## Voltage-Gated Calcium Channels: From Molecular Cloning to Novel Therapeutics for Human Disease

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The research focuses on the diverse roles that voltage-gated calcium (Ca) channels play in mediating events such as oscillatory firing patterns, gene expression, neurotransmitter release and neuromodulation. In addition to their normal physiological functions, Ca channels are also implicated in a number of human disorders including: congenital migraine, chronic pain, epilepsy, hypertension, ischemia, and some arrhythmias.

Ca channel physiology and pharmacology: T-type Ca channels are of considerable interest since they are responsible for rebound burst firing in central neurons and are implicated in normal brain functions such as slow wave sleep and in several diseased states. We have completed the molecular cloning and functional characterization of the family of T-type channels from rat and human brain. Our latest results concerning the contributions of T-type channels to both pain sensation/transmission and epilepsy will be discussed. We have also cloned and expressed the a1F (Cav1.4) Ca channel previously thought to be exclusively expressed in the retina. Functional expression of the Cav1.4 channel reveals that it encodes a high threshold L-type Ca channel that preferentially conducts Ba over Ca, but unlike other high voltage activated Ca channels. discernable Ca-dependent inactivation. shows no Our immunohistochemical studies reveal that in contrast with previous reports, Cav1.4 expression is not confined to the retina.

Calcium-dependent gene regulation in the CNS: Spatial and temporal changes in intracellular Ca levels play a critical role in controlling neuronal gene transcription and a novel Ca channel-dependent signaling pathway in mammalian brain will be discussed. We have found that influx selectively through a1A (P/Q-type) Ca channels activates transcription of syntaxin-1A, a presynaptic protein central in mediating neurotransmitter release. Initiation of syntaxin expression is transient with syntaxin ultimately interacting with the P/Q-type Ca channel to decrease channel availability. The results define a novel activity-dependent feedback pathway that we hypothesize modulates synaptic efficacy.

C. elegans as a genetic model for ion channel function: In addition to studies examining exogenously expressed Ca channels, there is a need to define the physiological roles of Ca channels using genetic model systems. The correlation of mutant phenotypes with defined alterations that affect physiological properties will identify important structural components not predicted using standard in vitro mutagenesis approaches. We have utilized molecular cloning and genetic analyses to characterize Ca channel homologues in C. elegans. Genetic mutations and phenotypic analyses of the ancestoral a1 subunits (unc-2, egl-19 and cca-1) as well as putative b (ccb-1 and ccb-2) and a2d (unc-36 and T24F1.6) subunits will be discussed