PERSPECTIVES: MUSCLE CONTRACTION

Coordinated Feet and the Dance of Ryanodine Receptors

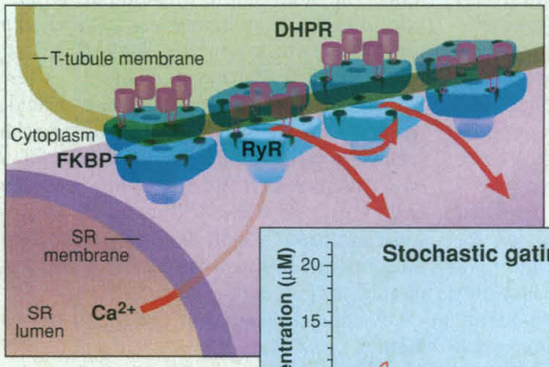
Donald M. Bers and Michael Fill

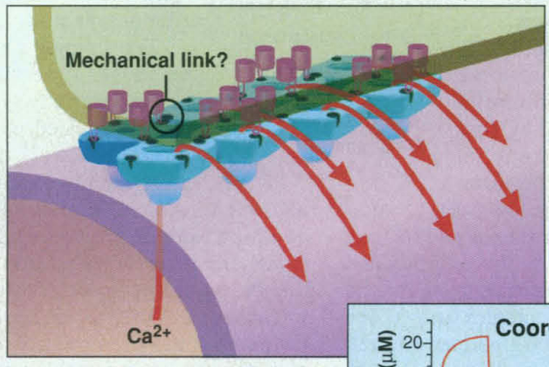
Highly coordinated movements of our skeletal muscles are needed to walk, play a piano, or throw a javelin. Such exquisite integration relies on the high fidelity of several signaling processes in the muscle. One of these, the action potential, assures nearly simultaneous membrane depolarization of even the largest skeletal muscle cells. Simultaneous contraction of the whole muscle cell is essential for efficiency; otherwise active regions would expend energy in stretching the intervening inactive regions. Force and efficiency would be reduced. Thus, the links between synchronous depolarization and contractile activation (excitation-contraction coupling) are critical for precise control of our muscles.

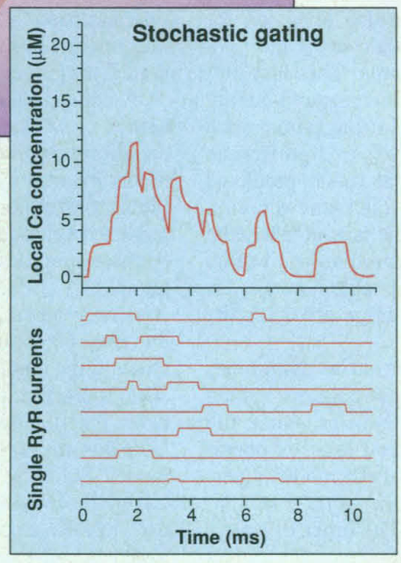
Another mechanism required for synchronous action of the muscle occurs at the molecular level. The sarcoplasmic reticulum (SR), a network of membranes inside the muscle cell, releases the calcium that triggers muscle contraction. This Ca release occurs through "feet" (tetrameric arrays of ryanodine receptors, RyRs) that bridge the gap between the plasma membrane T tubule and the SR. Now, a report by Marx *et al.* in this issue (*1*) presents provocative new evidence that clusters of RyRs function in a concerted fashion to release Ca, rather than as individual stochastic entities.

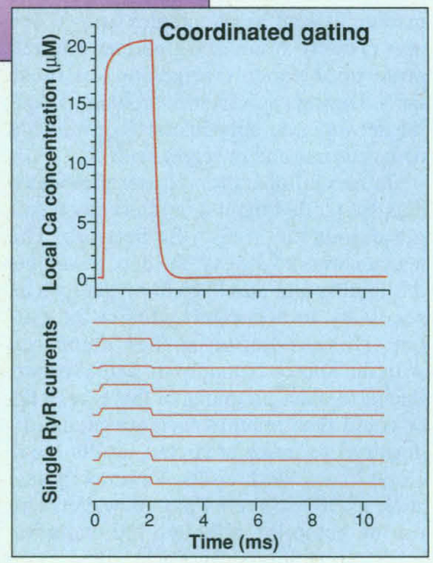
In skeletal muscle the RyR feet are packed in highly ordered arrays (*2*), possibly touching at the corners near where the Ca release seems to be crucial in activating the RyR [although direct skeletal muscle–like electromechanical coupling has not been entirely ruled out (*5*)].

