Abstract

This thesis provides a comprehensive exploration of Voltage-gated Calcium Channels (VGCCs), with a particular focus on T-type channels and their role in cellular physiology. It delves into the crucial function of VGCCs in controlling calcium ion influx during membrane depolarization, highlighting their importance in neurons. VGCCs are classified into two different subtypes, including T-type (low voltage activated) and high voltage activated channels (N-, L-, R-, P/Q-type), each with distinct functions and roles. One focus of this thesis was on the regulation of T-type channel expression, examining the impact of post-translational modifications and trafficking proteins, notably non-canonical N-glycosylation sites and SCAMP2, on channel trafficking and surface expression. In the context of neurological disorders, the research links T-type channels to conditions such as ALS, DEE, PDN, and TN, investigating the functional effects of *CACNA1H* gene variants, including ALS-associated loss-of-function and TN-associated gain-of-function variants in $Ca_v3.2$ channels. The final part of the thesis is dedicated to the development of new drugs targeting T-type channels, with a spotlight on S13, a novel quinolone-based VGCC blocker, demonstrating its efficacy in preclinical models of neuropathic pain. Overall, the thesis provides a detailed understanding of T-type channels, their regulatory mechanisms, involvement in diseases, and potential as therapeutic targets, underscoring their importance in various physiological systems and roles in neurological disorders.

Keywords: Ion channel, Calcium channel, T-type channel, Glycosylation, SCAMP2, Trafficking, Diabetes, Amyotrophic lateral sclerosis, Epilepsy, Encephalopathy, Trigeminal neuralgia, Pain, Mutation, Channelopathy, Quinoline, Neurons, Biophysics