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DISRUPTION OF LOCAL AND GLOBAL CALCIUM SIGNALING AS A PATHOGENIC MECHANISM IN FAMILIAL HEMIPLEGIC MIGRAINE 2.

Familial hemiplegic migraine (FHM) is an autosomal dominant, classical migraine subtype associated with missense mutations in ATP1A2, encoding the $\alpha 2$ isoform of the Na, K-ATPase. Recent evidence suggests a role for the Na, K-ATPase in regulating Ca^{2+} oscillations. The spatiotemporal properties of Ca^{2+} release enables a high degree of specificity of cellular response and regulates processes as diverse as differentiation, synaptic plasticity and apoptosis. We hypothesize that perturbations in Ca^{2+} homeostasis may be a proximal signaling defect in FHM2. To this end we investigated whether FHM2 mutants disrupt Ca^{2+} signaling in stable transformant human neuroblastoma cells expressing wild-type or the T345A or R689Q mutations of the $\alpha 2$ isoform of the Na, K-ATPase. Compared to responses in controls, Ca^{2+} signals evoked by 100 μM carbachol were significantly decreased in cells expressing the mutations, and Ca^{2+} oscillations were suppressed. Local IP_3 mediated Ca^{2+} signals were evoked using UV-flash photolysis of caged IP_3 in cells loaded with EGTA so as to 'balkanize' Ca^{2+} waves into discrete localized Ca^{2+} puffs. Ca^{2+} puffs evoked by photoreleased IP_3 in T345A and R689Q cells occurred with a similar frequency, yet lower amplitude when compared with wild type cells. Here we describe how cells expressing T345A and R689Q mutations in the $\alpha 2$ subunit of the Na, K-ATPase show similar significant disruptions in Ca^{2+} homeostasis. Given that these mutations effect Na, K-ATPase enzyme kinetics and pump function in different ways we hypothesize that alterations in Ca^{2+} homeostasis may be a common pathogenic mechanism of the FHM2 mutations, and may explain the similarity of that disease to FHM1 caused by P/Q calcium channel mutations. Supported by grants NIH GM 40871 (I.P.) and NIH MH 71433 (J.J.G.)