Investigating the pathogenesis of bipolar disorder using patient iPSC-derived brain and islet-like organoid models

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Bipolar disorder (BD) is considered a polygenic and complex disease. However, pedigree analyses have indicated a strong heritability of BD, raising questions about how these polygenic variants are stably inherited across generations. Notably, approximately 40% of BD patients also present with metabolic comorbidities related to insulin and glucose regulation. We hypothesized that the behavioral symptoms of BD and these comorbidities may share underlying molecular mechanisms, which could explain the high heritability of BD. Using iPSC-derived neurons and organoids from sporadic BD patients, as well as mouse models, we screened for genes with dual roles in insulin regulation and synaptic function. We found that deficits in the molecular pathway involving Synaptotagmin-7 (Syt7) recapitulate bipolar-like behavioral fluctuations in mice. Syt7 deficiency led to GluN2B-NMDAR dysfunction in the brain, resulting in mania-like behaviors during the dark phase, and impaired insulin secretion in pancreatic islets, leading to depression-like behaviors during the light phase. Pancreatic and neural activities exhibited opposing diurnal rhythms, with Syt7 deficiency causing a periodic antagonistic shift between the two systems, thereby producing behavioral fluctuations. Together, our study provides insight into how metabolic and circadian factors interact with the brain to generate behavioral fluctuations in patients with mental disorders.