Public Abstract
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Title:Regulation of L-type calcium channel sparklet activity by PKC and c-Src

Altered vascular function is a well-known precursor to cardiovascular disease, which is one of the leading causes of mortality in both developed and developing countries. For this reason, it is very important to appreciate the physiology of healthy blood vessels and the mechanisms underlying vascular pathologies. Blood vessels contain two prominent cells types: endothelium and vascular smooth muscle and vascular dysfunction can arise in either of the two cell types. My dissertation focuses on the normal function of vascular smooth muscle and endeavors to understand the regulation of L-type calcium (CaL) channel function by protein kinase C (PKC) and c-Src tyrosine kinase. CaL channels are a primary pathway of calcium entry in vascular smooth muscle cells and therefore play a central role in establishment of vascular tone, which is defined as the degree of constriction exhibited by a blood vessel at any given time. Changes in the activities of CaL channels by voltage, intracellular Ca2+ and various signaling proteins result in bidirectional modulation of vascular tone (vasodilation or vasoconstriction). PKC and c-Src are two intracellular kinases that are known to regulate the basal as well as the agonist-induced increases in CaL channel activity. However, it is not clear if these two protein kinases are activated in series by the same signaling pathways. I expressed wild type or mutant CaL channels along with PKC/c-Src in a secondary cell line and used electrophysiology and imaging techniques to investigate the mechanisms of PKC and c-Src action on CaL channels. The results of my study indicate that both PKC and c-Src enhance the activity of CaL channels independent of each other. The possibility of parallel actions of PKC and c-Src conforms to existing ideas about the complex regulation of CaL channels to fully explain their central roles in the regulation vascular tone as well as multiple other physiological functions. The findings of my study also suggest that both PKC and c-Src regulate vascular tone by increasing the activity of only a small population of CaL channels instead of having a global increase in CaL channel activity. The small population of CaL channels that exhibits enhanced activity and the molecular mechanisms underlying this effect may prove to be effective targets for drug therapy directed at pathological conditions associated with altered vascular tone.