressed in eukaryotic cells, and there are at least 11 distinct myosin classes, encoded for by a multigene family located on chromosome 17 in humans or 11 in mice (62). Myosin II is the predominant myosin found in mammalian skeletal and cardiac muscle, where it is both a structural and functional protein. In skeletal and cardiac muscles, myosin...
forms the thick filaments of the sarcomere, comprising \(~50\%\) of all muscle proteins. All myosin types function as molecular motors, converting the chemical energy stored in the terminal phosphate bonds of ATP into mechanical energy, thus driving muscle contraction [reviewed by Cooke (16)].

Myosin is a hexameric protein (molecular mass \(= 480\) kDa) comprising two myosin heavy chains (MHC) and four myosin light chains (MLC). At the COOH terminus, the myosin molecule is rod-shaped, as a result of the dimerization of the two heavy chains (molecular mass \(~200\) kDa) into a 200-nm alpha-helical tail (the S-2 fragment). Bundled together, this portion of the MHC forms the thick filament backbone. At the NH2 terminus, the heavy chains separate and branch out to form two distinct heads (the S1 fragment), which contain both actin and nucleotide binding domains. Chemomechanical transduction occurs at the S1-actin interface, where the intramolecular conformational change in the S1 structure induced by cleavage of the \(\gamma\)-phosphate of ATP is reversed by strong binding of the S1 fragment to the actin molecule (strongly bound cross-bridge formation) and subsequent release of ATP hydrolysis products (P_i and ADP) (reviewed in Ref. 26). The detailed mechanisms of the actomyosin ATPase reaction have been extensively studied in solution and in permeabilized skeletal muscle fibers (see Refs. 17, 26, and 32 for reviews).

**ACTOMYOSIN CROSS-BRIDGE CYCLING**

Skeletal and cardiac muscle contraction results from cyclic interactions between actin and myosin in which chemical energy from MgATP hydrolysis is converted into mechanical work, force, and shortening (chemomechanical transduction). The mechanisms of myosin and actomyosin ATPase activity have been studied extensively in solution and in situ in chemically permeabilized skeletal muscle fibers. Essentially, the cross-bridge cycle is an enzymatic reaction involving the consumption of one ATP molecule per cycle. However, the complexity of chemomechanical transduction during the cross-bridge cycle is illustrated by various multistage mass action models that have been introduced to include all experimental observations and transitional intermediate states (see Refs. 17, 26, 32 for reviews).

Although the cross-bridge cycle is obviously a complex enzymatic reaction, the chemomechanical transduction of one ATP molecule into a mechanical response can be simply presented as a two-stage process, as first described by Huxley in 1957 (33). In the original model, Huxley proposed that cross bridges cycle between two functional states: a force-generating state, in which cross bridges are strongly attached to actin, and a non-force-generating state, in which cross bridges are detached from actin (33, 34; Fig. 1). The transitions between these two primary functional states are described by two apparent rate constants, one for strong cross-bridge attachment (\(f_{\text{app}}\)) associated with force generation, and the second for cross-bridge detachment (\(g_{\text{app}}\)). The increase in isometric force with increasing myoplasmic Ca^{2+} can be explained by the recruitment of cross bridges into the force-generating state (independent of \(f_{\text{app}}\)). The transition of the cross bridge from force-generating to non-force-generating states (described by \(g_{\text{app}}\)) requires the hydrolysis of ATP (actomyosin ATPase). Thus, the original Huxley model included an implicit transduction of chemical to mechanical energy. Brenner (6, 7) and Brenner and Eisenberg (8) proposed an analytical framework based on Huxley’s two-state model of cross-bridge cycling in which chemomechanical transduction was more explicitly described. In this analytical framework, the steady-state fraction of strongly bound cross bridges in the force-generating state (\(\alpha_{fb}\)) is given by

\[
\alpha_{fb} = \frac{f_{\text{app}}}{f_{\text{app}} + g_{\text{app}}}
\]  

(1)

By rapidly releasing the muscle fiber to a shorter length (a length step of \(~20\%\) of \(L_o\), where \(L_o\) is optimal...
length) and then rapidly restretching the fiber to $L_o$, all cross bridges are broken and force decreases abruptly to zero. Subsequently, force redevelops as cross bridges reattach to actin. The relationship between $f_{app}$, $g_{app}$, and the rate constant for force redevelopment ($k_{tr}$) is given by Eq. 2

$$k_{tr} = f_{app} + g_{app}$$

(2)

Isometric force is then described by Eq. 3

$$\text{Isometric force} = nF\alpha_{fs}$$

(3)

where $n$ is the number of available cross bridges per half-sarcomere, $F$ is the average force generated per cross bridge in the strongly bound state, and $\alpha_{fs}$ is the fraction of available cross bridges that are in a strongly bound state. Sarcomere length (and therefore the extent of overlap between thin and thick filaments) affects $n$. This is the fundamental basis of the force-length relationship, which is particularly important in cardiac muscle function (the Starling mechanism).

