Design and applications of genetically-encoded ion channel modulators

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Ca2+ influx through high-voltage-activated calcium (CaV1/CaV2) channels transduces electrical signals into biological responses in all excitable cells. CaV1/CaV2 channel dysfunction underlies many serious disorders including autism, migraines, pain, ataxias, neurodegenerative diseases, and cardiac arrhythmias. In the nervous system, selective CaV1/CaV2 channel blockers are highly sought after as potential therapeutics for stroke, neuropathic pain, psychiatric disorders, and Parkinson's disease. Conventional CaV1/CaV2 channel blockers are small organic molecules or toxins that interact with extracellular portions of pore-forming $\alpha 1$ subunits and either obstruct the channel pore or modulate gating. Therapeutic use of traditional small molecule CaV1/CaV2 channel blockers is limited by their lack of tissue specificity, and their inability to discriminate among CaV1/CaV2 channels either on the basis of the identity of their associated proteins or their sub-cellular localization. I will discuss our progress in developing genetically-encoded selective blockers to address this gap in CaV1/CaV2 channel regulation.