Plasma membrane Ca^{2+} channel handling and arrhythmogenesis

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Perturbations in cellular calcium homeostasis and reactive oxygen species generation play central roles in the induction of arrhythmia. The L-type Ca^{2+} channel plays a critical role in cardiac excitation and contraction, and it is the main route for calcium influx into myocytes. The function of the channel can be modified during alterations in cellular redox state. A reduced cellular state such as during acute hypoxia can alter the basal channel activity and increase the sensitivity of the channel to β-adrenergic receptor activation. Thiol reducing agents mimic the effect of hypoxia in myocytes implicating an involvement of cysteines on the channel protein or a regulatory protein. We have demonstrated both *in vitro* and *in silico* that this can lead to altered cellular excitation, induction of early afterdepolarizations and arrhythmia. We are now determining how the function of the channel protein is directly altered during changes in redox state. We have evidence that protein kinase A can directly alter the function of the purified human Long NT isoform of $Ca_v1.2$ reconstituted in proteoliposomes. When we reduced thiol groups on the catalytic subunit of protein kinase A, open probability (P_o) of the channel is significantly increased but P_o is further increased approximately twofold when thiol groups on the channel are also reduced. This also occurred when Ser 1928 on $Ca_v1.2$ was mutated to Ala. In addition, protein kinase A increased P_o of $Ca_v1.2$ in the presence of 10 μM *st*-Ht31 peptide that uncouples protein kinase A from A kinase anchoring protein.

Our results suggest that increased sensitivity of the L-type Ca^{2+} channel to β-adrenergic receptor stimulation under hypoxic conditions involves the reduction of cysteines on both the α-subunit of the channel and protein kinase A. Contrary to current opinion, the β-adrenergic response does not require phosphorylation at Ser 1928 on the α-subunit of the channel or the presence of a regulatory protein.