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Review

Contractile system of muscle as an auto-oscillator

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ABSTRACT

It is widely known that the contractile system of muscle takes on either the state of contraction (force-generating) or the state of relaxation (non-force-generating), which is known as the "all-or-nothing" principle. However, it is important to note that under intermediate activation conditions there exists a third state, which demonstrates auto-oscillatory properties and is termed *SPOC* (*SP*ontaneous *O*scillatory *C*ontraction) state. We present a phase diagram, in which the states of the contractile system of muscle are divided into three regions consisting of contraction, relaxation and SPOC states. In the present review, experimental data related to the characteristics of SPOC are summarized and the mechanism of SPOC is described. We propose that the bio-motile system itself is an auto-oscillator, even in a membrane-less supra-molecular structure composed of an assembly of molecular motors and cytoskeletons (actin filaments and microtubules). Finally, the physiological significance of SPOC is discussed.

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1. Introduction

The contractile system of striated muscle is a biomolecular machine of which the function is to generate force and do mechanical work. Contraction occurs by mutual sliding (termed the "sliding mechanism") between two types of myofilaments, the thick (myosin) and the thin (actin) filaments. The experimental basis of the sliding mechanism was elucidated by optical microscopic observation (Huxley and Niedergerke, 1954) and electron microscopic observation (Huxley and Hanson, 1954); those studies demonstrated that the length of the thick and thin filaments is unchanged before and after shortening of the muscle, within the spatial resolution of each technique. Subsequently, the sliding mechanism gained solid support from a physiological study: it showed that the maximum force developed in skeletal muscle fiber is proportional to the overlap between the thick and the thin filaments (Gordon et al., 1966a,b), implying that the active force is a simple sum of the force generated by each cross-bridge, at least in skeletal muscle. On the other hand, in cardiac muscle, the increase in tension development is observed upon stretching of the fiber, which is known as the Frank–Starling law (mechanism).

The sliding mechanism is well explained by the theory proposed by Huxley (1957) for the properties which can be viewed during steady state, such as the force (P) to velocity (V) relationship. Regarding the response to transient mechanical perturbation, Huxley and Simmons (1971) performed excellent experiments and proposed a new theory based on the idea of a cross-bridge rotation mechanism (Huxley, 1969). It is to be noted, however, that these theories were proposed for the force-generating and energy consuming properties of the contractile system of muscle under full activation (ON state).

On the other hand, there is a mechanism that regulates the ON (contraction)–OFF (relaxation) states of the contractile system of muscle as an important part of the excitation-contraction (E–C) coupling pathway. It was found by Ebashi et al. that the troponin (Ca^{2+}-binding protein)–tropomyosin system located on the thin (actin) filaments, of which state is regulated by μM concentrations of free Ca^{2+}, is required for relaxation of the contractile system of striated muscle (Ebashi and Endo, 1968; Ebashi et al., 1969; Ebashi, 1991). In the presence of ATP, the formation of force-generating cross-bridges is inhibited when troponin does not bind Ca^{2+}. As schematically illustrated in Fig. 1, the E–C coupling pathway is not a one-way pathway. In other words, the contractile system located at the bottom end of this pathway is not a simple worker compliant to the regulation according to the electric impulse produced by a nerve system (skeletal muscle) or pacemaker cells (cardiac muscle). That is, there are several hierarchical feed-back loops. Among the feed-back regulations, mechano-electric feedback has been extensively investigated (Kohl and Ravens, 2003). It is also well-known that the Ca^{2+} binding to troponin induces cross-bridge formation, and conversely the cross-bridge formation enhances the Ca^{2+} binding affinity of troponin (Bremel and Weber, 1972). This is an example of the feed-back loop present at the level of protein assemblage. Thus, it is expected that other types of feed-back loops also exist, such as the regulation of Ca^{2+}-release/uptake of sarcoplasmic reticulum (SR) due to the deformation of SR by the force generated by cross-bridges.

