Energetics of Crossbridge Phosphorylation and Contraction in Vascular Smooth Muscle

J.S. Walker, C.J. Wingard, R.A. Murphy

Abstract Ca$^{2+}$-dependent crossbridge phosphorylation is the primary mechanism governing crossbridge cycling in smooth muscle. A four-state crossbridge model in which phosphorylation is the only proposed regulatory mechanism was successful in predicting the mechanical properties of the swine carotid media including latch (sustained force with reduced crossbridge cycling). This model also predicts that the ATP consumption of crossbridge phosphorylation is approximately equal to that of crossbridge cycling and that ATP consumption will rise hyperbolically with increases in steady-state force. This review shows these predictions to be consistent with the available energetics data for the carotid media. The absolute energetic cost of covalent regulation is modest and less than the energy savings associated with latch. However, covalent regulation should reduce the total mechanical efficiency of smooth muscle relative to striated muscle. (Hypertension. 1994;23[part 2]:1106-1112.)

Key Words • phosphorylation • metabolism • muscle, smooth, vascular

The coordinated constriction and dilation of kilometers of blood vessels is responsible for directing nutrients to every cell of the organism, yet the energy consumed in the considerable task of regulating peripheral vascular resistance is remarkably small (Fig 1). This review will focus on mechanisms that contribute to the frugal use of energy by vascular smooth muscle. The output of smooth muscle in quantifiable mechanical terms and its molecular basis will be considered first, followed by a review of smooth muscle energetics relating ATP use to mechanical output.

Vascular Smooth Muscle Mechanics

The sliding filament mechanism is generally accepted to underlie smooth muscle contraction as in striated muscle. However, structural evidence is lacking for a sliding filament mechanism, in which observed filament overlap is related to variations in muscle force. The evidence for a sliding filament mechanism is inferential and derived from biochemical studies of filament formation in vitro; electron microscopy, which shows filaments with little apparent organization; and mechanical studies, which demonstrate similar length-force relations across muscle types.

The principal variables of interest in studying the active mechanical properties of muscle are force, length, and time. It is usual to hold one constant while studying the relation between the other two. In an isometric contraction, length is held constant and force is measured as a function of time. In an isotonic contraction, force is held constant and length is measured as a function of time. These experimental simplifications of the complex behavior of the vessel in vivo allow quantitative relations between variables to be established in the laboratory.

\[ (F+a)(V+b)=b(F_0+a) \]

where \( F \) is force, \( V \) is velocity, \( F_0 \) is maximum isometric tension, and \( a \) and \( b \) are constants. The degree of nonlinearity in the force-velocity relation is specified by the ratio of \( a \) to \( F_0 \) and is similar in striated and smooth muscles. A comparison of actin-activated myosin ATPase activities and shortening velocities suggests that most of the difference in shortening velocity can be accounted for by different ATPase activities reflecting

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Crossbridge cycling continues until the Ca\(^{2+}\) level falls, whereupon Ca\(^{2+}\) dissociates from the troponin complex cannot yet be ruled out.\(^{18-20}\)

The crossbridge regulatory mechanism is Ca\(^{2+}\)-calmodulin-tropomyosin complex that permits a myosin head to interact with the actin filament. Binding produces a conformational change in the troponin regulatory light chain (MRLC) by myosin light chain kinase (MLCK), although other secondary pathways responsible for basal \(J_{\text{O}_2}\) are unchanged during contraction. Partitioning of suprabasal \(J_{\text{ATP}}\) in smooth muscle into that used for myosin regulatory light chain phosphorylation and that used for crossbridge cycling is based on estimates of the coupled four-state model.\(^2\) Numbers by each segment are energy consumption associated with the particular process and percentage cost relative to overall energy consumption rate. Smooth muscle is continuously generating much higher force/cross-sectional area than that elicited in the intermittent twitch of skeletal muscle. This comparison omits the ATP cost of Ca\(^{2+}\) pumping.

expression of different myosin isoforms.\(^9\) Other elements contributing to a slower shortening velocity in smooth muscle may be long myosin filaments and a unique Ca\(^{2+}\)-dependent regulatory mechanism.

