"Regulation of neuronal potassium channels by anti-epileptic drugs and unexpected accessory proteins"

Assoc Prof Harley Kurata
Department of Pharmacology, University of Alberta, Calgary, Canada

Ion channel proteins have evolved to generate electrical signals in response to diverse chemical, physical, or electrical stimuli. These rapid signals underlie our thoughts, movements, and moment-to-moment responses to the environment. It is well understood that disruption of ion channel function in the central nervous system causes a variety of neurological disorders, such as seizures, ataxias, and developmental delay. We are investigating the regulation of neuronal potassium channels with two distinct research themes. Firstly, from an applied pharmacology perspective, we have identified diverse mechanisms of action of a family of compounds that strongly activate neuronal potassium channels called M-channels (Kv7 family; Kim et al., PNAS, 2017; Kim et al., Nat Comm, 2015). These drugs are in development in a variety of settings for treatment of epilepsy, pain, tinnitus, and other diseases. The second research theme is the identification of accessory proteins that modulate ion channels. Although the identity of most ion channel types is known, they are often studied in isolation, and the effects of disease-linked mutations are not understood in the context of physiological protein complexes. With this general knowledge gap in mind, we have identified multiple previously unrecognized regulatory proteins with powerful effects on channel gating and expression of Kv1.1 and Kv1.2 potassium channels. Variable assembly with these accessory proteins endows Kv channels with behaviors that are not intrinsic to the channel-forming subunits, and often alters the functional outcome of epilepsy-linked mutations in Kv1.2 (Baronas et al., Nat Comm, 2018). These findings suggest an expanded view of the molecular diversity of neuronal potassium channels, with important implications for understanding genetic underpinnings of neurological diseases.