Altered emotionality and neuronal excitability in mice lacking KCTD12, an auxiliary subunit of GABAB receptors associated with mood disorders

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Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain, is fundamental to brain function and implicated in the pathophysiology of several neuropsychiatric disorders. GABA activates G-protein-coupled GABAB receptors comprising principal GABAB1 and GABAB2 subunits as well as auxiliary KCTD8, 12, 12b and 16 subunits. The KCTD12 gene has been associated with bipolar disorder, major depressive disorder and schizophrenia. Here we compare Kctd12 null mutant (Kctd12(-/-)) and heterozygous (Kctd12(+/-)) with wild-type (WT) littermate mice to determine whether lack of or reduced KCTD12 expression leads to phenotypes that, extrapolating to human, could constitute endophenotypes for neuropsychiatric disorders with which KCTD12 is associated. Kctd12(-/-) mice exhibited increased fear learning but not increased memory of a discrete auditory-conditioned stimulus. Kctd12(+/-) mice showed increased activity during the inactive (light) phase of the circadian cycle relative to WT and Kctd12(-/-) mice. Electrophysiological recordings from hippocampal slices, a region of high Kctd12 expression, revealed an increased intrinsic excitability of pyramidal neurons in Kctd12(-/-) and Kctd12(+/-) mice. This is the first direct evidence for involvement of KCTD12 in determining phenotypes of emotionality, behavioral activity and neuronal excitability. This study provides empirical support for the polymorphism and expression evidence that KCTD12 confers risk for and is associated with neuropsychiatric disorders.

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