

2. SUMMARY

The vanilloid receptor (also called 'capsaicin receptor') is a nonselective cation channel that is predominantly expressed by nociceptive primary sensory neurons. This receptor was termed vanilloid receptor subtype 1 (TRPV1) because it became the founding member of the vanilloid receptor subfamily of transient receptor potential (TRP) channels, a large superfamily of nonselective cation channels that play important roles in many sensory functions. The TRPV1 channel can be activated by pungent vanilloid compounds like capsaicin or resiniferatoxin, acid (pH < 6.5), noxious heat (>43 °C), phorbol esters, endogenous arachidonic acid derivatives, or depolarizing voltages. Upon activation by capsaicin, TRPV1 can regulate cellular calcium levels via direct permeation ($P_{Ca}/P_{Na} \sim 10$), which concomitantly downregulates its own activity and activates different G-protein- and phospholipase C-coupled signaling cascades. Understanding these underlying mechanisms is one of the key strategies that offer a way to alleviate neuropathic and inflammatory pain.

Although the molecular identification of the TRPV1 channels has greatly facilitated understanding the mechanisms of thermal hyperalgesia associated with inflammation and those by which vanilloids increase and subsequently modulate nociceptor activity, there is still no general consensus about the *in vivo* role of TRPV1 in pain sensation.

This dissertation aims to investigate three interrelated aspects of the TRPV1 channel function: 1) The general characterization of the calcium dependent acute desensitization of TRPV1 with a specific focus on a potential role of the phosphorylation sites for calmodulin kinase II. 2) To explore the sensitivity of TRPV1 to various reducing and oxidizing substances and identify a possible mechanism of modulation at the molecular level. 3) To characterize the mechanism(s) underlying the modulation of TRPV1 by gadolinium with the aim to understand and explain our experimental findings of the multiple distinct effects on this channel.

The results of this dissertation reveal a new functional role of the two calmodulin-kinase II phosphorylation sites in the calcium-dependent desensitization of TRPV1, identify the new mechanisms involved in the redox- and gadolinium-mediated modulation of TRPV1. These results may serve as a useful model for understanding and targeting the function of nociceptive neurons and will eventually allow us to understand the physiological roles these processes may play in thermal and inflammatory pain.