An anomalous property of smooth muscle that is not predicted by conventional sliding filament/crossbridge theories is that the shortening velocity for any given load can vary. This can be clearly seen as a decline in crossbridge phosphorylation and the maximum shortening velocity (ie, at zero load) during sustained contractions in the swine carotid,\(^7\) lower esophageal sphincter,\(^10\) rat uterine smooth muscle,\(^11\) rat anococcygeus,\(^12\) and canine trachea.\(^13\) Under steady-state conditions the maximum shortening velocity is linearly related to the level of myosin phosphorylation,\(^14\) suggesting that the velocity is regulated by phosphorylation.\(^15\) The ability for force to be maintained while shortening velocity is reduced, a state termed latch, is associated with a significant reduction in ATP consumption.\(^12,16,17\)

**Covalent Regulation and the Four-State Model**

It is well known that skeletal muscle is allosterically regulated by the reversible binding of Ca\(^{2+}\) to troponin. Binding produces a conformational change in the troponin-tropomyosin complex that permits a myosin head (the crossbridge) to interact with the actin filament. Crossbridge cycling continues until the Ca\(^{2+}\) level falls, whereupon Ca\(^{2+}\) dissociates from the troponin complex and inhibition is restored. In this system, Ca\(^{2+}\) binding to troponin acts as a switch but does not affect crossbridge cycle kinetics. In smooth muscle the primary crossbridge regulatory mechanism is Ca\(^{2+}\)-calmodulin-dependent phosphorylation of Ser\(^19\) of the 20-kD myosin regulatory light chain (MRLC) by myosin light chain kinase (MLCK), although other secondary pathways cannot yet be ruled out.\(^16-20\)

To explain latch, Hai and Murphy\(^21\) proposed a mechanism to simultaneously account for the time course of myosin phosphorylation and stress development (Fig 2). The sole regulatory mechanism was Ca\(^{2+}\)-calmodulin–dependent activation of MLCK. The only novel element introduced was a “latchbridge,” formed by the dephosphorylation of an attached crossbridge. This allows for force generation at low levels of MRLC phosphorylation. The latchbridge was postulated to have the same force-generating capacity as a phosphorylated crossbridge but a slower detachment rate (\(k_7<k_4\)) from actin. The mechanism of this alteration in kinetics was not specified. This simple kinetic model was able to fit both phosphorylation and stress data for the electrically stimulated swine carotid artery\(^21\) and, when later combined with Huxley’s 1957 model of muscle contraction, was able to account for the linear dependence of shortening velocity on phosphorylation.\(^22\)

The model (Fig 2) proposes four states for the myosin crossbridge: unattached to actin and dephosphorylated (M); detached, phosphorylated (Mp); attached, phosphorylated (AMP); and attached, dephosphorylated (AM) (latchbridge). Transitions between states follow first-order kinetics with rate constants derived from swine carotid isometric stress and phosphorylation data. During a single contraction, \(k_1\) varies with time as illustrated in the top graph. Other rate constants are as follows: \(k_2=0.5, k_3=0.4, k_4=0.1, k_5=k_2, k_6=k_1, k_7=0.02,\) and \(k_8\) is negligible (0.00001). This set of rate constants was used to derive all model fits illustrated in this review. The constant \(k_1\) was varied when necessary to simulate activation or steady-state phosphorylation. Pi indicates inorganic phosphate; P, phosphorylation of Ser\(^19\).
FIG 3. Line graphs show time-domain predictions of the four-state model. All predictions were based on a single set of rate constants as reported by Hai and Murphy,21 with k1 varying as depicted in Fig 1. A, Mean phosphorylation values for electrically stimulated swine carotid media (●) and predictions of myosin phosphorylation (—). B, Stress data from the same series of experiments (●) and the model's stress prediction (—). P indicates active tension; Po, maximum isometric tension; Pi, inorganic phosphate; and LC 20, 20 kD myosin light chain.

(MLCP). MLCK activity is presumed to be dependent on intracellular calcium ([Ca 2+]i), and MLCP activity is assumed to be constant. A simplifying assumption was that free and attached crossbridges are equivalent substrates for MLCK and MLCP (ie, k1=k6 and k2=k5). The equilibrium for latchbridge detachment (the transition from AM to M) lies far toward the detached state (M), but the forward rate constant is small. This implies that latchbridges dissociate from actin slowly and that the binding of dephosphorylated myosin to actin is highly improbable.

