REVIEW ARTICLE

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# The interaction of neuroimmunology, neuromodulator, and neurotransmitter with nociceptor and MAPK signaling

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## ABSTRACT

Physiological pain is a protection mechanism against tissue damage or potential tissue damage. Inflammation pain is followed by tissue damage due to temperature, mechanical and chemical stimuli which increase crosstalk between neuron nociceptor, immune system, neuromodulator and neurotransmitter, and MAPK (*Mitogen Activating Protein Kinase*) signal. Initially, immune cell is produced at the primary afferent nerve endings and spinal cord, modulate thermal sensitivity and mechanic through MAPK signaling, then neuromodulator and neurotransmitter at the afferent nerve endings will regulate the innate immune response, adaptive and vascular.

**Keywords:** *neuroimmunology, neuromodulator, neurotransmitter, sensory neuron, inflammation pain.*
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## INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[1] Pain can be physiological or pathological pain or described as clinical pain.[2] Physiological pain is an acute nociception pain as a protective mechanism against tissue damage or threat to tissue damage caused by activation nociception pathway by adequate peripheral intensity stimuli.[2,3] Physiological pain starts from the terminal nociceptor of the skin and muscles, transmitted to the small diameter unmyelinated C nerve fibers (slow conducting) and A myelinated nerve fibers (fast conducting) that is a sensitive polymodal nociceptor of mechanic, thermal and chemical stimuli.[4] Nociceptors are pain receptor located at the end organ of the skin, muscle, joint, and viscera, free encapsulated and selectively responds to noxious or threats to tissue damage.[5,6] The structures of nociceptors are spread as an axon, cell body, and central terminal related to the end organ, the cell body has a small diameter located at the dorsal root ganglia and sensory ganglia.[5,7] Expression of the ligand-gated ion channel and voltage-gated ion channel includes TRPV1, TRPA1, Nav1.7, Nav 1.8 and Nav 1.9 which are the key of transduction molecule noxious stimuli.[4,8] The first nociceptor will respond when the nervous system propagates signals in a few milliseconds when there is a pathogen or tissue damage.

## INFLAMMATION PAIN

Pathological pain is related to inflammation pain and neuropathic pain. Inflammation pain is pain following tissue damage either caused by mechanical, thermal, chemical, tissue ischemia and infection pathogen stimuli.[9] Neuropathic pain is related to peripheral and central nerve damage. Inflammation response is tissue control as a protection mechanism, but when it is over it will cause tissue damage and pathological condition, because the activation of target cell does not only affect the initial inflammation location but also in other locations which respond to the inflammation stimuli.[9] Inflammation mediator directly stimulates and sensitize the peripheral nociceptor located at the primary afferent nerve fibers at the peripheral tissue (dorsal ganglion and terminal ganglia).[10–12] The hyperactivity of primary sensory nerve fibers following an inflammation will also induce production of neurotransmitters (dopamine, acetylcholine, serotonin, glutamate), neuropeptide and neuromodulator (adenosine, purine, ATP, NO) at the central terminal of the primary afferent nerve fibers, spinal chord and trigeminal nucleus which cause postsynaptic nociceptive neuron hyperactivity (central sensitization). Most acute pain (*surgical incision, ankle sprained, burn*) will heal without permanent pain, this showed the nociceptor sensitization is temporary[7] Acute inflammation following the sensitization process is permanent and will cause chronic pain. Physiological threshold decrease with a noxious stimulus, as in cutaneous

