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Dysfunction in a Genetic Mouse Model of Mania

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Editorial Note

Polymorphisms in circadian genes such as CLOCK convey risk for bipolar disorder. While studies have begun to elucidate the molecular mechanism whereby disruption of Clock alters cellular function within mesolimbic brain regions, little remains known about how these changes alter gross neural circuit function and generate mania-like behaviors in Clock-Δ19 mice. Here we show that the phasic entrainment of Nucleus Accumbens (NAC) low-gamma (30-55 Hz) oscillations to delta (1-4 Hz) oscillations is negatively correlated with the extent to which Wild-Type (WT) mice explore a novel environment. Clock-Δ19 mice, which display hyperactivity in the novel environment, exhibit profound deficits in low-gamma and NAC single-neuron phase coupling. We also demonstrate that NAC neurons in Clock-Δ19 mice display complex changes in dendritic morphology and reduced GluR1 expression compared to those observed in WT littermates. Chronic lithium treatment ameliorated several of these neurophysiological deficits and suppressed exploratory drive in the mutants. These results demonstrate that disruptions of Clock gene function are sufficient to promote alterations in NAC microcircuits, and raise the hypothesis that dysfunctional NAC phase signaling may contribute to the mania-like behavioral manifestations that result from diminished circadian gene function. Bipolar disorder (BPD) is a debilitating heritable psychiatric disorder. Contemporary rodent models for the manic pole of BPD have primarily utilized either single locus transgenics or treatment with psychostimulants. Our lab recently characterized a mouse strain termed Madison (MSN) that naturally displays a manic phenotype, exhibiting elevated locomotor activity, increased sexual behavior, and higher forced swimming relative to control strains. Lithium chloride and olanzapine treatments attenuate this phenotype. In this study, we replicated our locomotor activity experiment, showing that MSN mice display generationally-stable mania relative to their outbred ancestral strain, hsd:ICR (ICR).

Pathogenesis of Bipolar Disorder

The pathogenesis of Bipolar Disorder (BD) has remained enigmatic, largely because genetic animal models based on identified susceptible genes have often failed to show core symptoms of spontaneous mood cycling. However, pedigree and Induced Pluripotent Stem Cell (Ipsc)-based analyses have implicated that dysfunction in some key signaling cascades might be crucial for the disease pathogenesis in a subpopulation of BD patients. We hypothesized that the behavioral abnormalities of patients and the comorbid metabolic abnormalities might share some identical molecular mechanism. Hence, we investigated the expression of insulin/synapse dually functioning genes in neurons derived from the iPSCs of BD patients and the behavioral phenotype of mice with these genes silenced in the hippocampus. By these means, we identified synaptotagmin-7 (Syt7) as a candidate risk factor for behavioral abnormalities. We then investigated Syt7 knockout (KO) mice and observed nocturnal manic-like and diurnal depressive-like behavioral fluctuations in a majority of these animals, analogous to the mood cycling symptoms of BD. We treated the Syt7 KO mice with clinical BD drugs including olanzapine and lithium, and found that the drug treatments could efficiently regulate the behavioral abnormalities of the Syt7 KO mice. To further verify whether Syt7 deficits existed in BD patients, we investigated the plasma samples of 20 BD patients and found that the Syt7 mRNA level was significantly attenuated in the patient plasma compared to the healthy controls. We therefore concluded that Syt7 is likely a key factor for the bipolar-like behavioral abnormalities.

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