Probing the lithium-response pathway in hiPSCs implicates the phosphoregulatory set-point for a cytoskeletal modulator in bipolar pathogenesis.

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Public Summary:
The molecular pathogenesis of bipolar disorder (BPD) is poorly understood. Using human-induced pluripotent stem cells (hiPSCs) to unravel such mechanisms in polygenic diseases is generally challenging. However, hiPSCs from BPD patients responsive to lithium offered unique opportunities to discern lithium's target and hence gain molecular insight into BPD. By profiling the proteomics of BDP-hiPSC-derived neurons, we found that lithium alters the phosphorylation state of collapsin response mediator protein-2 (CRMP2). Active nonphosphorylated CRMP2, which binds cytoskeleton, is present throughout the neuron; inactive phosphorylated CRMP2, which dissociates from cytoskeleton, exits dendritic spines. CRMP2 elimination yields aberrant dendritogenesis with diminished spine density and lost lithium responsiveness (LiR). The "set-point" for the ratio of pCRMP2:CRMP2 is elevated uniquely in hiPSC-derived neurons from LiR BPD patients, but not with other psychiatric (including lithium-nonresponsive BPD) and neurological disorders. Lithium (and other pathway modulators) lowers pCRMP2, increasing spine area and density. Human BPD brains show similarly elevated ratios and diminished spine densities; lithium therapy normalizes the ratios and spines. Consistent with such "spine-opathies," human LiR BPD neurons with abnormal ratios evince abnormally steep slopes for calcium flux; lithium normalizes both. Behaviorally, transgenic mice that reproduce lithium's postulated site-of-action in dephosphorylating CRMP2 emulate LiR in BPD. These data suggest that the "lithium response pathway" in BPD governs CRMP2's phosphorylation, which regulates cytoskeletal organization, particularly in spines, modulating neural networks. Aberrations in the posttranslational regulation of this developmentally critical molecule may underlie LiR BPD pathogenesis. Instructively, examining the proteomic profile in hiPSCs of a functional agent-even one whose mechanism-of-action is unknown-might reveal otherwise inscrutable intracellular pathogenic pathways.

Scientific Abstract:
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