

Overexpression of a Shaker-type potassium channel in mammalian central nervous system dysregulates native potassium channel gene expression

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ABSTRACT The nervous system maintains a delicate balance between excitation and inhibition, partly through the complex interplay between voltage-gated sodium and potassium ion channels. Because K⁺ channel blockade or gene deletion causes hyperexcitability, it is generally assumed that increases in K⁺ channel gene expression should reduce neuronal network excitability. We have tested this hypothesis by creating a transgenic mouse that expresses a Shaker-type K⁺ channel gene. Paradoxically, we find that addition of the extra K⁺ channel gene results in a hyperexcitable rather than a hypoexcitable phenotype. The presence of the transgene leads to a complex deregulation of endogenous Shaker genes in the adult central nervous system as well as an increase in network excitability that includes spontaneous cortical spike and wave discharges and a lower threshold for epileptiform bursting in isolated hippocampal slices. These data suggest that an increase in K⁺ channel gene dosage leads to dysregulation of normal K⁺ channel gene expression, and it may underlie a mechanism contributing to the pathogenesis of human aneuploidies such as Down syndrome.