A single set of rate constants accounts for stress and phosphorylation changes simultaneously (Fig 3A and 3B).21 The constant k1 reflecting MLCK activity was modeled as a dual-step function, with an early peak at 0.55 followed by a decline to a steady-state value of 0.3. This was the simplest form of regulation that could account for the data (Fig 3). During the early phase of contraction myosin is predominantly in the phosphorylated form. As k1 diminishes, latchbridges form with increasing frequency. Latchbridges have the effect of increasing the mean on-time of an average crossbridge and increasing the period of a crossbridge cycle. This maintains isometric force but reduces ATP consumption (JATP). This increase in economy (force/J ATP) is clearly desirable for a tissue that displays continuous tone.

The initial kinetic description of the four-state model did not couple the crossbridge cycle to mechanical events. As such it could not directly account for changes in shortening velocity or work production. To address this, Hai and Murphy22 adopted Huxley's 1957 formalism to describe crossbridge action in the four-state kinetic model. The coupled four-state model used attachment and detachment rate constants derived from the proportion of crossbridges in each state to calculate the shortening velocity for a given stress. Under this scheme the crossbridges and latchbridges have identical mechanical properties. The effect of the latchbridge is to slow down the average rate of crossbridge cycling by reducing the detachment rate constant. Several additional constants over and above those proposed for the kinetic model were introduced to quantify the shortening velocity and energy consumption in real terms. The confidence of such calculations is dictated in part by the overall scheme of the model and in part by the accuracy and appropriateness of the constants chosen.22 The coupled four-state model has been used to predict steady-state energy consumption, force-phosphorylation relations, and force-velocity relations under a variety of simulated experimental conditions (Fig 4).22,23,24,25

The coupled four-state model predicts a family of force-velocity relations of the familiar hyperbolic form, each curve corresponding to a different level of phosphorylation.22 In particular, the maximum shortening velocity should be a linear function of the MRLC phosphorylation, a prediction that fits well with existing data (Fig 4B).

When the model was coupled to the Huxley model of crossbridge action, the predicted JATP values for crossbridge consumption and crossbridge phosphorylation were approximately equal (Fig 4C). The predicted energy flux associated with covalent regulation was seen as unacceptably high by some and met with resistance.
The coupled model predicts a substantially higher energy output from crossbridge turnover in a shortening muscle than one held isometric. A specific prediction is that the ATP consumption associated with crossbridge cycling at 0.5 \( V_{\text{max}} \) would be 2.9-fold higher than during a maximal isometric contraction where \( V=0 \). The liberation of energy above that seen in a maximal isometric contraction is characteristic of the Huxley formulation and is not specific to the four-state model. Notably, cardiac muscle shows no increase above maximal isometric energy consumption during shortening. Nevertheless, this prediction is similar to experimental data collected on the rabbit taenia coli.18

### Smooth Muscle Energetics

Muscle energy consumption is conventionally divided into basal and active metabolism. Although a physiological state marked by the complete absence of vascular tone is unlikely, the division is useful because it helps identify the energy expenditure attributable to contractile events. Other than the brief description of basal metabolism, all measurements of energy consumption are given as suprabasal values. Estimates of active energy expenditure are usually based on measurements of oxygen consumption (\( J_{O_2} \)), lactate production (\( J_{lact} \)), phosphagen utilization in metabolically poisoned preparations, \( ^{31}P \) nuclear magnetic resonance, or heat production. Steady-state measurements are usually based on \( J_{O_2} \) and \( J_{lact} \) measurements, whereas high-time resolution is provided by measurements of muscle heat production.29

#### Basal Metabolism

Experimentally, basal metabolism is the energy consumption in the absence of active contraction or activation of the tissue. In spontaneously active tissues this may require either that calcium be omitted from or some pharmacologic agent be added to the bathing solution.

Smooth muscle is noted for a high rate of aerobic \( J_{lact} \) that is closely linked with membrane-associated Na,K-ATPase activity.20 Resting \( J_{lact} \) is approximately 0.14 \( \mu \text{mol/min g}^{-1} \). Estimates of basal \( J_{O_2} \) in swine carotid artery at 37°C range from 0.07 to 0.09 \( \mu \text{mol/min g}^{-1} \) (wet weight).16,21 This gives a basal \( J_{ATP} \) of approximately 0.6 to 0.7 \( \mu \text{mol ATP/min g}^{-1} \) (1 \( \mu \text{mol O}_2 = 6.42 \mu \text{mol ATP}; 1 \mu \text{mol lactate} = 1 \mu \text{mol ATP}).