The present review focuses on the auto-oscillatory properties inherent to the contractile system of striated muscle. The auto-oscillation of sarcomere length (SL) occurs under the steady conditions intermediate between full contraction and relaxation conditions. We termed this phenomenon *SPOC* taken after the *SP*ontaneous *O*scillatory *C*ontraction of myofibrils (Okamura and Ishiwata, 1988; Ishiwata and Yasuda, 1993). We want to stress that a chemo-mechanical feed-back (CMF) loop exists within the contractile system of striated muscle (Fig. 1). This loop is constituted by a cycle of enzymatic (ATPase) activity of actomyosin complex, force generation by cross-bridges, deformation of protein assemblage (additionally, changes in the size of the interaction space constrained by filament lattice), and then feed-back to the modulation of enzymatic activity.

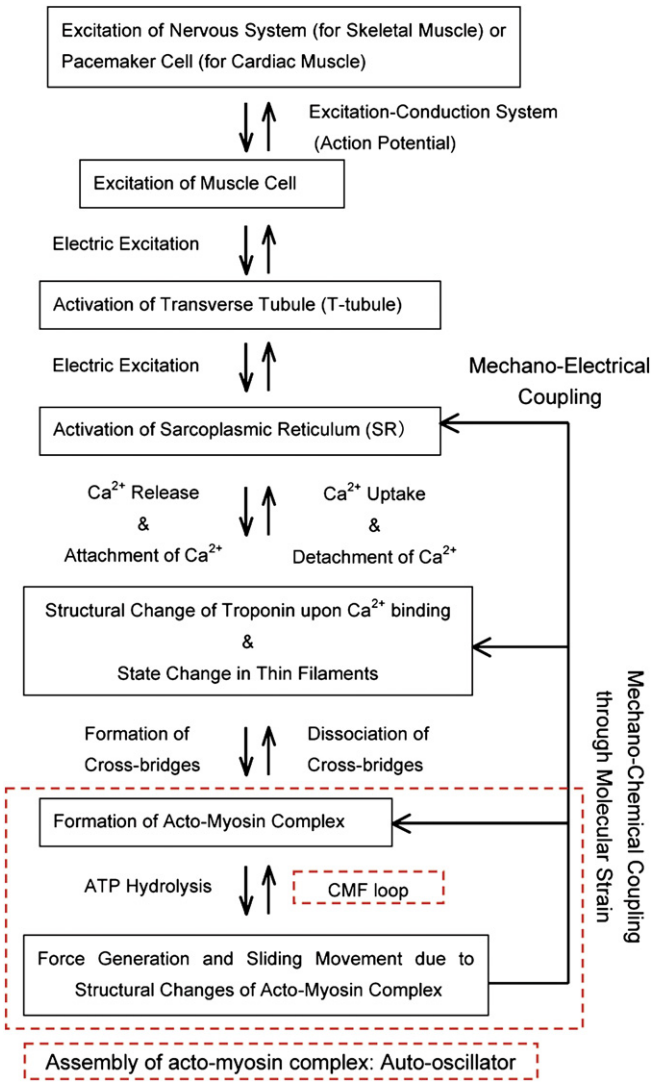

Fig. 1. Flow chart showing the feed-forward and feed-back regulation existing at each level of structural hierarchy of the contractile system of striated muscle. CMF loop: Chemo-Mechanical Feed-back loop. The present review proposes that the CMF loop exists on the level of individual myofibrils, i.e., a supra-molecular assembly.

It has been recently suggested that even a molecular system composed of a small number of myosin molecules and a single actin filament is an auto-oscillator (Plaçais et al., 2009). There is a possibility that the contractile system constituting a hierarchy structure from a molecular level, up to myofibrils and fibers has auto-oscillatory properties characteristic of each level of hierarchy (Ishiwata et al., 2010).

2. What is SPOC?

2.1. Definition and characteristics of SPOC

SPOC is the third state of the contractile system of muscle, which occurs under a fixed chemical condition. The SPOC state is