Review Article

Immune and Opioid System Interaction in Pain Modulation

Mona Taghizadeh[1,2], Homa manaheji[1,2], Mansoureh Baniasadi[1,2], Mola Mohammadi[1,2], Jalal Zaringhalam[1,2*]

Abstract

Inflammatory pain is caused by direct stimulation of nociceptors with the release of inflammatory mediators. Several studies about the roles of immune and opioid systems in the pain process have suggested that their crosstalk may have be in pain modulation. Purpose of this study was to review the effect of immune and opioid systems on pain modulation. Increasing demand for mitigating inflammatory pain has led to the introduction of the effect of immune and opioid system interaction in pain modulation. We reviewed 61 related articles from 1991 to 2016. In this study, we reviewed most of the existing papers on the role of opioid system in pain modulation especially with a focus of the immune system efficacy. Our review suggested that there is a close correlation between the expression of cytokines and opioid receptors. In addition, there is relationship in the process of inflammatory pain where immune cells have a notable effect on the expression of cytokines and opioid receptors. In the process of inflammation, different types of immune cells constitute a major source of opioid peptides. The endogenous opioids could modulate either their own secretion or secretion of other cytokines. They have also anti-nociceptive and anti-inflammatory effects. Exacerbation of immune and opioid system reactions via correlation between cytokines and opioid peptides in the context of inflammatory pain arises the possibility of the role of interaction of these two important systems in the pain process.

Keywords: Inflammatory pain, Opioids, Immune system, Cytokines, Hyperalgesia

1. Department of Physiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Neurophysiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author:
Jalal Zaringhalam, MD, PhD, Associate Professor, Physiology Department, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
E mail: jzaringhalam@yahoo.com

Please cite this article as: Taghizadeh M, Manaheji H, Baniasadi M, Mohammadi M, Zaringhalam J. Immune and Opioid System Interaction in Pain Modulation. J Cell Mol Anesth. 2019;4(1):24-30.

Introduction

Pain is described as an unpleasant sensory and emotional feeling accompanied by psychological and physiological components. The physiology of pain has been well described and the underlying origin of all type of pain is inflammation and inflammatory response (1–3). Inflammation, as a non-specific immune response, occurs in reaction to various kinds of injuries and can fuel a self-propelling cycle of neural death (4). In inflammatory diseases, rapid release of inflammatory mediators causes different alterations. Inflammatory factors sensitize the specialized sensory neurons leading to pain and disability, the principal clinical features of inflammation (5). Thus, immune system has an important role in the pain process. On the other hand, endogenous opioid system is the innate pain-relieving systems, which has an essential role in pain modulation. There is no clear study about the role

of interaction of these two systems in pain control. Therefore, in this review, we have highlighted the potential role of this interaction in pain modulation.

In this review, we probed into the effect of immune and opioid system interaction in pain modulation. The literature covers a variety of topics such as inflammation, immune system and pain interaction, opioid system and pain, and immune-opioid system interaction (Figure 1). In this study, we reviewed most of the existing papers on immune and opioid systems and the possible role of their interaction in pain modulation.

Inflammation, interaction between immune system and pain

Immune system sometimes involve in etiology and pathophysiology of inflammation. It is also one of the main players in the generation of hyperalgesia. Immune cells have an important role as pain modulators both in peripheral and in central nerve damages (5). Various immune cell types have contribute in abnormal pain sensitivity via releasing a wide range of inflammatory cytokines though to varying degrees (6). A large number of evidence suggests that cytokines have a crucial role in chronic pain and development of hyperalgesia and might alter the electrophysiological properties of neurons (7). Actions of cytokines include numerous effects on immune cells and modulation of inflammatory responses. Note that the outcome of cytokines' action greatly depends on where and when they are activated exactly.

It is interesting to note that several cytokines can induce their own production as well as the other cytokines, such as TNF-α which induces production of IL-1b and IL-6 (8). IL-10 is another inflammatory cytokine, which has been extensively studied. It is increasingly stated that IL-10 is one of the most important immune-regulating cytokines, which was previously called cytokine synthesis inhibiting factor (9). In contrast, Conti et al. concluded that this factor fails to inhibit the release of IL-6 from human umbilical cord mast cells (10).

