ZnT-1, a Novel Regulator of T- type Calcium Channels Mediating a Crosstalk Between T-type and L-type Calcium Channels.

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BACKGROUND: ZnT-1 is a transmembrane protein that was studied mainly in the context of zinc metabolism. New findings mark ZnT-1 as an inhibitor of L-type Calcium Channels (LTCC) and as a potent activator of Raf-1 in the Ras-ERK signaling pathway. Recently, we demonstrated that ZnT-1 inhibits the LTCC by direct binding to the LTCC β-subunit. In addition, we found that ZnT-1 expression in the heart is modulated by electrical pacing and ischemia\reperfusion. In the present study we explore the regulatory effects of ZnT-1 on the activity of T-type Calcium Channels (TTCC), which are known to co express with the LTCC in various cells including cardiomyocytes. **METHODS AND RESULTS:** Voltage clamp recordings in *Xenopus* oocytes revealed that ZnT-1 enhances the TTCC current (167.95±9.27 % of control, n=30, $p<0.005$). Biotinylation experiments indicated that ZnT-1 increases the surface expression of the TTCC (457.94±85.8 % of control, n=3, $p<0.005$). Overexpression of inactive Raf-1 abolish the augmentation of the TTCC current by ZnT-1 (103±4.1 % of control, n=25, $p=0.37$). In addition, we found that the ZnT-1 augmentation of the TTCC is inhibited by the expression of LTCC β-subunit. Finely, co-expression of LTCC, TTCC and ZnT-1 led to preferential inhibition of the LTCC with no effect on the TTCC. **CONCLUSION**: ZnT-1 inversely regulates the activity of TTCC and LTCC. ZnT-1 induced augmentation of TTCC activity involves activation ERK-MAPK and increased TTCC surface expression. The interaction of the LTCC β-subunit with ZnT-1 leads to a crosstalk between LTCC and TTCC. These findings suggest a key role for ZnT-1 as a regulator of cardiomyocytes excitability and calcium homeostasis.