An In-Depth Patch-Clamp Study of HCN2 Channel (Year II): Identification of Novel Biomarkers and Therapy for Ih Current Suppression in Autism Spectrum Disorders

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Ih currents in Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels play a crucial role in neuronal activity and synaptic transmission in the central nervous system. Autism spectrum disorder (ASD) is a developmental disorder that affects communication and behavior in 63,000,000 people worldwide. The purpose of this study was to investigate the effect of the Dexmedetomidine (DEX) sedative with/without cAMP and laser light stimulation with/without cAMP, Fluorescein isothiocyanate (FITC), and F002 (covalent compound of FITC+cAMP) on Ih currents in SHANK3-WT and SHANK3-Knock-out(KO) mice (model of ASD). Using whole cell patch-clamping, a pipette was inserted through cell membranes of single, live thalamus neurons of mice. Standard Krebs ACSF solution (control) contained blockers to inhibit all interfering currents, except the Ih current, which was measured. DEX caused a reduction of the Ih current in both SHANK3-WT and KO mice. Discovery of novel electrophysiological biomarkers for ASD was determined, as SHANK-KO mice had lower Ih current, lower resting membrane potential, and higher input resistance values than SHANK-WT mice. Laser pulses with F002 reduced Ih current, suggesting that photochemical generation of singlet oxygen can modulate physiologic channels. Laser with K+, cAMP, and FITC pipette compounds significantly raised the Ih current in SHANK-KO neurons. The study highlights that patients, especially with ASD, receiving sedation should be monitored closely for reduced arousal, and impaired cognition post-sedation due to suppressed Ih current. cAMP and Laser can be used as novel therapies to reverse Ih current suppression in patients undergoing sedation, and in patients with ASD.

Awards Won:
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