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Review article

Calcium alternans in cardiac myocytes: Order from disorder

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ABSTRACT

Calcium alternans is associated with T-wave alternans and pulsus alternans, harbingers of increased mortality in the setting of heart disease. Recent experimental, computational, and theoretical studies have led to new insights into the mechanisms of Ca alternans, specifically how disordered behaviors dominated by stochastic processes at the subcellular level become organized into ordered periodic behaviors. In this article, we summarize the recent progress in this area, outlining a holistic theoretical framework in which the complex effects of Ca cycling proteins on Ca alternans are linked to three key properties of the cardiac Ca cycling network: randomness, refractoriness, and recruitment. We also illustrate how this '3R theory' can reconcile many seemingly contradictory experimental observations. This article is part of a Special Issue entitled 'Calcium Signaling in Heart'.

Contents

1. Introduction

Intracellular calcium (Ca) alternans has been documented to occur under either current clamp or voltage clamp conditions [1–21], the latter unequivocally demonstrating that the Ca cycling system in cardiac myocytes is capable of producing dynamical instabilities that generate alternans, independent of electrical alternans. Indeed,

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the available evidence indicates that electromechanical alternans, a known risk factor conferring increased mortality in the setting of heart disease [22–25], is more often initiated by instabilities in the Ca cycling system than by restitution-related electrical properties [9,26].

Cardiac myocytes contain a network of ~20,000 Ca release units (CRUs or couplons) [27–29], each consisting of a cluster of L-type Ca channels (LCCs) in the sarcolemmal membrane apposed to a larger cluster of ryanodine receptors (RyRs) in the junctional sarcoplasmic reticulum (SR) membrane. By the process of Ca-induced Ca release (CICR), Ca entry through the LCCs triggers Ca release from a CRU, which is called a Ca spark [30,31]. Ca sparks are considered the elementary events in Ca signaling, not only in cardiac myocytes but also in many other cell types. Spontaneous Ca sparks (i.e. sparks not triggered by LCCs) may also occur. Since the openings of LCCs and RyRs are stochastic events, the timing of onset and other properties of Ca sparks exhibit randomness, even when elicited by action potentials [32,33]. It is not difficult to understand how the disorder inherent to the randomness of individual Ca sparks nevertheless produces the same whole-cell Ca transient from beat to beat, as the whole-cell Ca transient is the summation of all Ca sparks whether they arise from the same or different CRUs. That is, even though the macroscopic Ca transient is regular from beat to beat, the system is in a microscopically disordered state, similar to a typical thermodynamic system (e.g., a gas at constant temperature, volume and pressure). When Ca alternans occurs, the whole-cell Ca transient exhibits a large–small–large–small alternating pattern, which represents a new temporal order of the system. At the microscopic level, however, pure randomness cannot explain why a larger number of CRUs consistently release Ca on one beat (e.g. the even beat) rather than on the next beat (e.g. the odd beat). To give rise to the whole-cell (macroscopic) alternans, an order must be self-organized at the microscopic (spark) level. Therefore, the transition from no alternans to alternans represents a transition from disorder to order, a fundamental topic of nonequilibrium statistical physics and self-organization pattern formation in natural systems [34–38]. Such a transition has been demonstrated in recent experiments by Tian et al. [39] who showed that as the heart rate increased, alternans first occurred at the microscopic scale (CRU alternans) without macroscopic (whole-cell) alternans (Fig. 1A). Because alternans in different CRUs occurred in a disordered manner, the whole-cell Ca transient remained constant from beat to beat. As the heart rate was increased further, however, the microscopic CRU alternans developed an ordered pattern resulting in macroscopic alternans (Fig. 1B). The question is then: how does the distribution of CRUs become preferentially biased towards releasing Ca on one type of beat, rather than remaining equally distributed between odd and even beats? Put differently, how do randomly occurring Ca sparks self-organize to generate the beat to beat alternating pattern at the whole-cell level?

