P016 Localized Na^+/H^+ Exchanger 1 Expression Protects Ca^{2+}-regulated Adenylyl Cyclases from Changes in Intracellular pH

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Ca^{2+}-sensitive adenylyl cyclases (ACs) are exclusively regulated by capacitative Ca^{2+} entry (CCE) in nonexcitable cells. The present study investigates whether this Ca^{2+}-dependent modulation of AC activity is subject to local pH changes that can arise as a consequence of cellular activity. Ca^{2+} stimulation of heterologously expressed AC8 and inhibition of endogenous AC6 exhibited clear sensitivity to modest pH changes in vitro. Acid pH (pH 7.14) reduced the Ca2+ sensitivity of both ACs, whereas alkaline pH (pH 7.85) enhanced the responsiveness of the enzymes to Ca^{2+}, compared with controls (pH 7.50). Surprisingly, in the intact cell, the response of AC8 and AC6 to CCE was largely unperturbed by similar changes in intracellular pH (pH_i), imposed using a weak acid or weak base. This “immunity” to changing pH_i is conferred by the Na^+/H^+ exchanger, NHE1, which is functionally active in these cells, and like AC8 (and AC6), resides in lipid rafts or caveolae, which may create cellular microdomains where pH_i is tightly regulated. Inhibition of NHE1 reveals the expected sensitivity to changes in pH_i. An abundance of NHE1 in these cellular subdomains may generate a privileged environment that protects the Ca^{2+}-sensitive ACs and other caveolar proteins from local acid shifts.