Mini Review

Neural Mechanisms of Nociception

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Abstract

The pain is a kind of perception which involves several physiological phenomena. Many stimuli are capable to generate activation of nociceptors, in other words, they active specialized neurons that interpret the dangerous signals to the organism. In sense, several mediators participate of the impulses conducting processes, such as glutamate and P substance. In this work, we give a brief insight into the main physiological neural mechanisms involved in the nociceptive process.

INTRODUCTION

The pain is defined as a type of perception related to tissues damages which constitute an alert signal for the protection of own organism. It can be classified in nociceptive and neuropathic [1,2]. Nociceptive pain is mediated by physiological activation of receptors related to osseous, muscle, and/or ligamental tissues. In another hand, neuropathic pain is the most debilitating, it occurs as a consequence of traumas, infection, or diseases related to peripheral nerves, resulting in abnormal activation of the nociceptive pathway [2,3].

Neural processing and conditioning system of stimuli that lead to the painful sensation is called nociception [1]. This mechanism acts to ensure the physical integrity of the organism since it prevents the organism from damaging tissues by harmful stimuli [4,5]. The processes that originate the painful perception comprise the transduction, that is, the transformation of the harmful stimuli in neural message through nociceptors; the conduction, it is the transmission of painful stimuli to the central nervous system; and the transmission, that is the passage of information between neurons. In addition, all these functions are modulated by excitatory or facilitatory interneurons in the modulation process and, finally, the perception [4]. Based on these, this review manuscript gives highlights into main neural mechanisms involved in the nociceptive process.

DISCUSSION & CONCLUSION

Painful stimulus and the role of nociceptors

A variety of mechanical, chemical, physical, and even intense heat or cold stimuli have the ability to produce a harmful effect on the body through the activation of nociceptive pathways through of nociceptors [5]. These nociceptors are sensory neurons that have characteristics other than mechanoreceptive and proprioceptive neurons and can be classified according to their diameter, quantity of myelination or their speed of impulse conduction (fast or slow) [5,6].

These specialized neurons involved in the nociceptive phenomena are type 1 tyrosine kinase, they have cell bodies and are typically classified into two groups: Myelinated (Aδ fiber) with fast conduction which are related to the first phase of pain, fast and strong; Non-myelinated (C-fibers) with slow-conducting, they are responsible for the second, more diffuse and persistent phase of pain. In addition, a small number of nociceptors acts in response to excessive heat, chemical, mechanical, called polymodal type C fibers [7-9].

Several substances mediate the sensibilization of nociceptors, such as those generated in inflammatory damages, such as bradykinín, arachidonic acid, extracellular protons, serotonin, and lipid metabolic. The sensitized nociceptors are capable of generating an inflammatory process, known as neurogenic inflammation, where peptides and neurotransmitters (e.g., P substance, a peptide related to the calcitonin gene and ATP) are capable of inducing cellular activation, such as mast cells and neutrophils in the vascular system [6]. Inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor α also play an important role in the nociceptive process, since they mediate the activation of type 2 cyclooxygenase (COX-2), which promote the formation of prostaglandins capable of sensitizing the nociceptors in the C-fibers, reducing the threshold of nociception and increasing the excitability of the membrane, a phenomenon known as hyperalgesia [10].

Bujalska-Zadrozny and coauthors (2013), have investigated the effects of the administration of high dose of bradykinín, one of the mediators which exert their effects on metabotropic receptors (B1 and B2), present in various tissues, including nociceptive neurons when administered either intrathecally...
or intracerebroventriculally. The results of these studies demonstrated that bradykinin (when administered in high doses) was able to induce supraspinal analgesia [11].

**Pain modulation and transmission**

Sensory messages captured by the peripheral afferent pathway are transmitted as action potential by primary afferent fibers into the spinal cord [12]. Most nociceptors end in the dorsal horn of the spinal cord, with the exception of the trigeminal nociceptors, which are responsible for innervating facial areas that end in the medullary dorsal horn [13]. These nociceptive neurons release glutamate, ATP, P substance, peptide related to the gene calcitonin, and galanin that can mediate synaptic transmission in the dorsal horn by action in AMPA receptors, such as glutamate, or even promote peripheral action, such as P substance, producing neurogenic inflammation, as previously mentioned [14].

The dorsal horn is a region rich in interneurons that are responsible for the balance between excitation and neuronal inhibition, in sense, the neurotransmitter GABA plays an inhibitory role on the afferent neurons. From this region, the ascending neurons travel through the spinothalamic tracts and perform synapses in the parabrachial area and thalamus, where several other regions are activated, such as the somatosensory cortex, anterior cingulate, prefrontal cortex (PFC), and amygdala [13]. The region of the midbrain called the periaqueductal gray receives impulses from various brain regions, such as the amygdala, cortex, and hypothalamus, and it is responsible for controlling activity of neurons located mainly in the rostroventral medullary (RVM), that have a projection to dorsal and the lateral horns of the spinal cord, where they control the nociceptive autonomic information [12]. Thus, neurotransmitter serotonin and encephalin perform the inhibitory function of the pathway.

Nealon and coauthors (2017) recently investigated the effects of a high fat and sucrose diet (HED) on female and male mice. The data generated showed that the females were less sensitive to the analgesic effects of morphine. On the other hand, HED-fed males are resistant to the acute hypothermic effects of morphine, since the females were less sensitive to the analgesic effects of morphine. The results demonstrated that submission to HED is capable of altering the nociceptive signaling pathway in order to decrease morphine analgesia towards inflammatory pain and that the type of diet may influence the hypothermia associated with morphine treatment [15].

Finally, we have concluded that the pain is a subjective perception in response to harmful events. The coding and processing phenomena from the neural circuits involved in the interpretation of painful stimulus are called nociception. Additionally, several chemical mediators integrate the inflammatory process and transmission from the neurons to the superior neural pathways, such as bradykinin, P substance, and glutamate, induce or inhibit the analgesia. Finally, the pathways of neural transmission that integrate the nociceptive circuits are quite complex, which makes it a challenge to understand the physiological phenomena.

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**REFERENCES**