The Faculty of Biotechnology and Food Engineering

Seminar

Dr. Shani Stern

Using computational models with human derived neurons for the investigation of cellular, functional, and molecular mechanisms of lithium response in bipolar disorder

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Abstract

Bipolar disorder (BD) affects 1-2% of the worldwide population and is a leading cause of disability and suicide. The complex and heterogeneous genetic background of the patients makes human neurons derived from induced pluripotent stem cells (iPSCs) an attractive model since animal models do not fully reproduce the complex human genetics and behavior. Using functional and molecular assays, we have shown that human hippocampal neurons derived from BD patients are hyperexcitable with large after-hyperpolarizations. Training machine learning algorithms on electrophysiological features that were recorded from the derived neurons enabled an accurate prediction of the patients' response to lithium 1. The hippocampal neurons that we derived from lithium non-responsive BD patients exhibited a physiological instability, causing them to easily shift their excitability state. The neurons alternated between hypoexcitable and hyperexcitable states forming a network that resided in a multi-excitatory state, suggesting a mechanism that prompts mood episodes 2. A computational model that we developed of BD neurons recapitulated the hyperexcitability and physiological instability phenotypes with similar changes to the conductance of the ion channels that we have measured 3. RNA sequencing analysis revealed that the Wnt/beta-catenin signaling pathway is severely impaired in the neurons derived from the patients that do not respond to lithium. Furthermore, the severe down regulation of the LEF1 gene was associated with the hyperexcitability of the neurons and this hyperexcitability was rescued using LEF1 shRNAs 4. Overall, our studies have identified cellular, functional, and transcriptional deficits in neurons derived from BD patients and mechanisms for lithium response.

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