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Original Research

A theory on auto-oscillation and contraction in striated muscle

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ABSTRACT

It is widely accepted that muscle cells take either force-generating or relaxing state in an all-or-none fashion through the so-called excitation–contraction coupling. On the other hand, the membrane-less contractile apparatus takes the third state, i.e., the auto-oscillation (SPOC) state, at the activation level that is intermediate between full activation and relaxation. Here, to explain the dynamics of all three states of muscle, we construct a novel theoretical model based on the balance of forces not only parallel but also perpendicular to the long axis of myofibrils, taking into account the experimental fact that the spacing of myofilament lattice changes with sarcomere length and upon contraction. This theory presents a phase diagram composed of several states of the contractile apparatus and explains the dynamic behavior of SPOC, e.g., periodical changes in sarcomere length with the saw-tooth waveform. The appropriate selection of the constant of the molecular friction due to the cross-bridge formation can explain the difference in the SPOC periods observed under various activating conditions and in different muscle types, i.e., skeletal and cardiac. The theory also predicts the existence of a weak oscillation state at the boundary between SPOC and relaxation regions in the phase diagram. Thus, the present theory comprehensively explains the characteristics of auto-oscillation and contraction in the contractile system of striated muscle.

1. Introduction

Muscle contraction occurs through the coordinated force generation by collective molecular motors (muscle myosin II), which results in relative sliding of the thick (myosin) and the thin (actin) filaments accompanied by a change in the sarcomere length (Huxley and Niedergerke, 1954; Huxley and Hanson, 1954). The contractile properties at a steady state, e.g., force–velocity relationship, as well as the transient properties of force generation, have been extensively studied and well explained theoretically based on the sliding filament mechanism (Huxley, 1957; Huxley and Simmons, 1971).

Although striated muscle is usually considered to take either the contraction or the relaxation state depending on the Ca^{2+} concentration, a remarkable phenomenon is observed at an intermediate level of activation between contraction and relaxation: the spontaneous oscillatory contraction termed "SPOC" (Okamura and Ishiwata, 1988; Fabiato and Fabiato, 1978; Stephenson and Williams, 1981; Linke et al., 1993; Ishiwata and Yasuda, 1993; Fukuda et al., 1996; Telley et al., 2006; Shimamoto et al., 2007, 2008). This phenomenon is observed for both skeletal and cardiac skinned muscles at a constant concentration of Ca^{2+} without the involvement of sarcoplasmic reticulum (the organelle that stores and releases Ca^{2+} ions) (termed Ca-SPOC; Fukuda et al., 1996; Shimamoto et al., 2008). Furthermore, even under Ca^{2+}-free conditions, the addition of MgADP with MgATP induces force generation (Shimizu et al., 1992) and auto-oscillation within a narrow range of MgADP concentrations (Shimamoto et al., 2007), and further addition of inorganic phosphate (Pi) induces steady auto-oscillation (termed ADP-SPOC; Okamura and Ishiwata, 1988; Shimizu et al., 1992; Anazawa et al., 1992). Thus, SPOC is considered to be the third state of muscle, which is located in between contraction and relaxation states as revealed by the phase diagram constructed against the concentrations of ADP, Pi and Ca^{2+} at a fixed ATP concentration (Okamura and Ishiwata, 1988; Ishiwata and Yasuda, 1993; Fukuda et al., 1996).

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In SPOC each sarcomere exhibits stable length oscillation composed of slow shortening and quick lengthening phases, forming a saw-tooth oscillation waveform. Besides, the lengthening phase of a sarcomere propagates to the adjacent sarcomeres, forming a traveling wave of sarcomere lengthening along a myofibril (SPOC wave). Since these phenomena occur in skinned preparations, i.e., those devoid of sarcoplasmic reticulum, and under continuous flow of fresh solution, SPOC is not driven by the oscillation of chemical parameters, such as concentration of Ca^{2+} or ATP hydrolysis products, but owes to other factors that the contractile apparatus inherently possesses. Several models have been proposed (e.g., Jülicher and Prost, 1997; Smith and Stephenson, 1994, 2009; Gunther and Kruse, 2007), but so far there is no unified theory to fully describe all properties of the activation state including SPOC.

In this paper we propose a scenario for the auto-oscillation in the contractile system of muscle, based on the changes in the spacing of myofilament lattice. We provide a simple mathematical model, where the force balance is considered not only parallel, but also perpendicular to the long axis of muscle fibers (Fig. 1). We show that the balance of forces acting within the sarcomere structure in both directions, along with a simple two-state model for the interaction between myosin heads and an actin filament, can sufficiently recapitulate the phase diagram of muscle composed of relaxation, contraction, and SPOC, and reproduce the non-linear oscillation waveform characteristic for SPOC.

Our considerations are based on the following experimental observations.

Experimental observation (1): In the relaxed state, the myofilament lattice spacing decreases with an increase in sarcomere length (SL) (Matsubara and Elliott, 1972; Higuchi and Umazume, 1986). The tendency holds for both intact and skinned muscles, although in the latter the changes are smaller than in the former (Matsubara and Elliott, 1972).

