New insights into epilepsy drug Retigabine

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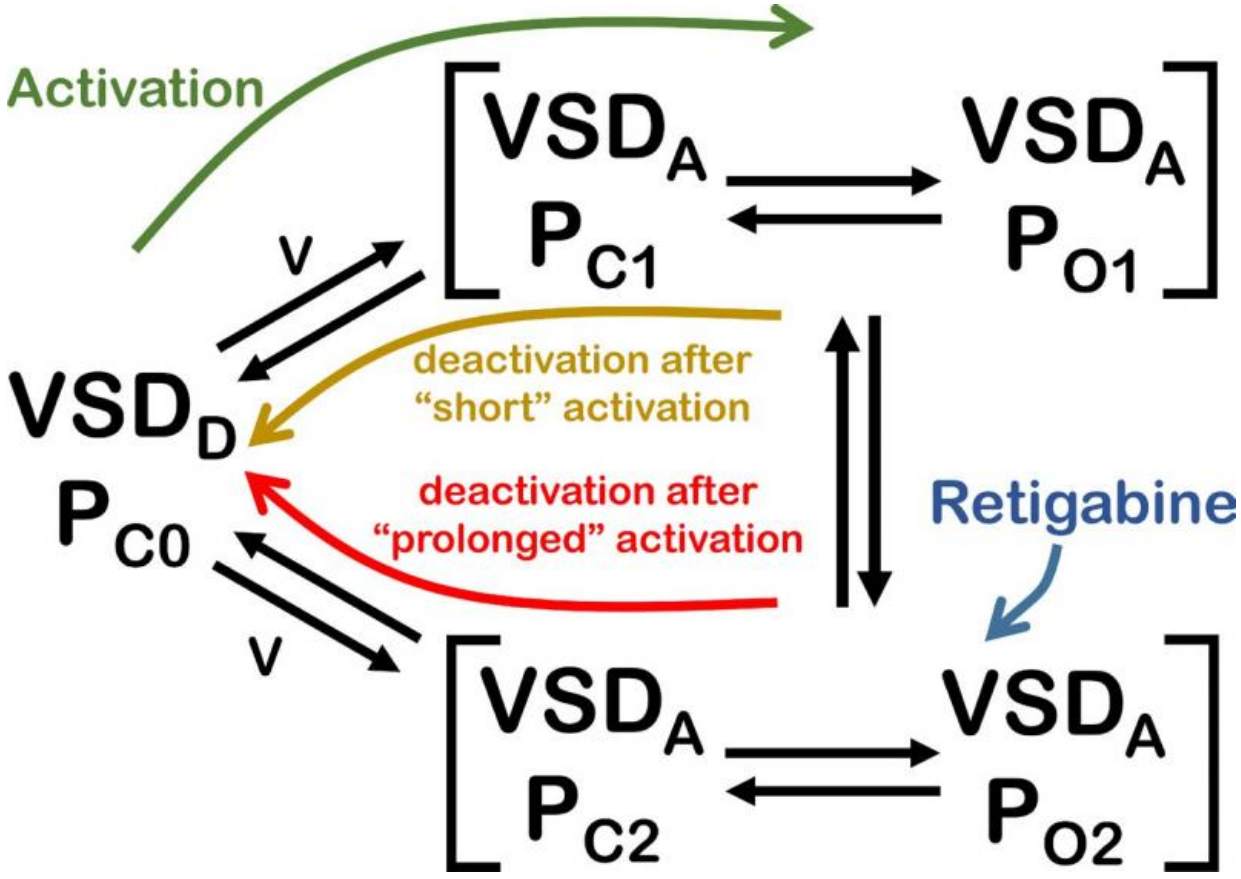

The proposed kinetic scheme for the activity of $K_V7.2/K_V7.3$ and the effect of Retigabine. The scheme contains five global states, which are different with respect to each other depending on the activation status of the VSD and the pore domain (P). In the scheme, VSD represents the four voltage sensors of the channel. Credit: © 2016 Corbin-Leftwich et al., 2016

A study published ahead of print in the *The Journal of General Physiology* has revealed new insights into Retigabine, a known pharmacological treatment for epilepsy.

Epilepsy is a family of encephalopathies characterized by abnormal synchronous and rhythmic neuronal activity in the brain that results in seizures. It is one of the most common disorders of the brain and has been diagnosed in 5.1 million people in the United States, according to the Centers for Disease Control and Prevention.

The heteromeric neuronal $K_V7.2/K_V7.3$ channel is the assembly of K_V7 subunits most commonly found in the central nervous system. Mutations that detrimentally affect the function of neuronal K_V7 channels cause hyperexcitability syndromes such as benign familial neonatal seizures, early onset epileptic encephalopathy, and peripheral nerve hyperexcitability. Pharmacotherapeutic approaches using drugs such as Retigabine have therefore been implemented to boost the activity of K_V7 channels.

However, detailed understanding of the molecular basis for the role of neuronal K_V7 channels in hyperexcitability syndromes has been lacking.

In their study using Xenopus laevis oocytes, Aaron Corbin-Leftwich, an undergraduate student at Virginia Commonwealth University, School of Medicine in Richmond, VA, under Carlos A. Villalba-Galea, PhD, assistant professor in the Department of Physiology and Biophysics, and colleagues found that Retigabine reduces excitability by enhancing the resting potential open state stability of $K_V7.2/K_V7.3$ channels. The stabilization of the channels that are already opened at neuronal resting potential levels is the clinically relevant effect of the anticonvulsant.

"Retigabine binds to K_V7 proteins, causing them to stay open for longer. This allows for a larger flow of potassium ions that are leaving the

neuron," the authors note. "This increases the magnitude of the stimulation required to excite neurons, decreasing the chance of spontaneous activity, and reducing unwanted electrical signals."

These findings may help in further refinement of the available pharmacotherapy for K_V7-related encephalopathies, as well as for the design of new ones.

More information: Aaron Corbin-Leftwich et al. Retigabine holds K 7 channels open and stabilizes the resting potential , *The Journal of General Physiology* (2016). DOI: 10.1085/jgp.201511517

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