Abstract

Pain is a common symptom of many clinical syndromes and diseases. In particular, the treatment of neuropathic pain represents a serious public health issue because currently available analgesia is ineffective in many cases or it has adverse effects. Treatment of pain-related suffering requires knowledge of how pain signals are initially generated and subsequently transmitted by the nervous system. A nociceptive system plays a key role in this process of encoding and transmission of pain signals. Modulation of the nociceptive synaptic transmission in the spinal cord dorsal horn represents an important mechanism in the development and maintenance of different pathological pain states.

This doctoral thesis has aimed to investigate and clarify some of the mechanisms involved in the modulation of the spinal nociceptive processing in different pain states. The main attention was paid to study the following issues: (I.) Which is the role of Transient Receptor Potential Vanilloid type 1 channels (TRPV1), Toll-Like Receptors 4 (TLR4), and phosphatidylinositol 3-kinase (PI3K) in the development of neuropathic pain induced by paclitaxel (PAC) chemotherapy in acute *in vitro*, and subchronic *in vivo* murine model of PAC-induced peripheral neuropathy (PIPN)? (II.) How is affected spinal inhibitory synaptic control under different pain states, using VGAT-ChR2-eYFP transgenic mice model of PIPN, acute peripheral inflammation, and chronic constriction injury injury (CCI) of the sciatic nerve? (III.) How does the $Na_v1.7$ receptor blocker protoxin II affect the spinal nociceptive signaling in the model of burn injury? (IV.) How 20:4-NAPE (*N*-arachidonoylphosphatidylethanolamine), the precursor of anandamide (AEA), modulates the nociceptive synaptic transmission under the acute inflammatory condition and which role plays cannabinoid receptor 1 (CB_1) in this process?

To investigate these aims, the main method used was the whole-cell patch-clamp recording of excitatory- and/or inhibitory postsynaptic currents (EPSCs, respectively IPSCs). We also used behavioral measurement of mechanical/thermal sensitivity and immunohistochemistry.

Our results have shown that: (I.) Direct functional interaction between TLR4 and TRPV1 receptors, in particular via PI3K signaling, play an important role in (*a*) PAC-induced increase of miniature EPSCs frequency in dorsal horn neurons, (*b*) in the modulation of TRPV1 sensitivity and tachyphylaxis of capsaicin-evoked responses, and (*c*) in the PAC-induced mechanical allodynia. All these PAC-induced changes have been prevented by PI3K blocker wortmannin. The TRPV1-dependent mechanism is also necessary to PAC-induced enhancement of c-Fos protein expression in the dorsal horn neurons. (II.) Our preliminary data clearly demonstrates that disinhibition occurs in a significant manner in all tested models of pain (PIPN, peripheral inflammation, and CCI). (III.) $Na_v1.7$ receptor blocker protoxin II significantly reduced aberrant activity induced by burn injury in the population of capsaicin-sensitive nociceptive spinal cord dorsal horn neurons in the rat. Finally, (IV.) we confirmed the hypothesis that 20:4-NAPE serves as a source for endogenous AEA synthesis in the spinal cord *in vitro*. Inhibitory effect of 20:4-NAPE is mediated by CB_1-dependent mechanism. However, this CB_1-mediated analgesic effect of 20:4-NAPE, is under inflammatory conditions partly modified by an additional TRPV1-dependent mechanism.

Taking together, these data support the view that spinal nociceptive synaptic transmission is substantially influenced under pathological conditions, and that appropriate intervention and pharmacological treatment can help alleviate increased nociceptive transmission or pain-related behavior in animals. Detailed understanding of these mechanisms is necessary for the improvement of pain therapy in the future.