Myofibrillar density and thick filament structure also influence $n$. The $\alpha_{fs}$ is primarily influenced by $Ca^{2+}$ activation of thin filaments. This underlies the force-$Ca^{2+}$ relationship of skeletal and cardiac muscle fibers.

With the assumption that, during each cross-bridge cycle, one ATP molecule is hydrolyzed, ATP consumption rate (actomyosin ATPase activity) is given by Eq. 4

$$\text{ATPase} = bng_{app}\alpha_{fs}$$

(4)

where $b$ is the number of half-sarcomeres within the fiber. Under conditions in which $\alpha_{fs}$ remains constant, actomyosin ATPase activity is proportional to $g_{app}$.

**MHC ISOFORMS**

The MHC isofrom expressed within a muscle fiber is the major determinant of $g_{app}$ during cross-bridge cycling and therefore ATP consumption rate. Different MHC isoforms are encoded by a highly conserved family of genes and include 1) embryonic (MHCEmb), 2) neonatal (MHCNeo), 3) slow (MHCslow), 4) fast type IIa (MHC2a), 5) fast type IIb (MHC2b), 6) fast type Ix (MHC2x), 7) cardiac alpha (MHCα), and 8) cardiac beta (MHCβ) (44, 45, 49, 51–53). The skeletal MHCslow and cardiac MHCα are the same isofrom. In adult skeletal muscles, MHC phenotype corresponds to the biochemical classification of fiber types based on the pH lability of myofibrillar ATPase (1, 27, 60, 67, 77). These different fiber types comprise motor units with characteristic physiological properties (9, 10, 63). The classification of discrete fiber types has provided an experimental framework to evaluate the biochemical and mechanical properties of MHC isoforms as well as the functional properties of other sarcomeric proteins. Although the focus has been placed on MHC isoform expression, there is usually a constellation of contractile, regulatory, and metabolic proteins that define a particular fiber type.

The ATPase activity of the S1 fragment varies with MHC isofrom (2, 4, 29, 64, 65, 69), a specificity that forms the molecular basis for differences in mechanical function between different skeletal muscle fiber types (see below). Although the amino acid sequences of different MHC isoforms are generally conserved, sequence divergence does exist in the COOH terminal as well as in the flexible hinge region of the neck. This heterogeneity in amino acid sequence may underlie differences in ATPase activity across MHC isoforms (4, 15, 74).

The ~20-kDa essential and ~17-kDa regulatory MLCs (MLC20 and MLC17, respectively) are bound to the S1 fragment near the hinge region and thus may provide structural support to the MHC (56) and may have a regulatory function that might affect ATP consumption (see Refs. 42, 71, and 73 for reviews). The MLC17 binds $Ca^{2+}$ and can be phosphorylated, modifications that may further modulate S1 activity of different MHC isoforms (19, 50, 54).

**Plasticity in MHC isofrom expression.** Numerous studies have reported alterations in MHC isoform expression under a variety of physiological and pathophysiological conditions (see Refs. 55 and 62 for reviews). Such plasticity is clearly reflected by the normal transitions in MHC isoform expression that occur with postnatal development, leading to differentiation into adult fiber types (11, 12, 14, 30, 31, 37, 38, 40, 41, 43, 48, 70, 76–78). During the early stages of myogenesis, primary myotubes appear to express MHCslow, perhaps in combination with MHCEmb, although such coexpression is difficult to discern at this early stage. Secondary myotubes apparently express MHCEmb with rapid transition to MHCNeo. During later stages of embryonic development, the predominant MHC isoforms expressed are MHCslow, MHCEmb, and MHCNeo. By birth, the predominant MHC isoform expressed is usually MHCNeo, although MHCslow and MHC2A are also expressed. The MHCNeo isoform continues to be expressed during early postnatal development, usually in combination with MHCslow and/or MHC2A isoforms. Expression of MHC2X and MHC2B does not appear until later, perhaps coincident with the completion of synapse elimination and disappearance of polyneuronal innervation of muscle fibers. This dramatic transition in MHC isoform expression across a relatively short developmental period represents an important stage of muscle fiber differentiation, especially with respect to the development of mature contractile and energetic properties. The etiology of fiber differentiation appears to depend on a number of factors, including 1) the genetic “program” of the specific muscle, i.e., the proportion of fiber types found in the adult; 2) the pattern of innervation, level of activation, and/or neurotrophic influences; and 3) the hormonal environment, e.g., insulin, thyroid hormone, and growth factors (12, 13, 35, 43, 61, 62, 66). The plasticity of MHC isoform expression that occurs under other conditions is not as well studied or characterized. However, as with early postnatal development, plasticity in MHC isoform expression is often marked by coexpression of MHC isoforms within individual muscle fibers, and such MHC polymorphisms may have a profound
effect on muscle fiber contractile and energetic properties.