IL-6 is known as pro- and anti-inflammatory factor during different stages of inflammation. It is involved in modulation of the opioid pathway, which alters the responses to thermal or mechanical stimuli and pain in animals. Previous work in our laboratory has emphasized the important time-dependent relationship between serum levels of this factor and hyperalgesia during adjuvant-induced arthritis (7,11). In case of neuro-inflammatory pain, it has been suggested that chemokines act as messengers between peripheral immune cells and sensory afferent neurons at inflamed sites (12).

Under inflammatory conditions, inflammatory factors induce the expression of opioids, while in some conditions they might have anti-nociceptive effects.

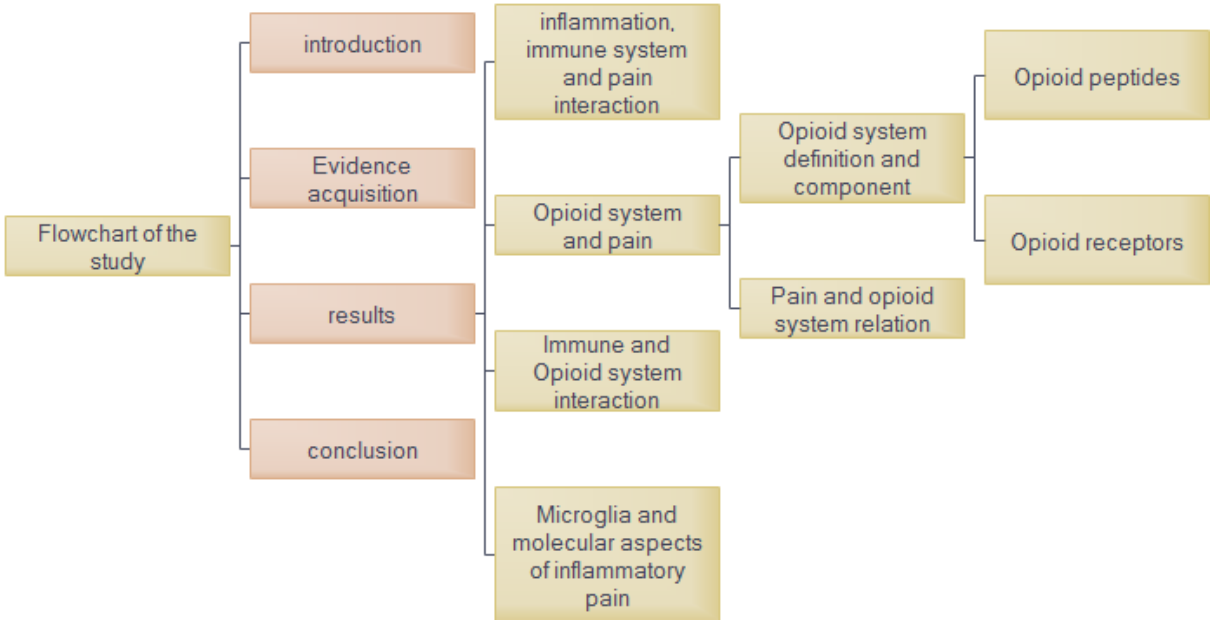

Figure 1. Flowchart of this study.

These factors have important homeostatic functions such as repairing tissues. Meanwhile, an imbalance in the immune response towards inflammation might contribute to persistent pain. Recently, it has been claimed that immune cell products might have a crucial role not just in inflammatory pain, but also in neuropathic pain caused by damage to peripheral nerves or to the CNS (13–15).

Opioid system and pain

***Opioid system definition and components*:** the opioid system is a biological communication system which acts through a group of endogenous opioid peptides and different classes of opioid receptors (16). In addition to nociception and analgesia, the opioid system plays significant roles in modulating a large number of addictive behaviors and cognitive functions, and has functional interaction with the endogenous cannabinoid (17–20). Further, in a study by Zaringhalam et al. demonstrated that the opioid system may also be involved in variations of hyperalgesia during 21 days of adjuvant-induced arthritis inflammation (21).

***Opioid peptides*:** three families of opioid peptides have been well characterized; the endorphins, enkephalins and dynorphins (22,23).

