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Regulation of volume-regulated outwardly rectifying anion channels by phosphatidylinositol 3,4,5-trisphosphate in mouse ventricular cells

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ABSTRACT

Volume-regulated outwardly rectifying anion channel (VRAC) plays an important role in cellvolume regulation in many types of cells. Little is known about the regulation of VRAC by phosphatidylinositides (PIs), which include phosphatidylinositol 3,4,5-trisphosphate (PIP3) and phosphatidylinositol 4,5-bisphosphate (PIP2). We examined the effect of PIs on the VRAC current activated in hypotonic solution in mouse ventricular cells. VRAC current was inhibited strongly by intracellular application of LY294002 (a phosphatidylinositol 3-kinase (PI3K) inhibitor) or anti-PIP3 antibody (PIP3-Ab), and less strongly by anti-PIP2 antibody (PIP2-Ab). LY294002 inhibited regulatory volume decrease in hypotonically swollen cells, which was in parallel with the VRAC inhibition. Intracellular PIP3 or PIP2 influenced neither the basal background current in isotonic solution nor the VRAC current in hypotonic solution. However, PIP3, but not PIP2, restored the VRAC current suppressed by LY294002 or PIP2-Ab. These results suggest that the activation of VRAC current requires the presence of intracellular PIP3, that PI3K-mediated increase in PIP3 level is sufficient to fully activate VRAC current, and that PIP3 alone without osmotic stimulation cannot induce VRAC current. We propose that VRAC in mouse ventricular cells is regulated by PIP3 and/or its down stream signaling pathways.

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