**MUSCLE FIBER MHC ISOFORM COMPOSITION AND MECHANICAL PROPERTIES**

*MHC isoform expression and maximum specific force.* Although it remains controversial (22), some studies indicate that maximum specific isometric force varies across fibers comprising different MHC isoforms (5, 20, 23–25, 59, 64, 65). Fibers expressing MHCslow generate less maximum specific force than fibers expressing fast MHC isoforms. Among fast fibers, those expressing MHC2X and MHC2B generate greater maximum specific force than fibers expressing MHC2A. In cardiac muscle, there does not appear to be a clear relationship between the expression of MHCa and MHCb and maximum specific force. The mechanisms underlying the association between MHC isoform expression and maximum specific force remain unclear. However, recent results suggest that differences in MHC content per half sarcomere (\(n\)) could account for the differences in maximum specific force between fibers expressing MHCslow and fast MHC (MHC2A, MHC2X, and MHC2B) isoforms (23–25, 64, 65). There may also be differences in the average force generated per cross bridge (\(F\)) in Eq. 3). However, differences in the fraction of strongly bound cross bridges (\(\alpha_{ns}\)) do not appear to contribute to fiber-type differences in maximum specific force (23–25).

**Plasticity in maximum specific force generation.** Changes in maximum specific force occur under a variety of conditions, including postnatal development, aging (sarcopenia), unloading (microgravity, bed rest, inactivity), exercise, and various diseases. Obviously, such changes in maximum specific force may reflect alterations in MHC isoform composition. However, changes in \(n\), \(F\), and \(\alpha_{ns}\) may also occur independent of MHC isoform expression. For example, there may be no change in MHC isoform composition, but \(n\) may be affected by changes in MHC protein turnover rate. Similarly, changes in thin filament regulation (e.g., alterations in troponin isoform expression) could occur independently of MHC isoform expression and thereby influence \(\alpha_{ns}\). Finally, changes in thin and thick filament lattice spacing may influence \(\alpha_{ns}\) without concomitant changes in MHC isoform expression.

**MHC isoform expression and the rate constant for force generation.** In chemically permeabilized skeletal muscle fibers (46, 57, 64, 65) and cardiac trabeculae (57), \(k_{tr}\) varies with MHC isoform composition. Fibers expressing MHCslow have a markedly slower \(k_{tr}\) compared with fibers expressing fast MHC isoforms. Among fast fibers, those expressing MHC2X and MHC2B have a faster \(k_{tr}\) than those expressing the MHC2A. In cardiac muscle, expression of MHCa is associated with much faster \(k_{tr}\) compared with MHCb expression (57). As mentioned above, \(k_{tr}\) is the summation of \(f_{app}\) and \(g_{app}\) (see Eq. 2), and, typically, \(f_{app}\) is severalfold faster than \(g_{app}\). In single skeletal fibers, \(k_{tr}\) is proportional to isometric ATP consumption rate and both vary with MHC isoform expression (64). This is consistent with a relationship between \(g_{app}\) and MHC isoform expression (see discussion of shortening velocity below). However, it should be emphasized that \(f_{app}\) predominates the \(k_{tr}\) measure; therefore, there is certainly a relationship between \(f_{app}\) and muscle fiber MHC isoform expression.

**Plasticity in the rate constant for force generation.** Changes in \(k_{tr}\) during conditions of muscle plasticity have not been systematically evaluated; however, any alterations in MHC isoform expression would certainly affect \(k_{tr}\). For example, treatment with propylthiouracil (PTU) switches rat cardiac MHC composition from fast (V1 or MHCa-MHCb) to slow (V3 or MHCa-MHCb) without concomitant changes in expression of other contractile or regulatory proteins, resulting in a greater than twofold reduction in \(k_{tr}\) (57). Alterations in thin filament regulation, MLC regulation, and associated steric hindrance have also been shown to influence \(k_{tr}\) (see review, Ref. 26). Thus any condition that affects \(\alpha_{ns}\) might be expected to influence \(k_{tr}\). Similarly, alterations in \(g_{app}\) such as increased internal or external loading would influence \(k_{tr}\).