- Endorphins: There are four types of endorphins (α, β, γ, σ) created in the human body (24,25). During severe pain, the endorphins cause an analgesic effects in human body, while during stress they act differently (26). The available evidence suggests that endorphins may have a role in preventing obesity and diabetes as well as psychiatric diseases (27).
- Enkephalins: There are two main forms of enkephalins, Met-enkephalin and Leu-enkephalins. Enkephalins are involved in the mechanisms of modulation of the extrapyramidal system, motivational processes, regulation of convulsive states, and nociception (28–30).
- Dynorphins: Dynorphin has been found to broadly regulate neuronal excitability in the brain and can affect learning, cognition and nociception. In addition, depending on the site of production, it also can act as a modulator of appetite control and body temperature. The increased spinal dynorphin levels observed in the neuropathic pain models in several studies indicated that dynorphin might be involved in chronic pain (31–34).

Opioid receptors: opioid receptors are the peripheral terminals of sensory neurons consisting of three families of receptors: μ, δ and κ. In addition to the well-documented role of opioid receptors in pain modulatory system, they also play a significant role in moderation of hyperalgesia in inflamed tissues. The evidence has also suggested a close correlation between the expression of cytokines and opioid receptors in the process of inflammation (35).

Pain and opioid system relationship: various studies have indicated that sustained pain and inflammation cause physiological and pharmacological changes in the pain modulatory system (36,37). The μ-opioid receptor is the most common receptor associated with analgesic therapy during persistent pain. Our previous studies also indicated that increased level of spinal μ-opioid receptor expression was involved in hyperalgesia reduction during chronic inflammatory phase of AA (38,39).

In addition, there is increasing evidence that peripherally restricted κ opioids effectively relieve hyperalgesia, pain, and allodynia. Further, κ opioid agonists are particularly efficacious for relieving pain associated with visceral inflammation and even relieving pain induced by the first and second phase of formalin, carrageenan, and CFA (34,40).

In another study, Wilson et al. demonstrated that κ opioids reduce inflammation in adjuvant arthritis model via directly inhibiting cytokine release from immune cells, specifically IL-4 and TNF from macrophages (41). Regardless of psychomimetic and dysphoric effects of delta receptors, there is strong evidence for the role of delta receptors in reducing hyperalgesia in inflammatory conditions and neuropathic pain (22,42,43).

Immune system and Opioid interaction

There is no doubt that opioid system plays an essential role in the crosstalk between the immune and nervous system. Opioids also function as regulators of both cellular and humoral immune responses. Cabot et al. demonstrated that within peripheral inflammation, immune system as a source of opioid peptides plays a sophisticated role in pain modulation (44).

The findings are consistent with studies revealing that opioid peptides are found in many