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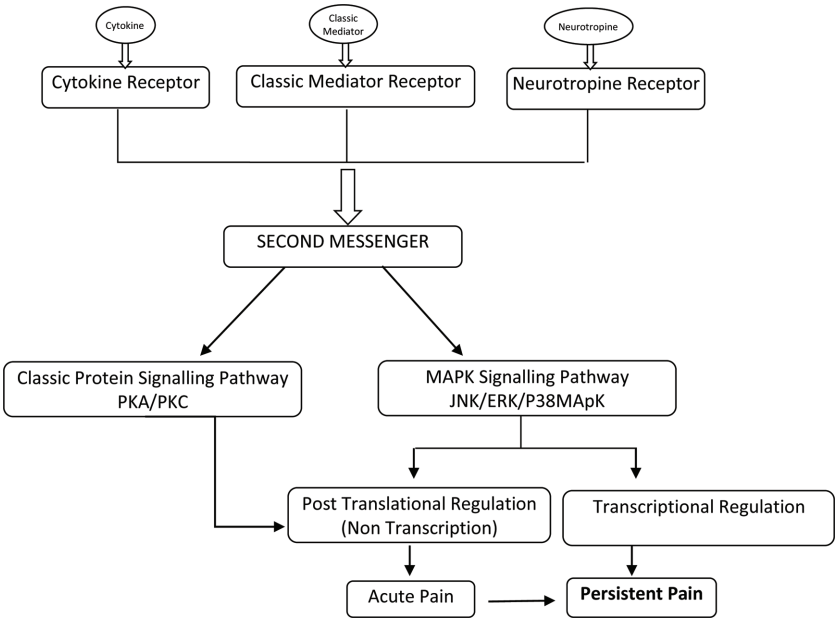


**Figure 1** Modulation of nociceptor on neuroimmune, neuromodulator and neurotransmitters

nociceptor sensitized by thermal stimuli and deep tissue nociceptor (muscle and joint) sensitized by mechanical stimulus.[4,13]

The innate immune cell is located at the tissue, includes macrophage, fibroblast, mast cell, monocyte, and neutrophil, identifies pathogen invasion when there is an invasion or cell damage through the expression of *pathogen recognize receptor* (PRRS).[14] The initial response of tissue damage known as sterile inflammation is mediated by *damage-associated molecular pattern* (DAMPs), if it is caused by pathogen will be mediated by *pathogen-associated molecular pattern* (PAMPs). DAMP is a heterogenic molecule group from the extracellular and intracellular compartment activating the immune system through PRRS when there is tissue damage.[15–17] Biglycan, decorate, fibrinogen, fibronectin, hyaluronan is an extracellular DAMPs. HMGB1, histon, DNA, RNA are from the nucleus, ATP, DNA is from mitochondria while *uric acid*, *heat shock proteins,* S100A, S100B are from the cytosol.[17] DAMP and PARS will activate PRRS i.e. Toll-Like Receptors (TLRs), *The Receptor for advanced glycation end products* (RAGE) and NLRP3 inflammasome.[15,17,18] Activated oligomerisated PRRS and union of most multisubunit will initiate signal cascade, stimulate productions of leukocyte recruitment factors.[19] Extracellular DAMP as in ATP, mitochondria formaldehyde peptide and mtDNA has an important role in neutrophil recruitment in sterile injury followed by other cytokines.[20] The neutrophil is an initial injury response released in a few hours, followed by macrophage in a few days and cell T infiltration in a few days until a few weeks.[21] Macrophage releases IL-1β, TNF-α, bradykinin, 5-HT, IL-6 and NGF (Nerve Growth Factor), has an important role in initiating, inflammation development and resolution, cleaning damaged cells and pathogen by phagocytosis and activating immune cell as neutrophil, dendrite cell, macrophage, and monocyte. The injury also involves the mast cell to produce bradykinin, serotonin, prostaglandin. All of those endogen substance work in each receptor known as the primary afferent nociceptor will generate the second messenger as Ca and cyclic AMP then activate multiple protein kinase i.e. protein kinase A (PKA), protein kinase C (PKC), extracellular signal-regulation kinase (ERK) and p38 MAPK and JUN N-terminal kinase (JNK). Activation of some protein kinase will result in sensitization by translational, posttranslational and transcriptional regulation, especially ERK and p38 which are activated by inflammation mediators in the primary sensory and second-order neuron of the dorsal horn that participates in generation and maintenance of inflammation pain.[14,22] Inflammation pain is manifested as spontaneous pain and hypersensitivity pain, spontaneous pain is a direct specific receptor and terminal nociceptor activation by inflammation mediators. Hypersensitivity pain is a consequence of posttranslational changes or acute posttranslational modification at the peripheral terminal nociceptor and the dorsal horn of the spinal cord continuing at the transcription of the effector gene, this repeats at the primary sensory and dorsal horn of the spinal cord responsible of the inflammation neuroplasticity.[23–25]

