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suggesting that the PKA/cAMP pathway was involved in CFTR activation. Amiloride, an inhibitor of the Na/H exchanger, prevented the lactic-acid-induced increases in intracellular cAMP and extracellular ATP; inhibitors of the Na/Ca exchanger, SN-6 and KB-R7943, also inhibited the lactic-acid-induced accumulation of ATP in the medium surrounding the cultured myocytes.

Based on these data, we propose that depression of the pH increases the activity of the Na/H exchanger, leading to increased intracellular Na: this drives reverse-mode operation of the Na/Ca exchanger, resulting in a localized increase of Ca in a microdomain close to the membrane, which then activates adenyl cyclase, elevating the intracellular cAMP; this, in turn, activates Protein Kinase A to phosphorylate CFTR, and CFTR finally regulates the opening of the ATP release channels.

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MOLECULAR MECHANISM OF CAPACITATIVE CALCIUM ENTRY DEFICITS IN FAMILIAL ALZHEIMER'S DISEASE

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Presenilin (PS) is the catalytic subunit of the gamma-secretase which is responsible for the cleavage of amyloid precursor protein to form beta amyloid (Aβ). Mutations in PS associated with familial Alzheimer's disease (FAD) increase the Aβ plaques formation in the brain and cause neurodegeneration. Apart from this, FAD-linked PS mutations have been demonstrated to disrupt intracellular calcium (Ca^{2+}) regulation. Accumulating evidence suggests that Ca^{2+} disruption may play a proximal role in the AD pathogenesis. Mutant PS exaggerated Ca^{2+} release from the endoplasmic reticulum (ER). It also attenuated Ca^{2+} entry through the capacitative Ca^{2+} entry (CCE) pathway, yet, the mechanism is not fully understood. Using a human neuroblast cell line SH-SY5Y and Ca^{2+} imaging technique, we observed CCE deficits in FAD-linked PS1-M146L retroviral infected cell. The attenuation of CCE in PS1 mutant cells was not mediated by the down-regulation of STIM1 and Orai1 expression, the known essential molecular players in the CCE pathway. Instead, we identified a molecular interaction between PS and STIM1 proteins by immunoprecipitation. On the other hand, immunofluorescence staining showed a significant reduction in puncta formation after ER Ca^{2+} depleted by thapsigargin in cells infected with PS1-M146L as compared to the wild type PS1 infected cells. Taken together, our results suggest a molecular mechanism for the CCE deficits in FAD associated with PS1 mutations. The interaction of mutant PS1 with STIM1 exerts a negative impact on its oligomerization and/or its interaction with Orai1. Our results may suggest molecular targets for the development of therapeutic agents that help to treat the disease.

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FUNCTIONAL TRANSIENT RECEPTOR POTENTIAL CHANNELS IN HUMAN CARDIAC C-KIT$^+$ CELLS

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Background and objective: Human adult c-kit$^+$ cardiac stem cell are characterized by the expression of c-kit in the absence of lineage markers such as Nkx2.5. They are self-renewing, clonogenic, and multipotent, giving rise to a minimum of three differentiated cell types: myocytes, smooth muscle, and endothelial vascular cells. These cells, although not specifically programmed for myocardial differentiation, have been shown to improve cardiac function in a myocardial injury/reconstitution assay. However, cell biology is not understood. The present study was to investigate the expression of transient receptor potential (TRP) channels in human cardiac c-kit$^+$ cells, and their role in regulating migration and proliferation.

Methods: Whole-cell patch voltage-clamp, RT-PCR, and Western blot approaches were used to determine functional expression of TRP channels in cultured human cardiac c-kit$^+$ cells. ShRNA targeting TRP channels were constructed to silence the related TRP channels. Wound healing and transwell