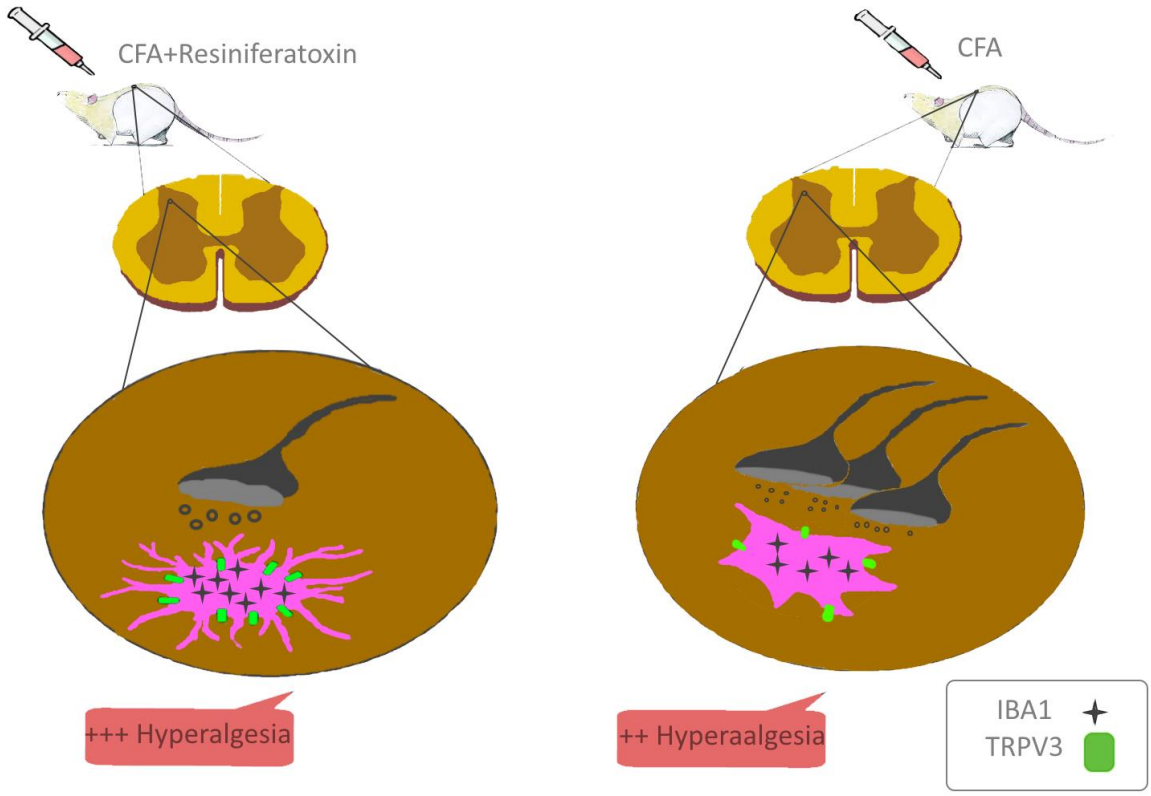

Figure 2. Hyperalgesia variation due to alteration of microglial morphology after elimination of spinal C fibers.

leukocyte subpopulations including lymphocytes, monocytes, and granulocytes in the peripheral blood. In peripheral inflamed tissues, opioid peptides such as b-endorphin, met-enkephalin, dynorphin, and endomorphins are produced by leukocytes and released upon certain types of stimulation such as inflammation and inflammatory factors including IL-1, IL-4, and TNF-α (45).

Kraus et al. primarily showed that pro-inflammatory cytokine tumor necrosis factor in human T lymphocytes and monocytes induced μ-opioid receptor gene transcription in the immunocytes (46). TNF-induction of μ-opioid receptors could allow a feedback regulation in which the endogenous opioids could modulate either their own secretion or secretion of other cytokines. Accordingly, many investigations support this hypothesis that endogenous opioids act in an anti-nociceptive as well as an anti-inflammatory manner, though further work should be done to better understand it (46). Opioid peptides can bind to opioid receptors on sensory neurons and can cause analgesic effects. Further, in different phases of inflammation, various types of immune cells constitute a major source of opioid peptides (47–51). There are two important points to emphasize here. First, regardless of the direct effect of opioids on the immune function, they must act via opioid receptors expressed on immune cells. Some studies support the view that opioid receptors (mostly κ and δ receptors) expressed by various immune cells are the same as neuronal-type opioid receptors. There is now considerable evidence pointing to the existence of novel morphine selective opioid receptors on lymphocytes (52).

Second, opioids can interfere with the immune system, modulating innate and acquired immune responses and alter resistance to a variety of infectious agents. A key issue regarding different opioids is to understand that they show different effects on the immune system: immunosuppressive, immunostimulatory, or dual effect. Meanwhile, the nervous system may release opioid peptides, which can bind with the immunocyte opioid receptors in order to regulate the immune function. Furthermore, immunocytes can regulate immune function by secreting opioid peptides like b-endorphin and the Dynorphin. Investigations have indicated that opioids can operate as cytokines which can induce the synthesis of opioid receptors in immune cells and the

expression of receptors in neuronal cells (37,52,53).

Microglia and molecular aspects of inflammatory pain

Microglia reside within the central nervous system and are activated after various insults such as nerve injury by displaying morphological changes and upregulation of microglial markers. The expression of Iba1 is upregulated in activated microglia following inflammatory condition, facial nerve axotomy, and viral infections. Activated glia releases various substances such as pro-inflammatory cytokines and other mediators which can enhance pain transmission (54–56). In line with previous studies, Gazerani et al. revealed that elimination of peripheral peptidergic fibers causes significant changes in the expression of TRPV3 and Iba1 molecule as well as hyperalgesia and allodynia (54)(Figure 2). Microglia are important contributors to the development of enhanced pain states as well as to the onset and maintenance of inflammation. (57–59). The data published in our previous study indicated the role of minocycline in reducing edema and hyperalgesia during different stages of inflammation caused by CFA. The continuing injection of minocycline could reduce the inflammatory symptoms such Asallodynia, where the effect of minocycline on allodynia and spinal Iba1 expression is age dependent (4,60). Interestingly, in another study, Nazemi et al. indicated that anti-nociceptive effect of morphine decreases during the development of neuropathic pain, and use of agents selectively inhibiting microglial activity may maintain the beneficial effect of opioids in neuropathic pain (56).

