Abstract

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Dendritic channelopathies contribute to neocortical and sensory hyperexcitability in Fmr1(-/y) mice.

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Abstract

Hypersensitivity in response to **sensory** stimuli and **neocortical hyperexcitability** are prominent features of Fragile X Syndrome (FXS) and autism spectrum disorders, but little is known about the **dendritic** mechanisms underlying these phenomena. We found that the primary somatosensory neocortex (S1) was hyperexcited in response to tactile **sensory** stimulation in Fmr1(-/y) **mice**. This correlated with neuronal and **dendritic hyperexcitability** of S1 pyramidal neurons, which affect all major aspects of neuronal computation, from the integration of synaptic input to the generation of action potential output. Using **dendritic** electrophysiological recordings, calcium imaging, pharmacology, biochemistry and a computer model, we found that this defect was, at least in part, attributable to the reduction and dysfunction of **dendritic** h- and BKCa channels. We pharmacologically rescued several core **hyperexcitability** phenomena by targeting BKCa channels. Our results provide strong evidence pointing to the utility of BKCa channel openers for the treatment of the **sensory** hypersensitivity aspects of FXS.

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