Abstract

Neuropathic pain represents a possible outcome of neural tissue injury; it occurs also as a concomitant symptom of different diseases or as a side effect of several treatments. Up to date, it constitutes a great challenge in clinical practice, as currently available treatments are still unsatisfactory. Mechanism-based treatment approaches are promising strategy in neuropathic pain management. However, there is still a lack of information about the exact mechanisms involved in the development and/or maintenance of neuropathic pain.

This Doctoral Thesis is aimed to explore the mechanisms underlying the development of neuropathic pain states in different models. The principal part of this work is focused on the study of anti-inflammatory effect of Angiotensin II receptor type 1 (AT1R) blocker, losartan, in two different models of peripheral neuropathy: paclitaxel-induced peripheral neuropathy (PIPN) and spinal nerve ligation (SNL). The work also aimed to access the involvement of spinal transient receptor potential vanilloid type 1 (TRPV1) channels in the process of neuronal activation induced by paclitaxel (PAC) and chemokine CCL2 treatment.

In order to fulfil the abovementioned aims, behavioral, immunohistochemical and molecular methods were used. For every model of peripheral neuropathy, the behavioral responses to thermal/mechanical stimuli were tested as a measure of increased pathological sensitivity - allodynia and hyperalgesia. Immunohistochemical methods were used to evaluate enhanced neuronal activation in the spinal cord dorsal horn (SCDH) and macrophage invasion in the dorsal root ganglia (DRGs). Western blot, ELISA, and RT PCR were used to determine the expression of specific proteins and mRNAs in SCDH and DRGs.

Our results demonstrate analgesic and anti-inflammatory effects of systemic treatment with losartan in the SNL and PIPN models of neuropathy. In both these models, losartan treatment, presumably through peroxisome proliferator-activated receptors gamma (PPARγ) agonism, attenuated the development of neuropathic pain and suppressed the expression of pro-inflammatory markers: CCL2, TNFα, CD11b, CD68, and others. Moreover, in the PIPN model, losartan treatment induced the expression of pro-resolving markers, indicating the possible approach for the modulation of neuroinflammation. Our

results also indicate active role of the spinal TRPV1 receptors in the mechanisms of central sensitization, as blockade of these receptors prevented increased activation of dorsal horn neurons in spinal cord slices, incubated with cytostatic PAC or chemokine CCL2. Moreover, TRPV1 antagonist intrathecal treatment prevented CCL2-induced thermal hyperalgesia in rats.

Studying mechanisms underlying the development of neuropathic pain is essential for the elaboration of new effective analgesic treatments. This work brings new information that may help to understand the complexity of neuropathic pain pathophysiology, and reveals new evidence about the mechanisms underlying the development of neuroinflammatory changes in the DRGs and spinal cord.