Basal metabolism is largely unaffected by changes in resting tension,16 changes in extracellular calcium concentration, anoxia, or the level of hypertrophy (at least in visceral smooth muscle)22 and shows little dependence on contraction history after a sufficient rest period between contractile events.31

The biochemical basis for basal metabolism is far from clear.30 However, it is likely that Na\(^+\)-K\(^+\) pumping and protein metabolism are major contributors. Paul14 estimates that the Na\(^+\)-K\(^+\)-ATPase consumes approximately 0.15 \( \mu \text{mol ATP/min g}^{-1} \) under resting conditions. This would represent approximately 30% of the basal energy consumption. Protein synthesis rates vary widely in smooth muscle, but a conservative estimate of 5% per day with a protein content of approximately 0.12 g/g tissue would produce a contribution of approximately 0.3 \( \mu \text{mol ATP/min g}^{-1} \).30 Current estimates of major biochemical processes seem to account for portions of smooth muscle basal metabolism, but many other contributing reactions remain to be identified or quantified.

#### Isometric Contraction

The energy flux associated with maximum isometric tension is far less in smooth muscle than in skeletal muscle (Fig 1). At similar levels of developed tension the energy consumption of skeletal muscle can be more than 60 times greater than vascular smooth muscle. This is due partly to intrinsic differences in actomyosin ATPase activities and partly to differences in the energetic strategies characterizing the different muscle types.

At 37°C the swine carotid media has a suprabasal \( J_{O_2} \) of approximately 0.08 \( \mu \text{mol/min g}^{-1} \) (wet weight) when stimulated with \( \text{KC}l \).16 If the stimulus includes histamine with the \( \text{KC}I, \) \( J_{O_2} \) is approximately 0.21 \( \mu \text{mol/min g}^{-1} \). By way of comparison, the \( J_{O_2} \) of canine semitendinosus twitching once per second at 35°C is approximately 50 \( \mu \text{mol O}_2/\text{min g}^{-1} \). The difference in energy expenditure is probably mostly due to a lower actomyosin ATPase activity. For example, the ratio of active to ATPase activities for chicken posterior latissimus dorsi, a fast skeletal muscle, to gizzard smooth muscle is about 30:1.15

A decline in energy expenditure during sustained contraction was found in taenia coli,17 swine carotid,16 and rat anococcygeus,12 with peak levels of energy expenditure ranging between two and four times the steady-state values. Although initially it was felt that the decline could be attributed to an associated decline in shortening velocity, the lack of correlation of energy expenditure with the changes in shortening velocity even with rapid heat measurements15 suggested that not all of the decline in energy expenditure could be accounted for by changes in crossbridge cycling alone.

Steady-state \( J_{ATP} \) was linearly related to steady-state stress under conditions of constant stimulus and varying tissue length in skinned rat portal vein,36 bovine mesenteric vein,37 and swine carotid artery.38 However, in experiments in which the level of activation was altered by varying the calcium concentration in the bathing solution, the relation between \( J_{ATP} \) and stress became nonlinear as stress approached the maximum isometric level. Energy consumption rose disproportionately more than the stress in swine carotid artery,39 skinned rat portal vein,36 and taenia coli.40 Studies on the swine carotid artery provided conflicting evidence on the relation between \( J_{ATP} \) and stress (Fig 5). Some groups found a linear relation, and others found a curvilinear relation. The reason for the divergence in results is unknown. In recent experiments in which the level of myosin phosphorylation ranged up to 50%, the relation between \( J_{O_2} \) and stress in swine carotid arteries was consistent with the four-state model's predictions of a hyperbolic dependence of \( J_{ATP} \) on active stress. This results from an increasing \( J_{ATP} \) by MRLC phosphorylation and crossbridge cycling at a higher level of Ca\(^{2+}\)-stimulated phosphorylation, which minimizes latch and latcheshox.2

#### The Energetic Cost of Activation

The energy consumption associated with isometric contraction can in theory be apportioned to those processes that activate, maintain, and abolish contrac-
tile activity. Debate over the regulation of smooth muscle has focused on subdividing the energy associated with the processes of activation and force maintenance.

Activation is not a simple function of [Ca$^{2+}$]$_0$, under all conditions for all muscles. In skeletal muscle, activation is taken to mean the initiation of crossbridge cycling by excitation-contraction coupling mechanisms. The level of activation is therefore simply the number of cross-bridges that are active at any given time. Under steady-state conditions activation is correlated with force. This elementary definition is possible because of the lack of large changes in the crossbridge turnover rate during isometric contraction.