Conclusion

Although some evidence supports the role of immune and opioid system in pain control via separate mechanisms, various studies indicated the effect of crosstalk of these two systems on the process of pain. In this regard, as previously mentioned, cytokines induce expression of opioid receptors in immunocytes. Meanwhile, opioids may operate as cytokines, which can induce the synthesis of opioid receptors in immune cells too. The expression of receptors in neuronal cells and immune cells is involved in anti-nociceptive effect of the opioid system. Nevertheless, recent data from our laboratory have revealed that opioid system itself may be involved in variations in hyperalgesia during 21 days of adjuvant-induced arthritis inflammation. Therefore, many aspects of interactions between opioid and immune systems have remained ambiguous.

Acknowledgment

This study was has done as a part of M.Sc. thesis and supported by School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

1. Omoigui S. The biochemical origin of pain: The origin of all pain is inflammation and the inflammatory response. Part 2 of 3 - Inflammatory profile of pain syndromes. Med Hypotheses. 2007;69(6):1169–78.
2. Streit WJ, Mrak RE, Griffin WST. Microglia and neuroinflammation: A pathological perspective. J Neuroinflammation. 2004;1:1–4.
3. Barton GM. A calculated response: control of inflammation by the innate immune system. J Clin Invest. 2008;118(2):413–20.
4. Nasseri B, Nazemian V, Manaheji H, Zaringhalam J. Microglia are involve in pain related behaviors during the acute and chronic phase of arthritis inflammation. J Cell Mol Anesth. 2016;1(4):137–45.
5. Zaringhalam J, Akbari A, Zali A, Manaheji H, Nazemian V, Shadnoush M, et al. Long-Term Treatment by Vitamin B1 and Reduction of Serum Proinflammatory Cytokines, Hyperalgesia, and Paw Edema in Adjuvant-Induced Arthritis. Basic Clin Neurosci J. 2016;7(4):331–40.
6. Stein C, Schäfer M, Machelska H. Attacking pain at its source : new perspectives on opioids. 2003;9(8):1003–8.
7. De Jongh RF, Vissers KC, Meert TF, Booij LHDJ, De Deyne CS, Heylen RJ. The role of interleukin-6 in nociception and pain. Anesth Analg. 2003;96(4):1096–103.
8. Sommer C, Kress M. Recent findings on how proinflammatory cytokines cause pain: Peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Vol. 361, Neurosci Lett. 2004;361(1-3):184-7.
9. Rittner HL, Stein C. Involvement of cytokines, chemokines and adhesion molecules in opioid analgesia. Eur J Pain. 2005;9(2):109-12.
10. Conti P, Kempuraj D, Kandere K, Di Gioacchino M, Barbacane RC, Castellani ML, Felaco M, Boucher W, Letourneau R, Theoharides TC. IL-10, an inflammatory/inhibitory cytokine, but not always. Immunol Lett. 2003 3;86(2):123-9.
11. Tekieh E, Zaringhalam J, Manaheji H, Maghsoudi N, Alani B, Zardooz H. Increased serum IL-6 level time-dependently regulates

