

Abstract

The TRPA1 channel is a universal, nociception-mediating cellular sensor activated by various environmental irritants, potentially harmful physical modalities and endogenous mediators of pathophysiological processes. The polymodality of TRPA1 channel allows the activation stimuli to further enhance or suppress each other's effect. While this modulation effect has its physiological importance in promoting the protective cellular and behavioral mechanisms, it may result into the unpleasant pain-related effects accompanying the chronic pain caused by aberrant TRPA1 channel activity. In order to effectively and selectively target the synergic properties of TRPA1 modulators, while preserving the sensitivity to the environmental threads, the knowledge of the mechanisms of polymodal regulation at the molecular level are required.

This doctoral thesis aims at the elucidation of three main mechanisms of TRPA1 regulation: 1) the regulation *via* intracellular signaling cascades and phosphorylation, 2) the interaction with membrane phospholipids and 3) the temperature-driven gating. The results presented in the thesis show that the effects of the inflammatory mediator bradykinin are decreased by the low-frequency high-induction electromagnetic field used in magnetotherapy. We have identified a residue S602 that may be involved in the phosphorylation-induced inhibition of TRPA1 channel. Furthermore, we have identified two putative binding sites for membrane phospholipids that, in a state-dependent manner, regulate the TRPA1 activation by voltage, agonists, calcium and temperature. Lastly, we demonstrated the bidirectional temperature activation of human and mouse TRPA1 orthologues and unveiled their specific mode of 'heat-induced cold activation'. Overall, our results provide valuable evidences of the regulatory domains, which have a pharmacological potential of targeting TRPA1 as a therapeutic strategy for treating chronic pain.