Smooth muscle activation is not so easily defined. During a tonic isometric contraction, tension is maintained while shortening velocity and the consequent energy expenditure decline. It is not reasonable to assume that because the force remains constant, the level of activation is constant. A definition of activation is required that takes into account both the force output and the shortening velocity. Because the four-state model predicts that both will depend on the level of myosin light chain phosphorylation, we propose that MRLC phosphorylation at Ser$^{19}$ is the best definition of the level of activation of a smooth muscle.

The measurement of the energy expenditure associated with activation processes is difficult. In striated muscle, lengthening the muscle beyond the optimum L$_0$ reduces filament overlap and the number of crossbridge interactions. This has the effect of reducing the energy consumption associated with crossbridge cycling. The finite energy consumption remaining at zero force is termed the tension-independent energy. In striated muscle this tension-independent energy is thought to be mostly due to activation processes, primarily calcium pumping. Measurements of muscle heat production indicate that approximately 25% of the total energy expenditure of the frog sartorius is activation related.

Several difficulties have hampered similar investigations in smooth muscle. The high passive elasticity makes it difficult to reversibly stretch a smooth muscle to lengths at which force falls to low levels and presumably crossbridges cannot interact with actin. By using very short and long lengths to reduce force and energy expenditure, Paul and Peterson estimated tension-independent energy expenditure in the bovine mesenteric vein at approximately 20% to 30% of the total Jo$_2$ at maximum isometric tension. The lower value came from shortening the muscle to presumptively reduce actomyosin interaction, and the upper value came from experiments in which the muscle was lengthened. This fraction is similar to the 25% activation heat observed in skeletal muscle. This differs from the coupled four-state model prediction that at least 50% of the energy expenditure is due to activation.

**Working Contractions**

Although it is common to think of vessels maintaining tone, vasoconstriction involves the performance of work against the pressure load generated by the heart, and vasodilation involves the performance of work by the heart on the vessels. Little energetic information is available for work-producing contractions of vascular smooth muscle, so much of the following discussion is inferred from results on visceral preparations.

As expected from studies on other muscle types, smooth muscle shows a curvilinear relation between load and work output. Peak work output for rabbit rectococcygeus at 27°C occurs in the range of 0.3 to 0.4 $E_0$. The taenia coli consumed more ATP in work-producing contractions than in a maximal isometric contraction much like amphibian skeletal muscle. By contrast, more heat was liberated in isometric contractions of the rabbit rectococcygeus than in equivalent isometric contractions. The rate of heat production in isometric contractions never exceeded the rate of heat production in maximum isometric contractions. In this respect the rectococcygeus was more like mammalian cardiac muscle than like skeletal muscle.

The Fenn effect is the name given to the regulation of the energy output of a muscle by the mechanical conditions. Both cardiac and skeletal muscle show a Fenn effect in that the energy output is regulated by the load, although it is not required that energy expenditure during shortening exceed that of a maximal isometric contraction. In cardiac muscle the energy expenditure during shortening is usually less than that seen in a maximal isometric contraction. The variance in the...
form of the Fenn effect shown by different smooth muscles could be related to the 10-fold range observed in shortening velocities and rates of energy usage. Further studies on other preparations are needed to better characterize the Fenn effect in smooth muscle.

Efficiency is the ratio of work (force \times distance) to the energy expended to do that work. The aim of efficiency measurements in muscle is to determine how much of the free energy of ATP hydrolysis can be used for the production of work.\textsuperscript{29,45} The ratio of work to heat plus work (the "mechanical efficiency") is often misused as a replacement for the thermodynamic efficiency (work/free energy). The mechanical efficiency includes an entropy term that does not represent energy available for the production of work. The problems associated with this rationale are discussed by Wilkie.\textsuperscript{45,46}

It is often said that smooth muscle is necessarily less efficient than skeletal muscle,\textsuperscript{30,47} but comparisons of mechanical efficiency across muscle types must be careful to define the basis for comparison. Activation processes as dissimilar as allosteric Ca\textsuperscript{2+} binding and covalent modification nevertheless are functionally regulatory processes and directly or indirectly consume ATP in addition to that consumed by the crossbridge cycle. It should be clearly stated whether or not the comparison includes activation energy expenditures.

