Abstract

Human body detects potentially damaging stimuli by specialized sensory nerve endings in the skin, the nociceptors. Their membranes are equipped with ion channels, molecular sensors, coding the outside stimuli into the trains of action potentials and conducting them to the higher brain centers. The most prominent group of transduction ion channels is the transient receptor potential (TRP) channel family followed by ion channels responsible for generation and conduction of action potentials from the periphery to the brain, the voltage-gated sodium channels (VGSCs). Understanding the mechanisms how particular stimulus is encoded and processed is of particular importance to find therapeutics for various types of pain conditions.

We characterized the properties of VGSC subtypes $Na_V1.9$ and $Na_V1.8$ at high temperatures. We showed that $Na_V1.9$ undergo large increase in current with increasing temperatures and significantly contribute to the action potential generation in dorsal root ganglion (DRG) neurons.

Ciguatoxins (CTXs) are sodium channels activator toxins causing ciguatera fish poisoning, a disease manifested by sensory and neurological disturbances. We elucidated the mechanism of CTX-induced cold allodynia, a pathological phenomenon where normally innocuous cool temperatures are perceived as pain. We showed that CTX actions manifest in TRPA1-expressing peptidergic C-fibers and also A-fibers in a TRPA1-independent way. The most potent ciguatoxin subtype, P-CTX-1 (Pacific-Ciguatoxin Subtype-1), did not directly activate TRPA1, but this channel was stimulated through an indirect mechanism. CTXs are also effective in releasing calcitonin-gene related peptide (CGRP) from nerve terminals. We showed that P-CTX-1 induces CGRP release from the mouse skin mainly through $Na_V1.9$, and the combined activation of $Na_V1.7$ and $Na_V1.1$.

Next, we investigated the actions of crotalphine, a 14-amino acid analgesic peptide from the venom of rattlesnake *Crotalus durissus terrificus*, on peripheral nervous system. We found that crotalphine selectively activates and subsequently desensitizes TRPA1, thus exerting the analgesic effects.

In the next part, we focused on determining the mechanism of action of well-known topical remedy for pain, the camphor, on nociceptors and elucidating the molecular action of camphor on TRPV1 specifically.

In the last part, we introduced an improved thermal gradient behavioral assay for testing the temperature preference of mice in an unbiased circular running track. It allowed discerning exploratory behavior from thermal selection behavior. This setup shed light on different temperature preference of TRPA1-/-, TRPM8-/- and TRPM8/A1/-/- mice.