hyperalgesia and spinal mu opioid receptor expression during CFA-induced arthritis. EXCLI J. 2011;10:23-33.
12. Boddeke EW. Involvement of chemokines in pain. Eur J Pharmacol. 2001;429(1-3):115–9.
13. Calvo M, Dawes JM, Bennett DLH. The role of the immune system in the generation of neuropathic pain. Lancet Neurol. 2012;11(7):629–42.
14. Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. Nat Rev Neurosci. 2005;6(7):521-32.
15. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428-35.
16. Cai Z, Ratka A. Opioid system and Alzheimer's disease. Neuromolecular Med. 2012;14(2):91-111.
17. Le Merrer J, Becker JAJ, Befort K, Kieffer BL. Reward Processing by the Opioid System in the Brain. Physiol Rev. 2009;89(4):1379–412.
18. Melzack R. From the gate to the neuromatrix. Pain. 1999;Suppl 6:S121-6.
19. Snyder SH, Childers SR. Opiate Receptors and Opioid Peptides. Annu Rev Neurosci. 1979;2(1):35–64.
20. Molaei M, Sanati MH, Zaringhalam J, Haghparast A. Microinjection of WIN55,212-2 as a cannabinoid agonist into the basolateral amygdala induces sensitization to morphine in rats. Basic Clin Neurosci. 2014;5(4):295–302.
21. Zaringhalam J, Manaheji H, Mghsoodi N, Farokhi B, Mirzaiee V. Spinal μ-opioid receptor expression and hyperalgesia with dexamethasone in chronic adjuvant-induced arthritis in rats. Clin Exp Pharmacol Physiol. 2008;35(11):1309–15.
22. Snyder SH, Pasternak GW. Historical review: Opioid receptors. Trends Pharmacol Sci. 2003;24(4):198–205.
23. Ananthan S. Opioid ligands with mixed mu/delta opioid receptor interactions: an emerging approach to novel analgesics. AAPS J. 2006;8(1):E118-25.
24. Chapman CL, De Castro JM. Running addiction: measurement and associated psychological characteristics. J Sports Med Phys Fitness. 1990;30(3):283–90.
25. Przewłocki R. Some aspects of physiology and pharmacology of endogenous opioid peptides. Pol J Pharmacol Pharm. 1984;36(2-3):137-58.
26. Koltyn KF. Analgesia following exercise: a review. Sports Med. 2000;29(2):85–98.
27. Dalayeun JF, Norès JM, Bergal S. Physiology of beta-endorphins. A close-up view and a review of the literature. Biomed Pharmacother. 1993;47(8):311–20.
28. Mika J. The opioid systems and the role of glial cells in the effects of opioids. 2008;185–96.
29. Comb M, Seeburg PH, Adelman J, Eiden L, Herbert E. Primary structure of the human Met- and Leu-enkephalin precursor and its mRNA. Nature. 1982;295(5851):663–6.
30. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11(2 Suppl):S133–53.
31. Day R, Lazure C, Basak A, Boudreault A, Limperis P, Dong W, et al. Prodynorphin processing by proprotein convertase 2. Cleavage at single basic residues and enhanced processing in the presence of carboxypeptidase activity. J Biol Chem. 1998;273(2):829–36.
32. Bruchas MR, Land BB, Chavkin C. The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. Brain Res. 2010;1314(1981):44–55.
33. Draisci G, Kajander KC, Dubner R, Bennett GJ, Iadarola MJ. Up-regulation of opioid gene expression in spinal cord evoked by experimental nerve injuries and inflammation. Brain Res. 1991;560(1-2):186–92.
34. Koneru A; Satyanarayana S; Rizman S. Endogenous Opioids : Their Physiological Role and Receptors. Glob J Pharmacol. 2009;3(3):149–53.
35. Nazemian V, Shadnoush M, Manaheji H, Zaringhalam J. Probiotics and Inflammatory Pain: A Literature Review Study. Middle East J Rehabil Heal. 2016;3(2):1–11.
36. Investigation of the relation between the hypothalamus-pituitary-adrenal (HPA) axis activity, IL-6 and hyperalgesia during chronic inflammation due to rheumatoid arthritis (RA) in male rats. Physiol Pharmacol. 2007;11(2):130–6.
37. Zaringhalam J, Tekieh E, Manaheji H, Akhtari Z. Cellular events during arthritis-induced hyperalgesia are mediated by Interleukin-6 and p38 MAPK and their effects on the expression of spinal mu-opioid receptors. Rheumatol Int. 2013;33(9):2291–9.
38. Akhtari Z, Zaringhalam J, Eidi A, Manaheji H, Tekieh E. Bidirectional effects of serum TNF alpha level and spinal p38MAPK phosphorylation on hyperalgesia variation during CFA-induced arthritis. EXCLI J. 2012;11:373–85.
39. Zaringhalam J, Hormozi A, Tekieh E, Razavi J, Khanmohammad R, Golabi S. Serum IL-10 involved in morphine tolerance development during adjuvant-induced arthritis. J Physiol Biochem. 2014;70(2):497–507.
40. Vanderah TW. Delta and kappa opioid receptors as suitable drug targets for pain. Clin J Pain. 2010;26(SUPPL.10):10–5.
41. Wilson J. L, Nayanar V, Walker J. S. Br J Pharmacol. The site of anti-arthritic action of the kappa-opioid, U-50, 488H, in adjuvant arthritis: importance of local administration. 1996 Aug; 118(7): 1754–1760.
42. Nadal X, Baños J-E, Kieffer BL, Maldonado R. Neuropathic pain is enhanced in δ-opioid receptor knockout mice. Eur J Neurosci. 2006;23(3):830–4.
43. Gavériaux-Ruff C, Karchewski LA, Hever X, Matifas A, Kieffer BL. Inflammatory pain is enhanced in delta opioid receptor-knockout mice. Eur J Neurosci. 2008;27(10):2558–67.
44. Cabot PJ, Carter L, Gaiddon C, Zhang Q, Schäfer M, Loeffler JP, et al. Immune cell-derived beta-endorphin. Production, release, and control of inflammatory pain in rats. J Clin Invest. 1997;100(1):142–8.
45. Rachinger-Adam B, Conzen P, Azad SC. Pharmacology of peripheral opioid receptors. Curr Opin Anaesthesiol. 2011;24(4):408–13.
46. Kraus J, Orner CB, Giannini E, Ollt VH. The Role of Nuclear Factor kB in Tumor Necrosis Factor- Regulated Transcription of the Human μ-Opioid Receptor. Mol Pharmacol. 2003;64(4):876–84.
47. Sacerdote P. Opioids and the immune system. Palliat Med. 2006;20 Suppl 1:s9-15.
48. Rittner HL, Brack A, Stein C. Pain and the immune system. Br J Anaesth. 2008 Jul;101(1):40-4.
49. Low HH. Receptor-Like lmmunoreactivities in Rat Dorsal Root Ganglia after Inflammation. 1995;75(December):8156–66.
50. Stanfa LC, Sullivan AF, Dickenson AH. Alterations in neuronal excitability and the potency of spinal mu, delta and kappa opioids