The initial mechanical efficiency of amphibian skeletal muscle at 0°C is approximately 45%. This corresponds to a total mechanical efficiency of approximately 22% when allowance has been made for recovery metabolism. This value can be considered to be near maximal for skeletal muscle, with efficiency decreasing as temperature is increased.\textsuperscript{48} The total mechanical efficiency of mammalian cardiac muscle at optimal loads is approximately 27% at 27°C,\textsuperscript{42} whereas the whole heart works at an efficiency of approximately 10% within the organism.\textsuperscript{42} The difference between cardiac and skeletal muscle is due to a higher activation-related energy expenditure in skeletal muscle than cardiac muscle, as evidenced by a larger activation heat in isometric contractions.\textsuperscript{42}

There are three possible ways in which smooth muscle could be less efficient than skeletal muscle. (1) The transduction efficiency could be less because of fundamental differences in the interaction of myosin and actin. (2) The transduction efficiency could be less because of internal energy dissipation, as cycling crossbridges may be loaded by latchbridges during shortening. (3) The initial or total mechanical efficiency could be less, as energy consumed by activation processes in smooth muscle could represent a greater proportion of total energy expenditure. In the four-state model, activation ATP consumption is at least 50% of the total energy consumption,\textsuperscript{2} a greater fraction than found in striated muscle. This suggests that the efficiency of the swine carotid can be no more than half that of striated muscle. This prediction of the upper limit of efficiency will depend on the coupling of the activation process to the power stroke of the crossbridge cycle, something that may vary considerably among smooth muscles, and on the cost of calcium handling, a factor often omitted from efficiency calculations.

Rabbit taenia coli has been reported to have an efficiency some fivefold less than skeletal muscle based on comparisons of the amount of phosphagen used per joule of active work done.\textsuperscript{49} This extremely low value was at odds with the results of Davey et al,\textsuperscript{41} who reported an efficiency for the rabbit rectococcygeus similar to that of mammalian striated muscle. The maximal mechanical efficiency of the rectococcygeus based on myothermometric measurements was approximately 18%. The variance could be related to the difference in shortening velocities between the tissues. At any rate, the limited evidence suggests that the total mechanical efficiency is somewhat less than that of striated muscle although the magnitude or significance of the difference is uncertain.

Because latchbridges are assumed to be mechanically equivalent to phosphorylated crossbridges, the four-state model implies that the efficiency will not depend on the myosin phosphorylation level. This lack of a phosphorylation dependence has some support from experiments designed to establish the presence or absence of an internal load. Butler et al\textsuperscript{50} found no difference in the efficiency of the metabolically poisoned taenia coli at two different extracellular calcium concentrations where shortening velocity changed by a factor of 2. However, they also detected no change in myosin phosphorylation. Paul et al\textsuperscript{51} also reported no change in the efficiency of contraction at different levels of activation, this time in the swine carotid artery in two different external Ca\textsuperscript{2+} concentrations. Although not conclusive, these studies suggest that efficiency does not appear to be strongly dependent on the level of activation.

Conclusions

One of the distinguishing features of smooth muscle is its ability to maintain force at a low energetic cost. Although much of this economy of function is accounted for by a low actomyosin ATPase activity, there is clearly modulation of the economy within a contraction. This modulation is due to the regulation of crossbridge turnover rate via myosin light chain phosphorylation. The four-state model proposes that the latchbridge is essentially a mechanism for increasing the period of a crossbridge cycle. This has the combined effect of reducing ATPase activity and shortening velocity and maintaining force. Covalent regulation also consumes ATP, with the four-state model proposing an ATP consumption equal to that of crossbridge cycling in the steady state. With increasing activation the model suggests that energy consumption should rise disproportionately to the stress. The experimental evidence for this prediction is divided although most data are consistent with the model, at least qualitatively. In theory, covalent regulation would lower the efficiency of smooth muscle relative to skeletal muscle. Again, the evidence is divided, with some tissues having very low efficiencies and others having efficiencies close to that of striated muscle. The four-state model allows for considerable variation depending on the rate constants for the proposed reactions (Fig 2) in different tissues. The prediction of a high fractional cost of phosphorylation is at the same time a prediction of low absolute cost. What is important is that covalent regulation makes latch possible with an extraordinarily low total ATP requirement for the maintenance of vascular tone.
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