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Role of Cav1.3 and fast inactivating BK channel coupling in pacemaking mouse chromaffin cells *

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Mouse chromaffin cells (MCCs) *in vitro* fire action potentials (APs) in a slow (1.5 Hz) irregular way. This firing pattern is sustained by a slowly rising L-type pacemaker current carried by Cav1.3 and Cav1.2 channels and is terminated by a robust Ca^{2+}-activated BK current. Using Cav1.3 KO mice we found that Cav1.3 deficiency drastically decreases the number of spontaneously firing MCCs, suggesting a critical role of Cav1.3 in MCCs spontaneous activity. This derives from the slow inactivation rate, sizeable activation at subthreshold potentials, and close coupling of Cav1.3 to fast inactivating BK channels (Marcantoni A, Vandael D, et al. 2010. J. Neuroscience 30(2): 491-504). Loss of Cav1.3 parallels the loss of fast inactivating BK currents in Cav1.3 KO MCCs and in a fraction of cells, AP firing undergoes sustained depolarization in response to Bay K 8644, indicative of weak coupling between Cav1.2 and BK channels. The same paradoxical response to Bay K 8644 occurs in BK KO MCCs indicating that deficiency of Cav1.3 may result in an expression-density reduction of functioning BK channels. Immunohistochemical staining using selective Cav1.3 α_1 and BK Slo_1 subunit antibodies (tested for their specificity on the adrenal medulla of WT and KO mice) confirm the close co-localization of the two subunits in WT tissues and the net reduction of BK Slo_1-immunofluorescent puncta in Cav1.3$^{-/-}$ MCCs. We are presently investigating the role that the fast inactivation-competent β_2 BK subunit plays in the functional coupling of Cav1.3 and non-inactivating BK channels in adrenal chromaffin cells.

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