Kinase activation increase nociceptor sensitivity and excitability are known as peripheral sensitization through a different mechanism. Potential cathion channel receptor subfamily A member 1 (TRPA1), potential vanilloid 1 receptor (TRPV1), voltage gate-ion channel Nav 1-.7, Nav 1.8, Nav1.9 has an important role in molecule transduction and conduction involved in the primary sensitization process. Nociceptor neuron also expresses Toll-like receptor (TLRs) activated by endogen or exogen ligand.[21]

The immune system has an important role in pain pathophysiology. Tissue immune response will affect the neuroimmune system at neuronal sensitization, therefore the neuroimmune mechanism in neuron sensitization should be understood. Neuron nociceptor express receptors for cytokine immune cell, lipid protease and growth factor. During activation through phosphorylation or another mechanism will mediate channel ion cascade TRPVi, TRPA1, Nav 1.7, Nav1.8 and Nav 1.9. therefore increase neuronal threshold. Potential action is transmitted to the cell body receptor in the DRG and forwarded to the spinal cord and brain to mediate the process of pain.[7]

IL-1β is the first cytokine involved in hyperalgesia process[13] DAMP activated cytokine production by activation of PRRs and caspase 1. Caspase 1 (cysteine-aspartic protease, cysteine aspartase, or cysteine dependent aspartate-directed proteases) is a family of protease enzyme involved in cell death program (apoptosis, pyroptosis, necroptosis) and inflammation, to maintain cell homeostasis.[26] Caspase 1 is named as ICE interleukin 1β converting enzyme activates pro IL-1β to IL-β.[13,27,28] cause immune cell recruitment towards the infected or damaged tissue cell[29] IL-1β increase TRPV1 expression through activation of IL1R1 which will increase thermal stimulus sensitivity, also sensitize neuron NaV 1,8 sodium channel receptor that will cause mechanical and thermal hyperalgesia through p38 MAPK phosphorylation.[13,27,28] IL-1R is at the nonneuronal cell, mostly expressed at the DRG and dorsal horn of the spinal cord. The cytokine involved in permanent pain is not limited at peripheral sensitization, but the proinflammatory cytokine and their receptors are also localized at the dorsal horn and brain.[30–3]and increased during induced mice arthritis by CFA.[8] As a response to the ligand bond with the receptor it activates intracellular signaling through p38, nuclear factor kappa B (NF-kB) and JNK activate. MAPK Intraplantar IL-1β injection increase the mechanical and thermal sensitivity, does not decrease with the administration of ibuprofen but decrease with adding p38 MAPK inhibition.[31,32] Activation signaling NfKb, JNK, and p38MAPK induce the expression of canoninal IL-1 target genes by transcriptional dan posttranscriptional. IL-6 also contributed to the inflammation pain process by increasing prostaglandin production and combined as an al gp130 transducer signal produce expression of TRPV1 and TRPA1.