**MHC isoform expression and muscle fiber shortening velocity.** In skeletal muscle fibers, there is a clear relationship between MHC isoform expression and maximum unloaded shortening velocity (\(V_o\)) (5, 20, 58–60, 64, 65, 72). Fibers expressing MHCslow have slower \(V_o\) than fibers expressing fast MHC isoforms. Among fast fibers, those expressing MHC2X and MHC2B have a faster \(V_o\) compared with fibers expressing MHC2A. As might be expected on the basis of differences in maximum specific force and \(V_o\), differences in the force-velocity relationship and maximum power output also exist across fibers expressing different MHC isoforms (64). The relationship between fiber shortening velocity and MHC phenotype undoubtedly reflects differences in \(g_{app}\) and actomyosin ATPase activity of different MHC isoforms. The factors controlling \(V_o\) have recently been reviewed in detail (26).

**Plasticity in muscle fiber shortening velocity.** Similar to \(k_{tr}\), changes in \(V_o\) during conditions of muscle plasticity have not been systematically evaluated, but clearly alterations MHC isoform expression would affect \(V_o\). For example, PTU-induced conversion of rat cardiac MHC expression from fast (V1) to slow (V3) slows \(V_o\) approximately threefold (57). However, a slowing of \(V_o\) can occur disproportionate to changes in MHC isoform composition under a variety of conditions (28, 36, 47, 68, 75, 79). Other factors such as alterations in the expression of MLC isoforms, thin filament regulatory proteins, or myofilament lattice spacing could influence \(V_o\). Obviously, any condition that induces alterations in \(g_{app}\), such as increased internal loading, would also affect \(V_o\).

**MHC isoform expression and ATP consumption rate.** Differences in the energetics of skeletal muscles predominantly composed of either slow or fast fiber types have suggested that the energy cost for contraction of slow fibers is approximately one-half that of fast fibers (18). Biochemical measurements of myofibrillar
ATPase activity have also indicated differences across fiber types (2). In single permeabilized skeletal muscle fibers, isometric ATP consumption rate varies with MHC isoform composition, such that fibers expressing fast MHC isoforms (MHC2A, MHC2X, and MHC2B) have faster ATP consumption rates compared with fibers expressing MHCslow (3, 29, 64, 65, 69).

In 1923, Fenn observed that energy utilization by skeletal muscle increases in proportion to work (Fenn effect) (21, 39). Thus, as muscle fibers are allowed to shorten and maximum power is reached, ATP consumption rate increases (67). In most muscle fibers, maximum power is achieved at a load corresponding to ∼33% of maximum specific force and ∼33% of Vg. Obviously, as load increases, gapp decreases, and, as velocity increases, αp decreases. Maximum power reflects the optimal combination of these two variables that influence ATP consumption rate (see Eq. 4).

Plasticity in ATP consumption rate. Unfortunately, changes in muscle fiber ATP consumption rate have not been systematically evaluated under conditions of muscle plasticity. However, as shown by Eq. 4, ATP consumption rate may vary with a number of factors, including MHC isoform expression (affecting gapp), muscle length (affecting both b and n), mechanical loading, both external and internal (affecting gapp), Ca2+ regulation of the thin filament and thin and thick filament compliance (affecting αfs and perhaps gapp), myofilament density (affecting n), and myofilament lattice spacing (affecting n, αfs, and gapp).

FUTURE DIRECTIONS

Although a number of factors have been shown to influence MHC isoform expression (see above), it remains unknown whether there is a direct linkage between energetic demands and MHC isoform remodeling. Conditions of muscle plasticity are often associated with MHC isoform polymorphisms. It remains unknown how coexpressed MHC isoforms are organized within muscle fibers. If different MHC isoforms are coexpressed within individual sarcomeres or across sarcomeres of a single fiber, a completely different impact on mechanical and energetic properties may be observed. Unfortunately, current techniques do not have sufficient resolution to determine the spatial distribution of coexpressed MHC isoforms within or across sarcomeres.

Muscle plasticity may involve alterations in MHC protein synthesis and degradation, thereby affecting n and myofilament lattice spacing (23, 24). Better techniques need to be developed to evaluate MHC turnover rate during conditions of muscle remodeling, as well as better estimates of changes in n and myofilament lattice spacing within single fibers.

As mentioned above, fiber types represent a coordinated expression of contractile, regulatory, and metabolic proteins. Muscle plasticity may impose discordance in protein expression and the disappearance of characteristic fiber types. The impact of mismatched protein expression on muscle fiber mechanical and energetic properties is poorly understood. Future research should systematically explore the factors controlling (coordinated) protein expression within muscle fibers as well as the dynamic protein-protein interactions that influence muscle fiber contractile properties and energetic demands.

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