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Voltage-Gated Calcium channels in Health and Disease

Voltage-gated Ca2+ channels (VGCC) are cellular membrane proteins critical for nerve, heart, and muscle function. VGCC opening directly triggers neurotransmitter release and muscle contraction, and can initiate slower processes such as cell migration, differentiation, or cell death. Not surprisingly, mutations in VGCC are directly implicated in epilepsy, migraine, Alzheimer's disease, blindness, pain, schizophrenia, atrial fibrillation, and several other neurological and cardiovascular channelopathies. The immediate effect of some mutations is to either slow or speed channel inactivation (a desensitization-like process) compared to Wild Type (WT) channels. My previously funded work (NIH grant 1R15GM124013-01), showed that RGK proteins (Rad, Rem, Gem/Kir), can further exacerbate the effect of these mutations. Namely, RGK proteins, which only moderately inhibit VGCC, completely blocked a fast-inactivating mutant VGCC associated with epilepsy, while sparing mutant slow- inactivating channels associated with autism and cardiac disease. This differential effect on WT and mutant channels may contribute to VGCC diseases and disorders. Here, we propose investigating a trilateral crosstalk between VGCC, RGKs, and clinically used drugs, such as diltiazem, that control calcium channel inactivation. These studies will be of great interest for cardiac and nerve physiology and pathophysiology. At the same time, we will be deeply engaging undergraduates in scientific research.