The new description of coordinated RyR gating by Marx *et al.* (*1*)—in which clusters of RyRs open simultaneously—represents a third, entirely new mechanical mode of activating neighboring SR Ca release channels. This mechanism is likely to create Ca release that is more synchronous over a cluster of RyRs, simply by activating one RyR (by either Ca or voltage sensors in the DHPR). It also provides redundant activation mechanisms that create a safety margin for excitation-contraction coupling. If the DHPR voltage sensors do not all move together or if released Ca does not immediately activate the neighboring RyR, release would be both slower and less synchronous. Coordinated activation could ensure that whole clusters of RyRs are simultaneously activated. And the extra coordination occurs with remarkably little energetic cost or inertia, as indicated by the fact that the open and closed times for coupled channels were the same as for the solo RyR (*1*).









Fancy footwork. New data from Marx *et al.* (*1*) suggest that the ryanodine receptors of skeletal muscle work together to all release calcium simultaneously (coordinated gating), in contrast to the traditional notion that each ryanodine receptor worked independently (stochastic gating).

FK binding protein (FKBP) interacts with the RyR (*3*) (see the figure). Every other RyR in the array is associated with a dihydropyridine receptor (DHPR) in the surface membrane. The leading theory is that surface membrane depolarization sensed by the DHPR triggers release of Ca from the SR through the RyR via a mechanical DHPR-RYR link (*4*). This theory also suggests that the RyRs adjacent to a DHPR-linked RyR are activated by the Ca released by the DHPR-linked RyR. Thus, DHPR-linked RyRs are activated through an electromechanical coupling mechanism, whereas neighboring RyRs are activated through a Ca-induced Ca release mechanism. In heart muscle, Ca entry through the Ca channel (or DHPR) and Ca-induced

The figure illustrates the existing stochastic-gating theory (left) and the Marx *et al.* (*1*) coordinated-gating hypothesis (right). The stochastic-gating theory proposes that RyR channels operate independently and that activation of one RyR may elevate local Ca levels sufficiently to activate neighboring RyR channels. The activation of neighboring RyR channels occurs at

ILLUSTRATION: TAINA LITWAK

The authors are in the Department of Physiology, Stritch School of Medicine, Loyola University Chicago, Maywood, IL 60153, USA. E-mail: dbers@luc.edu

different intrinsic latencies. The consequence is that the RyRs in a cluster open and close randomly, generating a relatively slow, damped, and irregular local Ca flux. The Marx *et al.* (*1*) coordinated-gating hypothesis suggests that adjacent RyRs are mechanically linked and that the linked RyRs function (open and close) in a coordinated fashion. The consequence is that RyR clusters operate as functional units and generate large, fast local Ca release events. Thus, concerted RyR gating would speed the SR Ca release process, starting with the most "eager" RyR in the cluster. Concerted RyR gating might also occur in cardiac muscle. Because there are fewer DHPRs per RyR in cardiac cells (*6*), concerted RyR gating may prove to be even more crucial in heart than in skeletal muscle.

Small, localized intracellular Ca release events called Ca sparks have been measured by using fluorescent Ca indicators in skeletal, cardiac, and smooth muscle cells (*7–9*). The Ca spark is generally considered to be the elementary unit of SR Ca release. Although there is not complete agreement, it is likely that the Ca spark (particularly in cardiac muscle) arises from the opening of several RyRs rather than from the opening of a single RyR channel. The concerted RyR gating hypothesis may explain the apparent stereotypical amplitude and duration of the Ca spark. It implies that local RyR clusters operate as all-or-none Ca release units (all channels in a cluster open or closed together). Thus, a Ca spark would represent the brief, simultaneous, concerted opening of all RyRs in a cluster. Global cellular Ca signaling would be the result of RyR group dynamics. For example, in skeletal muscle the all-or-none twitch may result from all RyR clusters firing simultaneously. The graded nature of cardiac Ca-induced Ca release (*10*) may simply represent Ca influx–dependent recruitment of additional RyR clusters to generate the global Ca signal.

