Key concepts of excitation-contraction coupling

Signals in striated muscle. The contraction of striated muscle is controlled by rapid changes of cytosolic Ca^{2+}.concentration, $[Ca^{2+}]_c$. But Ca^{2+} regulates multiple cell functions, spanning from milliseconds to years. To stay separate, Ca^{2+} signals are coded in spatial and temporal patterns, the fastest of which involve 100 to 1000-fold $[Ca^{2+}]_c$ changes in ~1 ms. The system must be capable of explosively fast jumps but must never explode. These two seemingly contradictory properties are realized by a sarcoplasmic reticulum membrane with channels organized in structural-functional units named couplons[1].

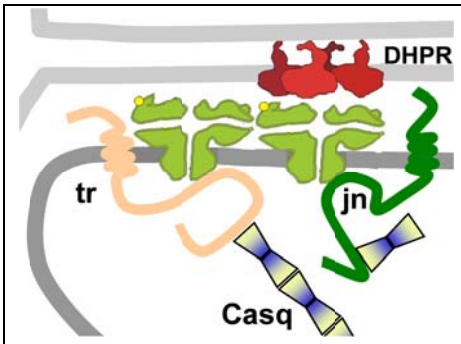

Fig. 1. The couplon—array of RyRs and their associated proteins: triadin, junctin and calsequestrin.

A couplon (figs 1 and 2) is the array of RyRs and their associated proteins on one side of a triad junction. In non mammals it additionally includes RyR of isoform 3 or β in the para-junction. Synchronized opening is started by an allosteric signal[2] from the voltage (V_m) sensor[3] in the membrane of the transverse tubule, leading to *depolarization-induced Ca^{2+} release*, DICR.

Allostery[94], a notion first introduced in EC coupling by Ríos et al., 1993[45], is any mechanical influence causing a change in a "different place" from that of contact. The DHPR to RyR signal is one example of "vertical" allosterics in the couplon (fig 4 illustrates "vertical" and "horizontal" directions of possible allosteric actions).)

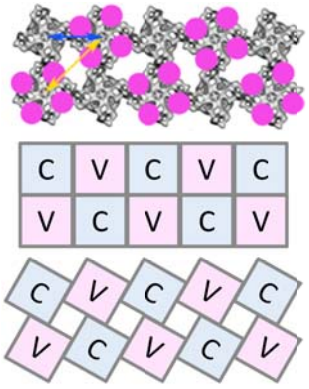

Fig 2. Couplon (from [89]), circles represent DHPRs.

CICR. Clustering of RyRs in couplons allows further coordination, either by horizontal (RyR-to-RyR) allosterics, or Ca^{2+}-induced Ca^{2+} release, CICR, which manifests itself as Ca^{2+} sparks (Cheng et al., 1993). The existence of CICR, whereby Ca^{2+} release channels are activated to open by Ca^{2+} itself, brings with it the *paradox of control*[4], i.e. why activation does not propagate explosively. Couplons are finite (no more than ~60 channels in the mouse) and separate, which explains the paradox. The whole system does not explode simply because excitation usually stays restricted to individual couplons[1]. CICR, and sparks, require the RyR3[42,17], located in the para-junction. The RyR1 strictly align with the V_m-sensing system (fig 3), which prevents their engaging in CICR[51]. Local disarray allows production of sparks[5].

Termination. The fast termination of Ca^{2+}release is equally important for a fast transient. It is due to de-activation of DHPRs upon repolarization, complemented by Ca^{2+}-dependent inactivation (CDI[6-8]) and possibly allosterics. Both activation and termination of signals are subject to modulation from inside the SR, through powerful processes—including "vertical" allosterics—that we are only starting to understand[8].

Fatigue. These events repeat at frequencies of 10-100 Hz, for brief periods of activity that in turn repeat at different frequencies, depending on muscle, motor unit and fiber type. Repeated activity leads to fatigue, which courses with substantial alteration of Ca movements[9].

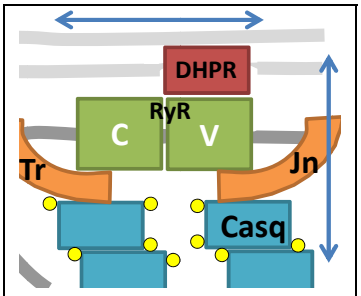

Fig 3. Horizontal and vertical allosterics in the couplon.

Disease. The goal of our laboratory has been to define these "Ca^{2+} movements in EC coupling". In fact, the picture of Ca^{2+} signaling presented above was in some measure built with advances produced by our laboratory and largely completed by methods originated here. We now use these methods to learn whether, how, and why Ca^{2+} movements are altered in disease. We will apply them to select conditions with altered couplons, which model muscle diseases or muscle repercussions of systemic diseases.