ACHIEVEMENTS

Novel Pathogenic Mechanisms of Epilepsy Revealed

Epilepsy is a common brain disorder. However, its pathogenic mechanisms have been a mystery. Mutations and deletions of *RBFOX3* were noted in persons with epilepsy but the mechanism of seizure mediation by RBFOX3 remained unknown. Now, in a recent article, Dr. Hsien-Sung Huang and his team at the Graduate Institute of Brain and Mind Sciences have revealed important clues for understanding the pathogenesis of *RBFOX3*-linked epilepsy (*PNAS*, August 11, 2022).

Seeking to identify the underlying mechanisms that drive *RBFOX3*-linked epilepsy, De-Fong Huang, NTU MS, led a series of experiments in Huang's lab that produced three main findings. First, RBFOX3 mediates the expression of VAMP1, an inhibitory neuron-specific protein that weakens the inhibitory strength of inhibitory neurons and increases the excitability of excitatory neurons. Hence, imbalances of excitation and inhibition contribute to seizure activities. Second, given the heterogeneity of inhibitory neurons in the brain, it is crucial to clarify which subtype of inhibitory neurons plays the key role in RBFOX3-linked epilepsy. By using cell-type-specific conditional knockout mice and other behavioral, electrophysiologic, cellular, and molecular approaches, neuropeptide Y (NPY)-expressing inhibitory neurons were found to be the key player. Third, notably, an FDA-approved drug, bumetanide, can recover seizure phenotypes due to *Rbfox3* deletion. Owing to the importance of these findings, the study was featured by *PNAS* Showcase.

Huang's research team is now studying the roles of NPY-expressing inhibitory neurons in the pathogenesis of epilepsy. Hopefully, they will reveal further insights into this disorder that will lead to new therapeutic strategies.

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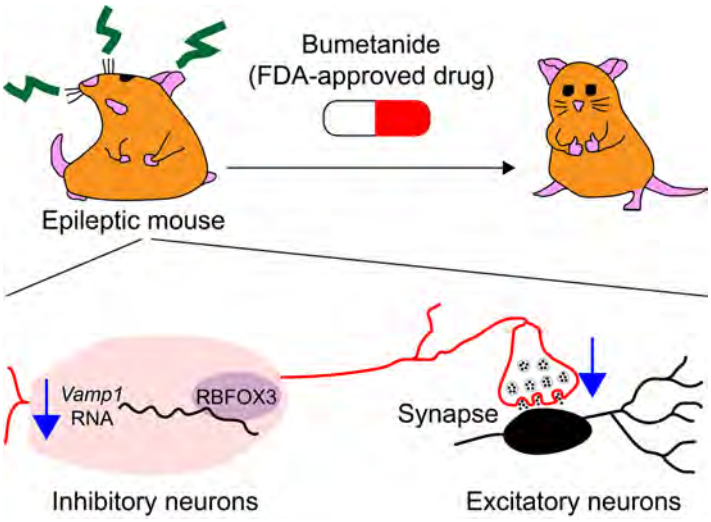

Bumetanide rescues seizure phenotypes from *Rbfox3* knockout mice. Mechanistically speaking, RBFOX3 mediates seizures via regulating *Vamp1* expression in inhibitory neurons, excitability of excitatory neurons and inhibitory synaptic transmission.

Click or Scan the QR code to read the journal article in *PNAS*.

Click or Scan the QR code to visit Dr. Hsien-Sung Huang's lab webpage.

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