Experimental observation (2): The cross-bridge formation changes the myofilament lattice spacing. For example, when a skinned muscle undergoes the transition from the relaxed to the contracted or rigor state, the lattice spacing shrinks (Matsubara et al., 1984; Brenner and Yu, 1985; Kawai et al., 1993). On the other hand, in the special case of a myofibril highly compressed by the osmotic pressure, the lattice spacing swells with activation (Matsubara et al., 1984, 1985; Irving et al., 1998).

Experimental observation (3): The myofilament lattice spacing affects the magnitude of the isometric force. In a skinned muscle the isometric force increases with decreasing the lateral width of myofibrils by a small compression, whereas at the large compression the opposite dependence is observed (Godt and Maughan, 1981; Zhao and Kawai, 1993; Krasner and Maughan, 1984; Gulati and Babu, 1985; Umazume et al., 1991; Shimamoto et al., 2007, 2008).

Based on these experimental observations, we now make the following assumptions concerning lattice spacing and lateral forces.

Assumption (1): Sarcomeres in the relaxed state have optimal lattice spacing for each SL. We assume that the filament lattice behaves in lateral direction like a simple elastic spring. The equilibrium length of the spring monotonically decreases with an increase in SL. This assumption is based on the experimental observation (1).

Assumption (2): Myosin heads attached to the thin filament generate force not only in the longitudinal, but also in the lateral direction of the sarcomere structure. This assumption corresponds to the experimental observation (2).

Assumption (3): The activation level of muscle (or, to be specific, the transition rates between the attached and the detached states of myosin heads) depends on the myofilament lattice spacing. This assumption is deduced from the experimental observation (3) and previously adopted by Ishiwata and Oosawa (1974) to explain the non-linear length–tension relationship under intermediate activation conditions.

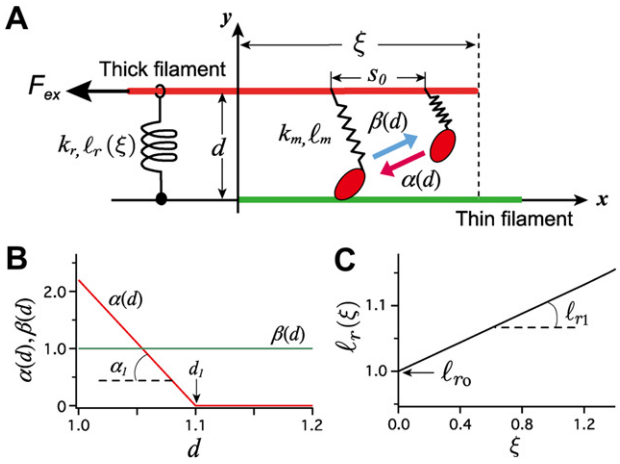

Fig. 1. Schematic illustration showing the details of the model. (A) Components of the model consisting of myofilaments, i.e., the thick and the thin filaments, and the elastic framework, i.e., the *Z*-line and the *M*-line, where ξ represents the length of overlap between the thick and the thin filaments. The cross-bridges are uniformly distributed at s_0 intervals along the thick filament. F_{ex} is the externally applied force; α and β are the rates of attachment and detachment of cross-bridges, respectively, which are assumed to depend on the distance between the thick and the thin filaments (filament lattice constant, d) as shown in (B). k_r and $l_r(\xi)$ are the elastic constant and the natural length of the lateral elastic component, respectively, and k_m and l_m are the elastic constant and the average length of myosin heads under the relaxing conditions, respectively. The coordinates x and y are defined as indicated. (B) The dependence of α and β on d assumed in the present model. For simplicity, we assumed that the value of α linearly decreases with an increase in d and becomes zero at d_1, whereas the value of β is constant (β_0). The activation level of the contractile system is represented by the slope of the dependence of α on d, i.e., α_1. In the following model simulations, $\alpha_1 = 22$ is mainly used to examine a typical SPOC. (C) The dependence of length of the lateral elastic component under relaxing conditions on ξ. l_{r0} is the natural length of the elastic component at no overlap. l_{r1} is a proportional constant of the dependence on ξ.

We demonstrate that the combination of these simple assumptions explains a non-linear force–length relationship and the auto-oscillation of muscle (SPOC) observed at intermediate levels of activation. Moreover, the state diagram of muscle contraction can be described by the balance of two parameters, namely, the level of activation and the elasticity of the sarcomere lattice structure.

2. Results

2.1. Theoretical framework of the model

The present model is based on the two-state model, i.e., only the attached and the detached states of myosin heads are considered (Fig. 1A). Each myosin head stochastically and independently attaches to and detaches from the thin filament characterized by certain transition rates. Additionally, we consider the balance of forces acting on the thick filament in both the longitudinal and the lateral directions. The force balance in the lateral direction determines the lattice spacing d as a function of the fraction of attached myosin heads and SL. The constitutive equations of the model consist of the following three equations:

$$dP/dt = \alpha(d)(1-P) - \beta(d)P \tag{1}$$

$$-F_{ex}(t) + a\xi P/s_0 - \eta\xi P(d\xi/dt)/s_0 = 0 \tag{2}$$

$$k_m\xi P(l_m - d)/s_0 + k_r(l_r(\xi) - d) = 0 \tag{3}$$