An Improved Model of Ba Current through L-type Ca Channels Including Voltage- and Ion-Dependent Inactivation

Stefano Morotti*, Eleonora Grandi, Aurora Summa, Kenneth S Ginsburg, Donald M Bers and Stefano Severi

Biomedical Engineering Laboratory, University of Bologna, Cesena, Italy

Background. Inactivation of the L-type Ca channel (LTCC) is regulated by both Ca- and voltage-dependent processes (CDI and VDI). CDI is due to binding of Ca to calmodulin (CaM), which causes a channel conformational change that accelerates inactivation. To differentiate VDI and CDI, several studies have considered the inactivation of Ba current through LTCC (IBa) as a measure of VDI. However, there is evidence that Ba can weakly mimic Ca, such that IBa inactivation is still a mixture of CDI and VDI. Methods. We incorporated an existing Markov model of ICa (in which VDI was modelled to fit experimental IBa inactivation)into an excitation-contraction coupling model. We extended the LTCC model to assess whether and how experimental IBa inactivation could be recapitulated by modifying CDI to account for Ba-dependent inactivation. A weaker apparent affinity of Ba for CaM (kBa<kCa) was simulated by making ion-dependent transitions less sensitive to Ba (vs. Ca) by a factor kCa/kBa, which varied from 1 to 100. Results. Modeling results show that IBa exhibits slower inactivation as Ba affinity decreases. The modest ability of Ba to mimic Ca-dependent inactivation is negligible when kCa/kBa is larger than 10. We found that a 10-fold reduction resulted in appropriate Ba-dependent IBa inactivation. With this model we were able to reproduce the U-shaped dependence of IBa inactivation rate on voltage and the increased extent of IBa inactivation that is observed in experiments with increasing peak IBa. These results hold true if intracellular Ba accumulation is avoided during the experiment. Conclusions. The extended LTCC model should be a more faithful representation of purely VDI during ICa. This may be an important distinction when one seeks to dissect the relative roles of Ca and voltage in regulating ICa in normal and diseased conditions.