Abstract

Present pain therapies are often insufficient and poorly managed, mainly for neuropathic pain treatment. In the past years, research has provided a body of evidence on the association of nerve injury and inflammation with mobilized immune reactions. Many cytokines and hormones are released during injury or inflammation, and these factors regulate neuronal encoding of painful sensations. For example, in pre-clinical models, inflammatory cytokines cause or amplify nociception by enhancing neuron excitability. Besides increased excitability via direct neuronal sensitization, it has also been demonstrated that a reduction of synaptic inhibition (disinhibition) occurs naturally in the course of neuropathic and inflammatory pain states. The spinal cord dorsal horn (SCDH) is the first relay station of the ascending pain pathway and a crucial modulatory site of painful stimuli transmission.

Three main aims characterize this doctoral thesis; each focused on the modulation of spinal nociceptive transmission by different molecules fundamental for pain processing. The **first** aim was to study the role of proinflammatory cytokine macrophage migration inhibitory factor (MIF) in nociceptive signalling following peripheral neuropathy induced by chronic constriction injury (CCI) of the sciatic nerve. The **second** aim was to investigate the role of anandamide (AEA) in the modulation of excitatory synaptic transmission at nociceptive synapses in the superficial spinal cord dorsal horn after carrageenan-induced peripheral inflammation. The **third** aim was to study the modulatory role of the cannabinoid receptor 1 (CB_1) regulatory protein, SGIP1, at first nociceptive synapses of the pain pathway in inflammatory conditions.

In vitro experiments were performed using whole-cell patch-clamp recordings from superficial dorsal horn neurons in acute spinal cord slices, supplemented by immunohistochemistry, PCR method, and in vivo behavioural tests to accomplish these goals.

Our results showed that a systemic administration of MIF inhibitor, ISO-1, attenuated mechanical and thermal hypersensitivity induced by CCI of the sciatic nerve in males but not in female mice. Moreover, ISO-1 administration partially restored the loss of balance between excitatory and inhibitory synaptic transmission in the superficial dorsal horn and decreased macrophage infiltration to the site of peripheral nerve injury and dorsal root ganglion (DRG). In addition, inhibition of MIF activity regulated signs of neuroinflammation. Concerning the second aim, our published data demonstrated that peripheral inflammation promoted the AEA-mediated inhibitory effect in the spinal cord dorsal horn. Furthermore, SGIP1 protein deletion enhanced the inhibition of spinal nociceptive transmission induced by CB_1 receptor activation.

The results of this PhD study revealed that modulation of neuroinflammation and nociceptive synaptic transmission by MIF, AEA and SGIP1 protein plays an essential role in the nociceptive signalling after peripheral neuropathy and inflammation. These findings need further implementation to contribute to chronic pain treatments.