ABSTRACT

Ankyrin receptor TRPA1 is an ion channel widely expressed on primary afferent sensory neurons, where it acts as a polymodal sensor of nociceptive stimuli. Apart from pungent chemicals (e. g. isothiocyanates, cinnamaldehyde and its derivatives, acrolein, menthol), it could be activated by cold temperatures, depolarizing voltages or intracellular calcium ions.

TRPA1 channel is a homotetramer in which each subunit consists of cytoplasmic N and C termini and a transmembrane region. The transmembrane part is organized into six alpha-helices connected by intra- and extracellular loops. The N terminus comprises a tandem set of 16 to 17 ankyrin repeats (AR), while the C terminus has a substantially shorter, dominantly helical structure. In 2015, a partial cryo-EM structure of TRPA1 was resolved; however, the functional roles of the individual regions of the receptor have not yet been fully understood.

This doctoral thesis is concerned to elucidate the role of highly conserved sequence and structural motifs within the cytoplasmic termini and the S4-S5 region of TRPA1 in voltage- and chemical sensitivity of the receptor. The probable binding site for calcium ions that are the most important physiological modulators of TRPA1 was described by using homology modeling, molecular-dynamics simulations, site-directed mutagenesis and electrophysiological techniques. Next, the molecular mechanism of a heritable disorder called “familial episodic pain syndrome”, which is caused by a point mutation within the S4-S5 region, has been proposed. The latest study was focused on the functional role of T/SPLH motifs within the N-terminal ankyrin repeats AR2, AR6 and AR11-13 in the TRPA1 modulation.

Key words: Ankyrin receptor (TRPA), C terminus, N terminus, S4-S5 region, structure-function relationship, calcium ions, voltage-dependent gating, point mutation.