Distinct localization and modulation of Cav1.2 and Cav1.3 L-type Ca2+ channels in mouse sinoatrial node.

Dysregulation of L-type Ca(2+) currents in sinoatrial nodal (SAN) cells causes cardiac arrhythmia. Both Ca(v)1.2 and Ca(v)1.3 channels mediate sinoatrial L-type currents. Whether these channels exhibit differences in modulation and localization, which could affect their contribution to pacemaking, is unknown. In this study, we characterized voltage-dependent facilitation (VDF) and subcellular localization of Ca(v)1.2 and Ca(v)1.3 channels in mouse SAN cells and determined how these properties of Ca(v)1.3 affect sinoatrial pacemaking in a mathematical model. Whole cell Ba(2+) currents were recorded from SAN cells from mice carrying a point mutation that renders Ca(v)1.2 channels relatively insensitive to dihydropyridine antagonists. The Ca(v)1.2-mediated current was isolated in the presence of nimodipine (1 ?m), which was subtracted from the total current to yield the Ca(v)1.3 component. With strong depolarizations (+80 mV), Ca(v)1.2 underwent significantly stronger inactivation than Ca(v)1.3. VDF of Ca(v)1.3 was evident during recovery from inactivation at a time when Ca(v)1.2 remained inactivated. By immunofluorescence, Ca(v)1.3 colocalized with ryanodine receptors in sarcomeric structures while Ca(v)1.2 was largely restricted to the delimiting plasma membrane. Ca(v)1.3 VDF enhanced recovery of pacemaker activity after pauses and
positively regulated pacemaking during slow heart rate in a numerical model of mouse SAN automaticity, including preferential coupling of Ca(v)1.3 to ryanodine receptor-mediated Ca(2+) release. We conclude that strong VDF and colocalization with ryanodine receptors in mouse SAN cells are unique properties that may underlie a specific role for Ca(v)1.3 in opposing abnormal slowing of heart rate.