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Editorial

New Targets for Treating Chronic Pain and Inflammation

Inflammatory response is originated by tissue injury and triggers a cascade of biochemical reactions that prime the nervous system for pain perception. Protracted inflammation supports adaptive changes that can cause altered pain signal processes. Indeed, different chronic (*i.e.* neuropathic) or inflammatory injuries to nervous system trigger structural and functional changes in the peripheral or central sensory circuits, resulting in behavioral dysfunctions, such as hyperalgesia and allodynia, and comorbidities. Current treatments for chronic pain are quite unsatisfying. Hence, there is a great, unmet need for research aimed at discovering novel biological targets together with the development of new pharmacological approaches for optimizing the side-effects of the classical drugs.

In this mini special issue, different signaling pathways in the peripheral and central nervous systems implicated in inflammation and chronic pain and possible therapeutic approaches have been described.

- The review by Magni *et al.* [1] focuses on the pathophysiology and therapeutic potential of purinergic signaling in pain, by reporting the available literature pre-clinical data together with the results of clinical trials. The authors accurately illustrate the complex organization of purinergic system by providing the vast variety of different (neuronal and non-neuronal) targets for resolution of chronic pain and inflammation. They also highlight the role of purines in non-conventional therapeutic approaches.
- Posa and collaborators [2] show the analgesic properties of the neurohormone melatonin in several preclinical studies and patients. They systematically describe the melatonin receptor functions in the neurobiology of pain. Given the weakness of pharmacokinetic profile of melatonin *per se*, they suggest the importance of developing new pharmaceutical formulations or synthetic drugs acting on melatonin receptors, giving particular emphasis to the effects mediated by MT2 receptors. Indeed, they discuss the analgesic properties of MT2 receptor partial agonists in different chronic and acute/inflammatory pain conditions.
- Negri *et al.* [3] summarize the evidence for the involvement of a new class of chemokine, the prokineticins and their receptors, in chronic pain. They appropriately describe distribution of ligands and their receptors in the periphery and at central nervous system level, by giving detailed information on their role in nociceptive, as well as, chronic pain modulation. Indeed, they indicate that a number of preclinical studies proved the effects of endogenous ligands or novel non-peptide drugs in controlling inflammation and inflammatory/neuropathic pain. They discuss the possible molecular mechanisms responsible for prokineticins effects, by highlighting the neuron-glia and neuron-immune cells interaction in prokineticins signaling.
- Bedini *et al.* [4] remark advantages and drawbacks in the pharmacological manipulation of opioid system, by highlighting the poor effectiveness of opiates in neuropathic pain condition. In this context, they describe innovative opioid peptides (analogues of endomorphin 1 and dermorphin), showing similar analgesic properties, but reduced side effects, as compared to classic opiates (*i.e.* morphine), as possible lead compounds for the development of new drugs.
- Roohbakhsh *et al.* [5] describe the orexinergic system as a potential candidate for finding alternative analgesics with good efficacy and low side effects. Indeed, they clearly describe the cellular and molecular mechanisms responsible for orexins effects in pain control at both spinal and supraspinal levels. Moreover, they give information about recent preclinical findings on the manipulation of orexin signaling in pain modulation.
- Russo and collaborators [6] discuss the possible involvement of gut-brain axis in the regulation of inflammation and pain, that nowadays represents a hot topic research area. They report recent studies showing that the deregulation of intestinal microbioma, commonly associated with gut inflammatory disorders, is responsible for the development of several CNS pathologies. In this context, they highlight the role of endogenous lipids, as NAEs (AEA, PEA and OEA) and the most well studied short fatty acid (butyrate) in the inflammation process, pain perception and in the CNS dysfunctions, by mainly focusing on endocannabinoids system involvement.

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