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Association of inflammatory mediators with pain perception

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ABSTRACT

Treatment of pain has always been a major goal in the clinic, as it is related to several pathological conditions of inflammatory origin and surgical procedures, which are associated with inflammatory mediators. Understanding the molecular mechanisms underlying the association between inflammatory mediators and pain perception, from peripheral to central sensitization, can provide the basis for the development of new pharmacological treatments. Despite safety concerns, till date, the use of non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to be efficacious, safe, and well tolerated by patients. Thus, choosing the appropriate administration route, developing new formulations and lowering the efficacious dose represent, currently, effective means of treating inflammation and relieving the pain, without inducing significant side effects.

1. Introduction

Inflammation is a process that has been well studied since ancient times. It is characterized by five typical signs: *rubor* (redness), *calor* (increased heat), *tumor* (swelling), *dolor* (pain), and *functio laesa* (loss of function). The first four signs were described by Celsus in the 1st century AD, while the fifth was added in 1871 by Virkow [1]. There has been considerable progress in our understanding of the cellular and molecular mechanisms of inflammation in the late 20th century. It has been revealed that inflammation is not just a sum of clinical signs, but a complex network of integrated signals between immune cells and injured tissues. Inflammation can be systemic (when it is caused by a trauma, surgery or severe infection) or local (when it is caused by an external injury). Pain is always associated with the region where the inflammation is localized. The detection of noxious stimuli, which is known as nociception, and the transmission of these stimuli to the brain lies at the basis of the pain. Primary afferent neurons can detect noxious chemical, thermal and mechanical stimuli, and the cell body of these neurons reside in the trigeminal and dorsal root ganglion (DRG). During the inflammatory process, the responses to noxious stimuli are enhanced (hyperalgesia) or pain is triggered by normal innocuous stimuli (allodynia). Sometimes, the pain becomes chronic if the inflammation is not promptly resolved. Moreover, it can persist even after the injury that causes the inflammation is healed. The hypersensitive state that underlies inflammatory pain is partially dependent on the plasticity of the nervous system, as a mechanism of adaptation to the nociceptive stimulus [2,3]. Such modifications include both post-translational changes and transcription-dependent changes, which all result in modification of the nociceptive pathway.

Although several molecular mechanisms underlying the inflammatory process have been revealed, some of them still remain to be elucidated. Once these mechanisms are elucidated, more molecules that are involved in the inflammatory process may be identified as targets of specific drugs, which could be used to resolve inflammation as well as relieve the associated pain.

A number of drugs are used to treat inflammatory pain, and there are several new drugs that are being developed. This review focuses on the molecular mechanisms that link inflammation to pain and on the treatment methods that are currently in use.

2. The nociceptive system

The nociceptive system contains neurons that are activated by noxious stimuli, such as mechanical, thermal and chemical stimuli. The primary nociceptive neurons are cutaneous nociceptors that are found at the terminals of Aδ and C-fibres, which are thinly- and un-myelinated fibres, respectively. Peripheral afferent signals convey nociceptive stimuli to the grey matter of the dorsal horn in the spinal cord and if these stimuli persist, the C-fibres increase synaptic conduction in the dorsal root neurons, thus sensitizing the central nervous system. Some of these neurons project to the brain stem or to the thalamocortical system and this consequently leads to a conscious pain response. This central sensitization is essential for the development of hyperalgesia and allodynia and involves activation of the NMDA (*N*-methyl-D-aspartic acid) receptors by glutamate. On the other hand, the descending neural tract that inhibits transmission of the pain signal represents the

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antinociceptive system, and includes opioid peptides, serotonin, norepinephrine and dopamine. These neurotransmitters are released by intermediate neurons within the dorsal horn of the spinal cord, which in turn are activated by the opioid and GABAergic mechanism of the periacqueductal gray region [4,5].

3. Inflammation, pain and cytokines

The inflammatory pathway is typically triggered by a peripheral trauma or injury. This is accompanied by the release of arachidonic acid, which is subsequently converted to prostanoids by cyclo-oxigenase enzymes (COXs). COX-2 is the predominant isoform of COX, but it is not an exclusive source of prostaglandins, which are constitutively expressed in the brain and induced in injured tissues by IL-1β, TNF-α and IL-6 [6,7]. COX-1 is the major source of prostanoids that mediate physiological functions, but it may also be involved in pathological processes [8]. COX-2 transforms arachidonic acid into prostaglandin E2 (PGE2) [7]. PGE2 promotes local vasodilation and the activation and migration of neutrophils, macrophages and mast cells, and it can directly trigger nociceptors *via* the prostaglandin E (EP) receptors [9]. PGE2 is generally considered to be a sensitizing agent because it (i) enhances the sensitization of nociceptors by lowering the threshold of the tetrodoxin-resistant sodium channels, (ii) modulates the transient receptor potential vanilloid (TRPV) 1 channel for heat sensation, and (iii) sensitizes primary afferent neurons (peripheral sensitization) to bradykinin [10–14]. Bradykinin, which is released by mast cells and damaged tissues, binds to receptors located in all tissues, including the bradykinin 2 receptors that are constitutively expressed on neurons, such as the polymodal C-nociceptors [15]. As a consequence, the heat threshold is lowered, which causes the long-lasting pain associated with inflammation. In addition, the central production of PGE is believed to be the cause of fever. Studies on conditional *COX-2*-knockout mice have revealed important findings on the role of COX-2 in mediating pain. For example, Vardeh et al. demonstrated that when COX-2 is present at the site of inflammation, it plays a role in hypersensitivity to both mechanical and thermal pain after peripheral inflammation, while neural COX-2 contributes only to mechanical pain [16]. Since mechanical pain is the main symptom of postoperative pain and diseases such as arthritis, drugs that inhibit COX-2 can directly exert their effects on pain that has a mechanical origin. In the neuropatic pain, the up-regulation of COX2 and PGE2 is involved in the functions of EP-receptor bearing primary sensory neurons, thus contributing to the development of chronic pain, *via de novo* synthesis of pain mediators, such as IL-6 and BDNF [17]. BDNF contributes to the central sensitization of dorsal horn nociceptive neurons and it is also induced by inflammatory stimuli [18]. Furthermore, it has been recently demonstrated that the concentration of BDNF is increased in the anterior cingulated cortex (ACC) during peripheral inflammation, and that this is sufficient to induce certain plastic changes. ACC is believed to be important in the anticipation of a painful stimulus, so BDNF could be considered as a facilitator of pain and as a contributor to the mechanisms underlying chronic pain [19].

