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Specific ablation of phospholipase Cγ1 in forebrain causes manic-like behavior

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It is well known that manic episodes are one of the major diagnostic symptoms in a spectrum of neuropsychiatric disorders that include schizophrenia, obsessive-compulsive disorder and bipolar disorder (BD). Despite a possible association between BD and the gene encoding phospholipase Cγ1 (PLCG1), its etiological basis remains unclear. Here, we report that mice lacking phospholipase Cγ1 (PLCγ1) in the forebrain (Plcg1f/f; CaMKII) exhibit hyperactivity, decreased anxiety-like behavior, reduced depressive-related behavior, hyperhedonia, hyperphagia, impaired learning and memory and exaggerated startle responses. Inhibitory transmission in hippocampal pyramidal neurons and striatal dopamine receptor D1-expressing neurons of Plcg1-deficient mice was significantly reduced. The decrease in inhibitory transmission is likely due to a reduced number of γ-aminobutyric acid (GABA)-ergic boutons, which may result from impaired localization and/or stabilization of postsynaptic CaMKII (Ca2+/calmodulin-dependent protein kinase II) at inhibitory synapses. Moreover, mutant mice display impaired brain-derived neurotrophic factor-tropomyosin receptor kinase B-dependent synaptic plasticity in the hippocampus, which could account for deficits of spatial memory. Lithium and valproate, the drugs presently used to treat mania associated with BD, rescued the hyperactive phenotypes of Plcg1f/f; CaMKII mice. These findings provide evidence that PLCγ1 is critical for synaptic function and plasticity and that the loss of PLCγ1 from the forebrain results in manic-like behavior.

Keywords
Forebrain, Bipolar Disorders, Phospholipase Cγ1, Signalling