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# Pain Sensation Caused by the Activation of Nociceptors

**Barkin R***

*Department of Medicine and Health Sciences, Universiti Sultan Zainal Abidin, Malaysia*

**Abstract**

Fundamentally, pain transmission is strictly dependent on the balance of the excitatory and inhibitory influences that act on the neuron circuits of the somatosensory system. There are multiple levels of CNS involved in the transmission of pain. These include the spinal cord, the brainstem, and the cortical regions.

**Keywords:** Supraspinal; Spinothalamic; Pain; Neurons; Medulla; Stimuli

## Introduction

Typically, the DH of the spinal cord plays a crucial role in integrating multiple inputs entering the spine, including the primary afferent neurons and local interneuron networks, and is also responsible for the descending signals from the supraspinal center. Within the ascending system, primary afferent nociceptors are responsible for conveying the noxious information received to the projection neurons in the DH of the spinal cord. Following that, a subset of these projection neurons in turn transmit these sensory information up to the thalamus reaching the somatosensory cortex through the spinothalamic tract, thus providing information on the intensity and the location of the noxious stimulus. The spinothalamic tract is located in the white matter of spinal cord and consists of two parts, the lateral spinothalamic and anterior spinothalamic tracts, which have different courses of function. The lateral spinothalamic tract focuses on transmission of the pain and temperature sensation, while the anterior spinothalamic tract carries information related to the crude touch and firm pressure sensation towards the thalamus in the brain. Other projection neurons engage the cingulate and insular cortices via the connections in the para-brachial nucleus and the amygdala, hence contributing to the pain experiences. Such ascending information accesses the neurons of the periaqueductal gray and rostral ventral medulla that is found in the midbrain to engage the descending feedback systems, in order to regulate the output from the spinal cord.

## Discussion

The core function of the PAG is to integrate the information received from the higher centres of the brain, including the hypothalamus, amygdala and frontal lobe, as well as receiving the ascending nociceptive input from the DH. The PAG regulates the processing of the nociceptive information in the DH of the spinal cord via the projection neurons to RVM and dorsolateral pontine tegmentum. The endogenous opioid and cannabinoid systems and other neurotransmitters, such as 5-hydroxytryptamine and norepinephrine, are heavily expressed through the PAG/RVM pathways. Typically, pain can be classified into three type nociceptive, neuropathic and inflammatory pain, based on three characteristics, such as symptoms, mechanisms and syndromes. Nociception used interchangeably with nociperception is the response of our bodies' sensory nervous systems towards actual or potentially harmful stimuli. The sensory endings that are activated by such stimuli are known as nociceptors, which are mainly responsible for the first stage of pain sensations. Fundamentally, the Aδ- and C-fibers are two types of primary afferent nociceptors responding to noxious stimuli presented in our bodies. Both these nociceptors have specialized free nerve endings that are widely located in the skin, muscle, joint capsule, bone and some major internal organs [1]. They are functionally used to detect potentially damaging chemical, mechanical and thermal stimuli that might put us in harm's way. The major nociceptive pain can be categorized into two types including visceral somatic pain. Both the Aδ- and C-fibers are mostly found in superficial organs, such as the skin, whereas other deep somatic structures, such as muscles and joints, are mainly supplied with C-fibers. Aδ-fibers are activated under thermal or mechanical stimuli and result in a short-lasting-pricking type of pain sensation. However, the activation of C-fibers is stimulated by thermal, mechanical or chemical stimuli, which often results in poor localization and dull pain sensation [2]. There are three major roles for the receptors in the primary afferent neurons, which are excitatory, sensitizing and inhibitory response. Once these receptors are being stimulated and have reached the pain threshold, the resulting impulses are propagated along the afferent fibers towards the DH and medulla. On top of that, there is an additional nociceptor known as silent nociceptors. Silent nociceptors are located within the viscera and these afferent nerve fibres have no terminal morphological specializations without responses to noxious stimuli, but can only be sensitized by the chemical mediators produced during inflammatory reactions. Neuropathic pain is commonly described as a nerve injury or nerve impairment and is often associated with allodynia. Alloydnia is a central pain sensitization that is a result of repetitive non-painful stimulation of the receptors. It triggers a pain response from a stimulus that is deemed as non-painful in normal conditions, due to sensitization process from said repetitive stimulation. This condition can be described as pathologic pain, because neuropathic pain actually serves no purpose in terms of defense system for our body, and the pain could be in the form of continuous sensation or episodic incidents. The major causes of this type of pain could be primarily due to inflammation or metabolic diseases, such as diabetes, trauma, toxins, tumors, primary neurological diseases and herpes zoster infection. The central sensitization plays a rather important role in this process [3]. Neuropathic pain can be caused by the damage of the nerve, affecting the somatosensory nervous system, and may be generated by the disorders of the PNS or CNS. The neurochemistry of the damaged

