Excitation-contraction coupling from 1969 to 2005

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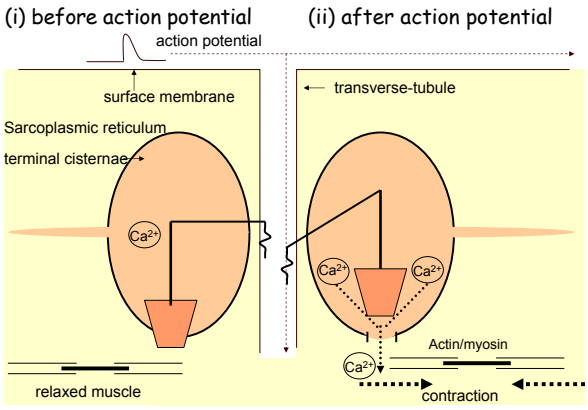
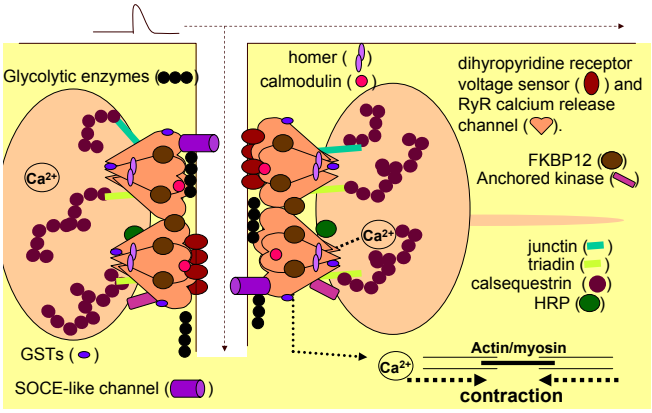
The past 40 years have seen an explosion of information about the molecular components of many cell processes including the excitation-contraction (EC) coupling which controls Ca^{2+} release and triggers contraction in muscle. In the 1960's it was understood that "a switch" allowed the action potential that travelled along the transverse (T-) tubular invaginations of the surface membrane to release Ca^{2+} from the sarcoplasmic reticulum (SR). Nothing was known of the molecules or signalling systems involved. There was hot debate about the nature of the switch, whether it was chemical, mechanical or electrical. The early 1970's saw the discovery of a tiny electrical "charge movement" which reflected the movement of a dipole in the T-tubule membrane that was linked to, and preceded, Ca^{2+} release. The charge movement was likened to a lever that pulled a plug from the terminal cisternae to dump Ca into the myoplasm.



The molecule that generated the charge movement was thought to be the dihydropyridine receptor (DHPR) L-type Ca^{2+} channel. The >2 million dalton ryanodine receptor (RyR) Ca^{2+} release channel was identified in the 1980's. Expression of recombinant proteins in DHPR- or RyR-null cells in the late 1980's and 1990's confirmed that the α_1 subunit of DHPR and the RyR were essential for EC coupling. In the following decade, several interactions between the proteins have been defined and the very important role of associated proteins recognised. It is no longer thought that the DHPR and RyR transiently connect after an action potential. Rather, a tightly coupled macromolecular complex is thought to respond to changes in surface membrane potential in a manner that is highly regulated by cytoplasmic factors and by the Ca^{2+} load in the SR.



The molecular complex extends from the extracellular space into the lumen of the SR, spanning the T-tubule and SR membranes and the junctional gap between them. The RyR is coupled to the II-III and III-IV cytoplasmic linker loops and C-terminal tail of the α_1 subunit of the DHPR and to the soluble β subunit. Among many proteins that associate with the cytoplasmic domain of the RyR and regulate its activity are the critically important FK506 binding proteins, anchored kinases, calmodulin, Homer and members of the glutathione transferase (GST) structural family. Glycolytic enzymes are abundant around complex. Within the SR lumen, the RyR communicates with the calcium binding protein, calsequestrin (CSQ), with the CSQ anchoring proteins triadin and junctin, with a histidine rich protein (HRP) and with GSTs. The activity of the channel is modulated by phosphorylation and oxidation. The complex not only regulates Ca^{2+} release from the SR, but also Ca^{2+} influx from the extracellular environment through the DHPR and store-operated calcium entry (SOCE)-like channels. Despite the extent of current knowledge, there is much to learn - we remain ignorant about the atomic structures of the proteins, the molecular nature of the interactions between them and indeed the residues involved in most of the interactions.