α1-,α2-Na,K-ATPase and Kir 2.1 expression and their implications for cerebral artery function and migraine etiology in a mouse model of Familial Hemiplegic Migraine type 2

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Localized microdomain Na,K-ATPase-Kir2.1 channel interaction modulates vascular tone, blood flow and tissue perfusion; with alterations therein contributing to disease. Familial hemiplegic migraine type 2 (FHM2) results from mutations in the α2-Na,K-ATPase ATP1A2 gene, including the G301R mutation, presumably causing expressing cells to have reduced Na,K-ATPase activity. In FHM2, vasoconstrictive cerebral hypoxia underlies an aura phase, and subsequent vasodilation, a pain phase. However, the vascular signaling mechanisms of this activity are unknown. Confocal immunohistochemistry measured relative fluorescence intensity of α1- and α2-Na,K-ATPase and Kir2.1 in endothelium (EC) and smooth muscle (SM) of middle cerebral arteries (MCA) of WT and heterozygous G301R+/- mice (*n*=5, each from a different animal). Isometric myography and sharp electrode recording with pharmacological intervention characterized Na,K-ATPase and Kir2.1 function. α1-, α2-Na,K-ATPase and Kir2.1 MCA EC fluorescence was reduced by ~50% in G301R+/-, compared to WT. α1-, α2-Na,K-ATPase MCA SM fluorescence was reduced by ~20 and 50%, respectively in +/-, compared to WT; with SM Kir2.1 being the same in ± and WT. Kir2.1 mRNA was elevated ~2-fold in ± compared to WT. Endothelium-dependent relaxation to bradykinin and the response to barium was the same in ± and WT; although the barium-sensitive response to high $[K^+]$, as relaxation and hyperpolarization was elevated in ± compared to WT. MCA diameter was larger in arteries from ± compared to WT; with a larger constriction to U46619, endothelin and K^+-induced depolarization, and increased sensitization to $[Ca^{2+}]_i$. Inhibition of Na,K-ATPase-dependent Src activation with pNaKtide abolished differences between ± and WT. FHM2-related α2-Na,K-ATPase mutation leads to elevated MCA constriction and relaxation. Such changes in tone are mediated at least in part by altered and differential expression and function of EC and SM microdomain α1-/α2-Na,K-ATPase-Kir2.1 signaling complexes. Targeting the α1-/α2-Na,K-ATPase-Kir2.1 signaling complex is a logical means of treatment for FHM2.