FKBP coordianates the gating of the RyR multimer, which is the fundamental SR Ca release channel and individual foot structure (*11*). The new work suggests that FKBP may also help in the cooperative gating of multiple RyRs (although it does not appear to be the glue that sticks them together). Interestingly, targeted knockout of the mouse FKBP12 gene produces a severe cardiomyopathy (and altered cardiac RyR gating), while skeletal muscle can still function (*12*).

This report of the coordinated gating of multiple RyR channels will stimulate new investigation to further define how the remarkable "molecular dance" of the RyR "feet" allows precise control of our muscles.

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PERSPECTIVES: PALEOMAGNETISM

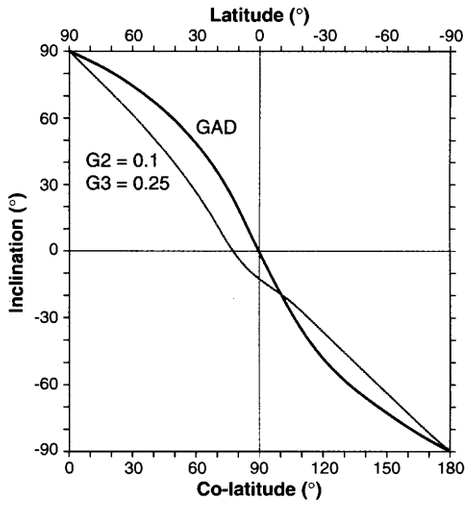
A Complex Field

Rob Van der Voo

Our knowledge of ancient locations of continental blocks is based in part on paleomagnetic data—the direction of the magnetic field in rock samples. Assuming that Earth's magnetic field is a dipole, a formula can be used to determine paleolatitude from the inclination of the rock's magnetic field. However, this formula is only appropriate if the long-term field was purely dipolar and early paleomagnetic publications always stated the premise explicitly. In the past several decades, a purely dipolar field, on average, has been tacitly assumed by paleomagnetists, even though it has become common knowledge that small nondipole contributions were probably long lasting (*1*). These quadrupole and octupole fields are thought to have been mostly zonal (that is, having symmetry about the rotation axis) and were estimated to cause paleolatitude errors of typically some 5° and were therefore not of great concern.

The blissfully ignorant are about to be rudely awakened, however, because of an analysis by Kent and Smethurst (*2*) that reveals a shallow bias in paleomagnetic inclinations older than about 250 million years (the Paleozoic and Precambrian eras). Such an analysis had been carried out in 1976 (*3*), but since that time the database has more than quadrupled, and this time the Precambrian data have also been included. The premise for the analysis is that spatially random sampling of observed inclinations for a given time window produces a frequency distribution that can be compared with the distinctive distributions theoretically calculated for a pure dipole field or for fields of a more complex nature. Representing each observed inclination by its absolute value $|I|$ takes care of sign changes because of reversals of the magnetic field and allows data from the Northern and Southern Hemispheres to be combined.

Kent and Smethurst conclude that, for the past 250 million years, the frequency distributions of $|I|$ are not demonstrably different from those for a purely dipolar field. However, the shallow bias in $|I|$ for rocks older than 250 million years could well be caused by a considerable octupole contribution with a relative magnitude of some 25% of the ambient dipole field; I will call this the "0.25G3" model, where G3 is the ratio of the octupole and dipole fields. Kent and Smethurst examined and rejected several other possible causes for this bias, such as inclination shallowing in sedimentary rocks, which is the flattening of the magnetic vector as the sediments compact over time. They do allow an alternative explanation that involves a geographic (low-latitude) bias in the ancient locations of the continents; if the polar areas were mostly oceanic, the steep inclinations of higher latitudes would be underrepresented, and the database would con-



A new angle. Inclination as function of co-latitude (latitude is measured from equator, whereas co-latitude is measured from north pole) for a purely geocentric coaxial dipolar field (GAD model; burgundy) and for a model that includes a quadrupole and octupole contribution (blue) [adapted from (*2*)].

The author is in the Department of Geological Sciences, University of Michigan, Ann Arbor, MI 48109–1063, USA. E-mail: voo@umich.edu