Answering these questions not only is necessary for understanding the mechanisms of Ca alternans in general but can also provide essential precursors for understanding how the properties of specific Ca cycling proteins affect the genesis of Ca alternans. The difficulty in understanding the effects of a specific Ca cycling protein on Ca

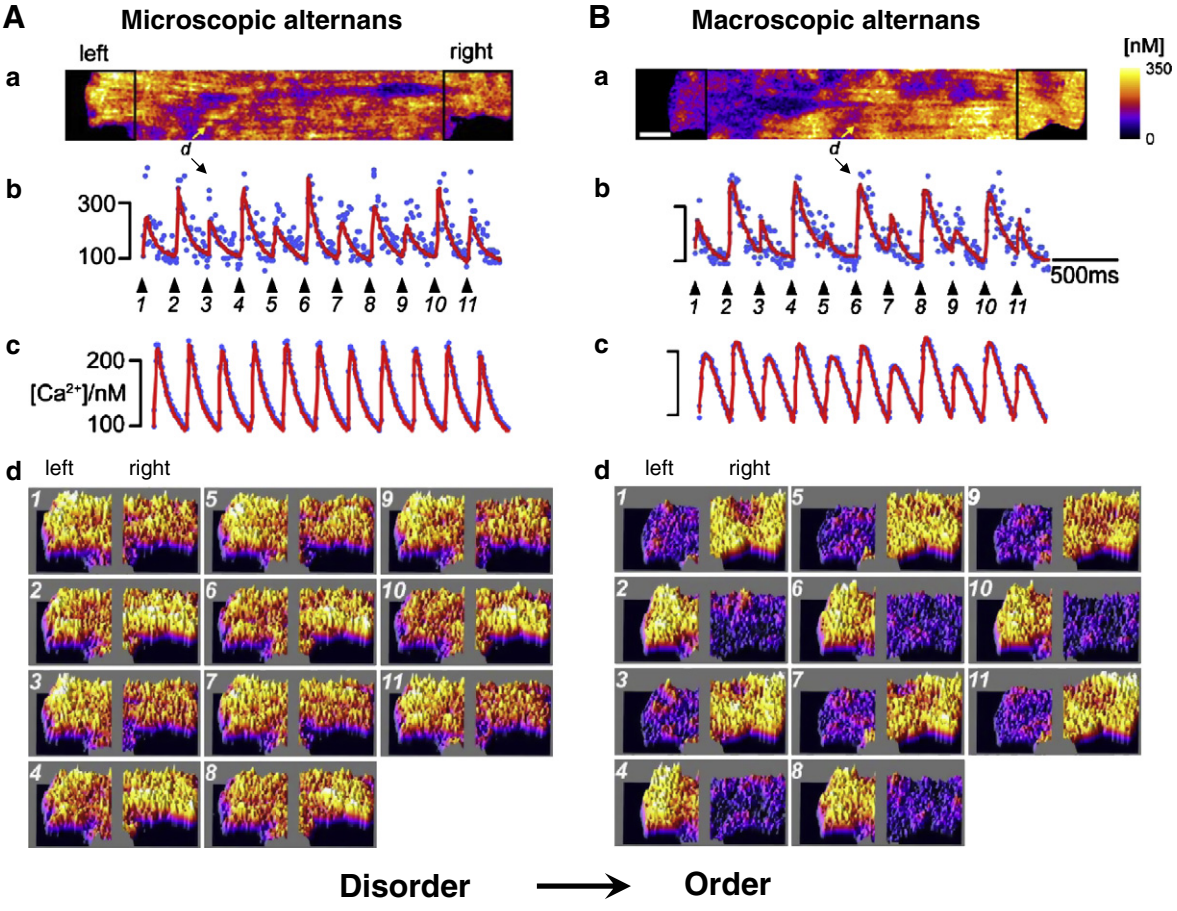

Fig. 1. Transition from microscopic to macroscopic alternans (or from disorder to order). A. At a slower heart rate, microscopic alternans occurs (panel b) but no macroscopic alternans is present (panel c) due to random distribution between even:odd and odd:even phases of alternans among CRUs. B. At a faster heart rate, macroscopic alternans occurs as the phase of alternans among CRU synchronizes. Panel a: Snapshot of the spark amplitude distribution in the myocyte. Panel b: Local alternans for a site as marked in panel a. Panel c: Whole-cell Ca transient. Panel d: Snapshots of spark amplitudes from the left and right ends of the myocyte. This figure was modified from Tian et al. [39].

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