after carrageenan-induced inflammation. 1992;50:345–54.
51. Receptors PO. Peripheral Opioid Receptors Mediating Evidence for Involvement Receptors Antinociception in of Mu, Delta and Kappa. 1989 vol: 248 (3) pp: 1269-75
52. Bidlack JM. Detection and function of opioid receptors on cells from the immune system. Clin Diagn Lab Immunol. 2000;7(5):719–23.
53. Liang X, Liu R, Chen C, Ji F, Li T. Opioid System Modulates the Immune Function: A Review. Transl Perioper Pain Med. 2016;1(1):5–13.
54. Gazerani S, Zaringhalam J, Manaheji H, Golabi S. The Role of C Fibers in Spinal Microglia Induction and Possible Relation with TRPV3 Expression During Chronic Inflammatory Arthritis in Rats. Basic Clin Neurosci. 2016;7(3):231–40.
55. Nazemi S, Manaheji H, Noorbakhsh SM, Zaringhalam J, Sadeghi M, Mohammad-Zadeh M, et al. Inhibition of microglial activity alters spinal wide dynamic range neuron discharge and reduces microglial Toll-like receptor 4 expression in neuropathic rats. Clin Exp Pharmacol Physiol. 2015;42(7):772–9.
56. Nazemi S, Manaheji H, Zaringhalam J, Sadeghi M, Haghparast A. Post-injury repeated administrations of minocycline improve the antinociceptive effect of morphine in chronic constriction injury model of neuropathic pain in rat. Pharmacol Biochem Behav. 2012;102(4):520–5.
57. Watkins LR, Milligan ED, Maier SF. Glial proinflammatory cytokines mediate exaggerated pain states: implications for clinical pain. Adv Exp Med Biol. 2003;521:1–21.
58. Watkins LR, Hutchinson MR, Ledeboer A, Wieseler-Frank J, Milligan ED, Maier SF. Norman Cousins Lecture. Glia as the "bad guys": implications for improving clinical pain control and the clinical utility of opioids. Brain Behav Immun. 2007;21(2):131–46.
59. Nasseri B, Nazemian V, Manaheji H, Zaringhalam J. Microglia are involve in pain related behaviors during the acute and chronic phase of arthritis inflammation. J Cell Mol Anesth. 2016;1(4):137–45.
60. Zeinali H, Manaheji H, Zaringhalam J, Bahari Z, Nazemi S, Sadeghi M. Age-related differences in neuropathic pain behavior and spinal microglial activity after L5 spinal nerve ligation in male rats. Basic Clin Neurosci. 2016;7(3):203–12.