Immune cells together with glia and neurons constitute an integrated network in which an immune response triggered by an inflammatory stimulus modulates the resulting pain. The interaction between immune cells and glial cells characterizes the neuroinflammation, in which release of inflammatory mediators has a critical role in the pathogenesis of chronic pain [20]. Immune cells are recruited at the site of inflammation, and their activation leads to the release of pro-inflammatory mediators such as cytokines and chemokines. Moreover, degranulation of resident mast cells is involved in triggering nociception, both *via* direct interaction with the peripheral nerve terminals through the cell adhesion molecule N-caderin, and indirectly *via* the release of histamine, bradykinin and other vasodilating mediators. In addition, mast cell degranulation leads to the rapid onset of nerve growth factor-induced hyperalgesia [21]. Interestingly, it was very recently postulated that the cross-talk between mast cells and nerves may be bi-directional [22].

Certain proinflammatory cytokines, such as TNF-α, IL-6 and IL-1β, play a direct role in the generation and maintenance of pain, facilitating central sensitization and hyperalgesia. Nociceptive neurons possess receptors for these cytokines on their surface, and neutralization of these cytokines may result in quick reduction of the pain before the attenuation of inflammation. These cytokines are released by activated macrophages, T lymphocytes and mast cells, both systemically and locally at the site of inflammation. Several works have demonstrated that TNF-α is an initiator of neuropathic pain, and that intratecal injection of exogenous TNF-α has a pro-nociceptive effect [23,24]. In addition, impairment of TNF-α signaling attenuates hypersensitivity in rodent models of neuropathy [25].

IL-6 is a cytokine that transfers peripheral immune signals to the CNS [26]. IL-6 has been shown to play an important role in the neuropathic pain following nerve injury, and the administration of anti-IL-6 antibody significantly attenuates mechanical allodynia [27,28]. However, it seems to play a dual role, since IL-6-deficient mice show increased levels of cartilage loss in a spontaneous model of osteoarthritis [29]. Very recently, another cytokine, IL-17, released by specialized CD4+ T cells, was found in the spinal dorsal horn in a rat model of spinal nerve ligation, together with IL-1β and IL-6; these factors are believed to contribute to the development of neuropathic pain [30].

IL-1β is the first cytokine involved in peripheral nerve injury [31]. Its expression increases in a variety of autoimmune diseases in which pain is a main feature, and it is largely produced by glial cells and upregulated after peripheral nerve injury [23,32,33]. IL-1β has the ability to induce the expression of other pro-inflammatory factors that together contribute to the induction and maintenance of pain. The mechanism of its upregulation was recently discovered in the inflammasome, a multiprotein complex that, upon oligomerization, induces activation of pro-caspase1, initiating the processing of pro-IL-1β. Different inflammasomes are recruited in various diseases, ranging from neuropathic pain to infectious and autoimmune diseases, and they might be possible targets of pharmacological interventions for pain relief [34].

Interestingly, cytokines have been implicated in the cross-talk between the immune system and the brain: stress conditions induce the release of peripheral cytokines, which act on the endothelial cells of the blood-brain barrier, and activate microglia, which release pro-inflammatory cytokines [35]. Activation of microglia has been implicated in the regulation of mood and behaviour after prolonged exposure to psychological stress [36]. Psycological stress is a condition that causes activation of the neuroendocrine pathways towards the periphery that ultimately leads to the release of glucocorticoids by the hypothalamic-pituitary-adrenal (HPA) axis. The very well known modulation of the immune system by glucocorticoids includes changes in cellular trafficking, cytokine secretion, antibody production, and activation and proliferation of immune cells. An acute response to stress stimulates the immune system to react, while a prolonged one causes anti-inflammatory effects and immunosuppression. Therefore, glucocorticoids represent a fundamental link between the nervous system and the control of inflammation [37–39].

During an infection, as a result of activation of the immune response and release of pro-inflammatory cytokines, the body undergoes certain changes and exhibits sickness behavior. This sickness behavior is also observed in the early onset of major depression, which may indicate that these immunoinflammatory pathways are involved in the pathophysiology of major depression [40,41]. There is some interesting literature linking inflammation, pain and depression, but so far, anti-inflammatory drugs have not proven useful for the treatment of depression [42,43].

Bacterial infections activate the immune system, thus inducing inflammation and consequently triggering the nociceptive pathways. This is an indirect effect that indicates the correlation of infection with pain.