TNF has a role in the pain process pathway through activation of TNF subunit receptor i.e. TNFR1 and TNFR2, where TNFR2 has a more important role in neuron excitability modulation.[32] Forty until fifty percent of TNFR1 and TNFR2 is expressed in the DRG neuron, with the immunohistochemical and immunofluorescence examination increased from the basal level during nerve trauma.[32–35] Intraarticular injection of etanercept (TNFR fusion protein) reduce the sensory nerve fiber response (A delta and C) against mechanical stimulus for 30 minutes after injection.[33] With PCR analysis of the DRG of naive mice the TNFR1 is only expressed at the neuron, while TNFR2 in the nonneuron cell with analysis.[8] TNF increase rapidly from the thermal and mechanical stimulus of the inflamed knee. TNF-α sensitizes receptor Nav 1.8 and Nav 1.9 through TNFR1, therefore, affect the neuron excitability through p38 MAPK phosphorylation, while TNFR2 will increase TRPV1 expression which causes thermal hyperalgesia.[35,37] In the cultured DRG neuron stimulated by TNF there is activation of p38 MAPK and c-Jun N-terminal kinase (JNK), but not at p42/p44 (*extracellular signal-signal regulate proteinkinase1 and 2* (ERK1/2).[32,38,39] But TNF is confirmed to mediate upregulation expression of TRPV1 at murine DRG neuron through p42/p44.[37] In the pathway of pain process, TNF cannot act solely as a mediator in pain induction.

The role of adenosine in the nociception process was first found in 1970, then investigated more thoroughly in 1980 with the administration of selective agonist intravenously and intrathecally.[40,41] Adenosine works in several subtype G-protein adenosine receptor involved in peripheral, spinal and supraspinal pain signaling. Adenosine has four subunit receptors, i.e. A1Rs, A2ARs, A2BRs, and A3Rs. Receptor A1s, A2As is located at the terminal end of the sensory nerve,[39,40,42] while A2BRs and A3Rs has a direct border with the nociception cell type (mast cell) examined from immunohistochemical,[41–44] contributed indirectly to the inflammation reaction through inflammation mediator[41] A1Rs is also widely expressed at the transmission area and pain regulator at the central nervous system (spinal chord) specifically the microglia contributes to the pain process in the central, either in physiological, inflammatory or neuropathic pain.[45] Adenosine has a variable high affinity to A1Rs, A2ARs, A2BRs, and A3Rs, some cases have the same affinity to the subtype receptors.[43] Activation of A1s and A2As receptors cause antinociception effect.[46] Some inflammation studies use the caragenan, formaldehyde, surgical incision model.[47,48] Some studies use the neuropathic pain model, such as spinal cord trauma[48] and diabetic nephropathy[49,50] show A1Rs agonist have analgesia and antihyperalgesic effect. Part of the A1Rs signaling pathway will inhibit cyclic AMP/PKA and interact with the Ca+ dan K+ channel through Ga, interact with PLC/IP3/ DAG pathway through Ga subunit or bc and b-arresting mediating receptor and downregulation. Adenosine can activate ERK1/2, p38, and JNK in the rabbit heart, therefore there is a possible clear relationship between the adenosine receptor and MAPK.[51]

Neurotrophins include nerve growth factor (NGF), brain derived growth factor (BDNF), neurotrophin 3 (NT3) and neurotrophin 4 is a family of small secreted protein which has a role to maintain functional physiological activity of neurons to regulate life, growth, and differentiation of synapse creation, plasticity related to the neuron during growth process.[52–54] NGF is the most abundant neurotrophin, secreted by the nonneural tissue target cell, i.e. skin, muscle, testicle, and salivary

