Abstract

Modulation of nociceptive synaptic transmission in the spinal cord dorsal horn plays a key role in the development and maintenance of pathological pain states and chronic pain diseases. Important role in this process play Transient receptor potential Vanilloid 1 receptors (TRPV1), present on presynaptic endings of primary afferents in the superficial spinal cord dorsal horn. Changes in TRPV1 activity have significant impact on nociceptive transmission. There are number of processes that influence the function of spinal TRPV1 receptors. This work is focused on the role of protease-activated receptors type 2 (PAR2), C-C motif chemokine ligand 2 (CCL2) and the effect of chemotherapeutic drug paclitaxel in modulation of synaptic nociceptive transmission and activation of TRPV1 receptors.

PAR2 receptors belong to a family of four G-protein-coupled receptors activated by proteases. The role of PAR2 receptors in pain perception is closely related to their presence in a population of dorsal root ganglion neurons, where they are also co-expressed with TRPV1. Activation of PAR2 may lead to peripheral and central sensitization. Chemokine CCL2 and its main receptor CCR2 were suggested to be an important factor in the development of neuropathic pain after peripheral nerve injury. In our study we focused on the effect of CCL2 application on TRPV1 receptor activation and nociceptive signalling. Paclitaxel is an antitumor drug which clinical use is limited by the appearance of neuropathic pain conditions. The aim of our study was to investigate paclitaxel effect on presynaptic TRPV1 receptors in the spinal cord dorsal horn.

Experiments in this thesis were preferentially aimed to study the role of PAR2 receptors in nociceptive processing and modulation of synaptic transmission, using behavioural and electrophysiological techniques. We showed that intrathecal application of PAR2 activating peptide SLIGKV-NH2 caused hyperalgesia in naïve animals that was prevented by pre-treatment with TRPV1 antagonist SB 366791 and protein kinases inhibitor Staurosporine. Patch-clamp recordings of post synaptic excitatory currents from superficial dorsal horn neurons in acute spinal cord slices was used to demonstrate that activation of PAR2 receptors by SLIGKV NH2 caused a decrease in the frequency of mEPSC, but increased the frequency of sEPSC and also increased the amplitude of dorsal root stimulation evoked EPSC. These effects were also significantly attenuated by application of SB 366791 and staurosporine. Our results suggest that presynaptic PAR2 receptors may play an important role in the modulation of nociceptive synaptic transmission in the spinal cord dorsal horn.

Results of another study demonstrated that changes induced by CCL2 application were largely mediated through activation of TRPV1 receptors, suggesting importance of PAR2 receptors in pain modulation. Paclitaxel application induced increased frequency of mEPSC currents that was prevented by TRPV1 receptors antagonist, implying their contribution to paclitaxel-induced acute and chronic neuropathic pain.

Our results demonstrate an important role of spinal TRPV1 receptors in modulation of nociceptive transmission in the spinal cord dorsal horn. We have shown that activation of PAR2, application of CCL2 and paclitaxel induced changes which lead to modulation of synaptic transmission mediated primarily by TRPV1 receptors. This further confirms the fundamental role of TRPV1 receptors in pain modulation at spinal cord level and supports their importance in pathological pain states.