***Corresponding author:** Barkin R, Department of Medicine and Health Sciences, Universiti Sultan Zainal Abidin, Malaysia, Tel: 01 096658236, E-mail: barkin@gmail.com

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axons can be altered due to the initiations of complex reaction upon compression, stretching, or transaction of the periphery nerves, followed by a spontaneous hyper-excitability on the site. During neuropathic pain, nociceptors demonstrate a dynamic expression of ion channels, such as Nav channels [4]. In fact, Nav channels are the major channels in regulation of the neuronal excitability, initiation and propagation of the action potentials. The Na+ current in the dorsal root ganglion can be classified into three types, namely, fast tetrodotoxin-sensitive, slow tetrodotoxin-resistant with high-activation thresholds and persistent TTX-R with lower activation thresholds. TTX is a potent neurotoxin and acts as a Nav channel blocker whereby its binding with the Nav channels inhibits the firing of action potentials generated in the neurons. Inflammation is a natural biological response produced by the tissues within our body as a reaction to the harmful stimuli in order to eradicate the necrotic cells and initiate the tissue repairing process. Neutrophils are usually the first respondents of an inflammatory response and gather at the site of injury via the bloodstream, followed by the release of other chemical mediators. Inflammation may lead to three major responses: hyperalgesia, allodynia and sympathetic maintained pain [5]. An inflammation can also induce mast cell degranulation, which subsequently leads to the release of platelet activating factor and stimulates the release of 5-HT from the circulating platelet [6]. The cardinal signs of inflammation include the hot inflamed site due to increase in blood flow towards the region, redness, and swelling due to vascular permeability pain caused by the activation and sensitization of primary afferent neurons and lasting loss of function. The localized inflammatory response then induce the release of free arachidonic acid from the phospholipids, which are converted into prostaglandins via the cyclooxygenase pathways. Pain from inflammation can be further classified into two types, chronic and acute pain [7]. Acute inflammatory pain is normally intense and occurs for a short period of time, which is initiated as a response to harmful stimuli that are normally mediated by the Aδ-fibers. Leukocytes and plasma from the bloodstream are accumulated at the site of the injury to assist in the inflammatory process. However, prolonged inflammation, better known as chronic inflammatory pain, lasts beyond the expected period of healing, which is typically mediated by C-fibers. There is a progressive shift of mononuclear cells at the site of the inflammation as well. Inflammatory pain causes the increase of afferent input into the DH of the spinal cord and leads to the development of central sensitization. There are some mediators produced at the site of injured tissue, which include HT, kinins, histamine, nerve growth factors, adenosine triphosphate, PG, glutamate, leukotrienes, nitric oxide, NE and protons [8]. During the process of inflammation, these chemical inflammatory mediators are produced from the necrotic tissues, and interact to activate the nociceptors within the inflamed area. Arthritis in layman terms can be defined as joint inflammation. The major causes of arthritis include bone erosion, formation of new bones, synovial hyperplasia, ankylosis of the joint and infiltration of inflammatory cells. The cardinal signs involved include redness, swelling, hotness, and large reduction in the range of motion of the affected joints. There are currently more than a hundred types of arthritis at patients suffer from. Among them, osteoarthritis, rheumatoid arthritis and gout are easily described as the most common type of arthritis reported. Osteoarthritis often occurs in patients with advanced age due to the degeneration of joint cartilage or its underlying bone. Its pain is well-localized and occurs during weight-bearing movement, whereas rheumatoid arthritis is an autoimmune disease of the synovium that leads to polyarthritic conditions [9]. It commonly affects our hands or feet. Gout is one of the most painful forms of arthritis, which is caused by the persistent elevation of uric acid in the bloodstream, leading to significant presence of crystal formation in the joints, tendons and surrounding tissues. It commonly occurs in those who are regularly consuming red meat and beer. Along with the inflammation of joints, pain is an accompanying factor in patients suffering from arthritis, especially during movements due to its restrictions. Hyperalgesia is a natural phenomenon that refers to tenderness or lowered threshold to the thermal or mechanical stimulation-induced pain [10]. This results in an enhanced perception of pain at the site of injury. The pain messengers, such as cytokines and chemokines, are distributed to chemical receptors at and around the trauma site to cover a larger area than the actual injured region. PG is the major component for sensitizing procedure of the nociceptors. Due to pain messengers attaching to receptors around the injury site, it causes the sensitization of the adjacent uninjured tissue to the mechanical stimuli, which is commonly known as secondary hyperalgesia or allodynia.

## Conclusion

In conclusion, Although many have long been believed that opioids are the strongest pain medications and should be used for more severe pain, scientific literature does not support that belief. There are many other treatments that should be utilized for treating pain. Studies have shown NSAIDs are just as strong as the opioids.

### Acknowledgement

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### Conflict of Interest

None

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