glands.[55] NGF work through two receptor classes, i.e. tropomyosin-related kinase (TrkA) which takes the tyrosine kinase activity at the intracellular domain and p75 neurotrophin (p75NTR) receptor which is the death receptor family.[55] The binding of TrkA and NGF cause phosphorylation of TrkA on the tyrosine residue and kinase activity followed by activation of the MAPK cascade.[56,57] Also phosphatidylinositol 3 kinases (PI3K-Akt) and phospholipase C pathway. This pathway eventually will cause cellular proliferation, differentiation and life activation of p38 at the dorsal root ganglia (DRG) from NGF peripheral production during inflammation process and retrogradely will increase TRPV1 level which contributes to maintaining heat hypersensitivity during inflammation.[58] Further studies show TRPV1 ion channel mediated by NGF cause thermal and mechanical hypersensitivity in mice.[59] TRPV1 mechanism and the oxidative mechanism through NGF permanent effect cause thermal hypersensitivity through peripheral action, spinal and mechanical allodynia through spinal action which needs de novo protein.[60] NGF regulates sensory activity, affects neuronal function through CGRP expression and plays an important role in the ERK5 / CREB signal transduction process during inflammatory pain. In DRG some sensory neurons are peptidergic neurons derived from calcitonin gene-related peptide (CGRP) which is very closely related to NGF.[61] After NGF binds to TrKA on neurons it will activate several pathways simultaneously including the ERK5 / CREB pathway which will increase gene expression and play a role in neural plasticity through BDNF expression. Regulation of BDNF activity through MAPK contributes to persistent inflammatory pain and neuropathic pain.[61–63]

Glutamate is a neurotransmitter produced by primary afferent nerve fibers, it activates postsynaptic glutamate receptor at the dorsal horn of the spinal cord. Inotropic receptor (AMPA, kainate, NMDA) and metabotropic are also expressed at the presynaptic terminal end of the afferent nerve fibers that regulate the production of neurotransmitters.[64] The production of glutamate at the axonic synaptic axon is irrelevant with the GluR presynaptic activity therefore further study is needed to know the presynaptic GluR physiology.[64,65] The NMDA receptors are of NR1, NR2 (A, B, C, D) and NR3 (A,B) subunits which are ionotropic receptors with special attention for its role in excitation synapse transmission and plasticity.[66] Some articles mention that NMDA receptor activation during tissue damage and inflammation will facilitate the process at DRG and spinal cord.[64,67,68] The NMDA receptor at microglia of the spinal cord has a role in the process of peripheral inflammatory pain induced by the venom in mice.[68] NMDA receptors expressed at the DRG participates in the primary afferent neuron excitation modulation which has a role in primary sensitization in inflammation.[69] Inflammation induction with carrageenan will increase the NMDA receptor function in the spinal cord in the nociception transmission.[67] Gene expression regulation by the glutamate receptor will increase the intracellular signaling cascade activation phosphorylation factor through MAPK protein kinase activating mitogen (ERK, JNK, and p38). Some studies show an increase of ERK phosphorylation is an activation response of the NMDA receptor that activation of ERK 5 through the NMDA receptor is a nociception signaling transmission block.[63,70] ERK5 and ERK1/2 regulates cell signaling transduction that is a homolog of ERK/CREB pathway in the DRG and spinal cord has a role in pain hypersensitivity and allodynia after peripheral inflammation.[63]

## CONCLUSION

Pain following tissue damage by mechanical, temperature and chemical stimuli cause an inflammatory response either temporary or permanent. The inflammation mediators released during inflammation response will activate each receptor, ILB activates IL1R1 and TNF activates TBFR1 and TNFR1 followed by activation of some other neuromodulator receptors i.e. adenosine, neurotrophin, and glutamate neurotransmitter. All endogenous substance that activates its own receptor will generate a second messenger which will, in turn, activate some other protein kinases such as protein kinase A (PKA), protein kinase C (PKC), extracellular signal-regulation kinase (ERK) and p38 MAPK and JUN N-terminal kinase (JNK). The kinase activity increases the nociceptor sensitivity and excitability known as peripheral sensitization by a different mechanism, the translational and transcriptional regulation. The activation of protein kinase A and C is temporary through posttranslational regulation while the MAPK activation through posttranslational and transcriptional regulation. The translational and transcriptional regulation through MAPK activation is related to permanent inflammation pain. The activation of each specific nociceptor to the specific MAPK is through a quite complex cross communication. ERK and p38 activated by inflammation mediators at the primary sensory and second-order neuron of the dorsal horn participates in generating and maintaining inflammation pain.

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