New and Notable

The Regulation of Muscle Contraction: As in Life, It Keeps Getting More Complex

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An article by Shimamoto et al. (1) in this issue examines a phenomenon called length-dependent activation (LDA). This is an important but unexplained anomaly in which contractile force increases as the overlap of thick and thin filaments decreases. It occurs in both cardiac and skeletal muscles although it is better known in the heart.

The Frank-Starling law tells us that increased filling of the heart (i.e., stretching the sarcomeres) produces increased ventricular pressure (i.e., stronger muscle contraction). How then does the sarcomere produce a greater force in the face of a decrease in the number of myosin ''motor'' units (myosin heads) able to interact with actin? The distance between the heads and the actin filaments may decrease, allowing the interaction to be more efficient, hence an increase in force as both Shimamoto et al. (1) and another independent article by Pearson et al. (2) in this issue demonstrate. LDA may also be explained by a cooperative enhancement of the binding of actin-myosin by the tropomyosin-troponin system as the sarcomere is stretched.

Pearson et al. (2) used x-ray diffraction to directly measure changes in the distance between the myosin motor and the actin filaments. Their method compelled them to use whole rat hearts, but wouldn't it be better if they could have examined single cardiomyocytes or, even better, single myofibrils where sarcomere length and uniformity can be precisely measured? So, is there a technique that can reproducibly induce stretch activation of single sarcomeres while monitoring sarcomere dimensions and force?

In this issue, Shimamoto et al. (1) meet this challenge. They analyze optical microscopy images of single skeletal muscle myofibrils to determine the width (interfilament distance) and the length of each sarcomere with an accuracy of ± 5 nm (± 0.2 nm) and ± 40 nm, respectively. They also monitor contractile force (in the absence of membrane systems such as sarcolemma, sarcoplasmic reticulum, and mitochondria) using various concentrations of ATP, ADP and a wide range of free Ca^{2+}. These conditions include those needed for partial activation (elevated concentrations of ADP in the absence of Ca^{2+}).

The authors focus their attention on SPontaneous Oscillatory Contractions (SPOCs) that, once induced, travel back and forth along a single myofibril, thus providing a highly reproducible rate of contraction (at the rapid front edge) and relaxation (at the slower trailing edge) of the traveling wave of contractions). SPOCs can continue for several minutes, thus allowing precise averages of sarcomere length and diameter to be obtained under conditions where activation can be chemically controlled (see Movie 1 in the Supplementary Material of Shimamoto et al. (1)).

To explain the molecular mechanism of LDA, Shimamoto et al. (1) used several key assumptions that they had previously proposed (3):

1. The interaction probability between myosin cross bridges in thick filaments and actin-troponin-tropomyosin in thin filaments depends on the distance between them.
2. The isovolumic nature of the sarcomere suggests that interfilament distance depends on sarcomere length.
3. Thin filament stiffness depends on both the Ca^{2+} concentration and cross-bridge formation.
4. The extension of myosin heads from the thick filaments depends on the ADP concentration.

As John Solaro points out in the prior New and Notable in this issue (4), hearts normally operate at submaximal Ca^{2+}-activation and perhaps it is for this reason that LDA is more difficult to demonstrate in skeletal muscle that is either fully activated or completely relaxed. Surprisingly, LDA was first reported in skeletal muscle (5) more than 30 years ago, and SPOCs have been known for almost as long (6).

SPOC may not be as well known as twitches or tetanic contractions, but it is not new. The Ishiwata laboratory is certainly the best protagonist for the phenomenon (7), but several other laboratories (6,8–10) have reported SPOC for both skeletal and cardiac muscle, suggesting it is not merely a curious artifact. It can even be argued that SPOC is relevant to normal physiology. The frequency of the SPOC oscillations is linearly correlated with the resting heart rate of different animals (mouse, rat, guinea pig, rabbit, dog, pig, and cow, see (7,11)) and the oscillations occur in Ca^{2+} concentration range (pCa <6 to >7) that occurs in vivo (11).

It is likely that SPOC will be useful for examining the effects of isoform switching and posttranslational modifications of specific myofibrillar proteins in striated muscles, or even for examining myofibrils isolated from biopsies failing human hearts (12).

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