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Morphine at inflammatory experimental pain: A review

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Abstract

Pain is a complex entity that can be described in several dimensions, such as, acute pain and chronic pain, characterized by its duration. After the tissue injury, the activation of the sensory nervous tissue occurs from where the different pro-inflammatory mediators are released with the consequent nociceptive transmission that characterizes the genesis of inflammatory pain. The main objective of this study was to review the role of the opioid system, using morphine and MOR opioid receptors as paradigm, in the antinociceptive modulation of inflammatory pain, by means of the formalin test as a model. Various pieces of evidence are compiled that establish the fundamental role of morphine in the inflammatory pain. Morphine has noticeable antinociceptive efficacy in to decrease the inflammatory pain. This review demonstrates the fundamental role that morphine plays in inflammatory pain states and that it could serve as the basis for a new pharmacotherapy of inflammatory pain.

Keywords: Morphine; Formalin assay; Inflammatory pain; Glia

1. Introduction

Pain is a complex entity that can be described in several dimensions, such as, acute pain and chronic pain, characterized by its duration. It is also described by the noxa that causes it, such as nociceptive, inflammatory, neuropathic and idiopathic pain, both being first of short duration (phasic pain) and the others of significantly longer duration (tonic pain). Animal nocifensive or algesimeter tests use electrical, thermal, mechanical, or chemical stimuli to assess pain and, at the same time, preclinically, analgesic or antinociceptive drugs.

2. Formalin test

In this test, the intradermal administration of formalin produces a biphasic nocifensive reaction, with an initial phase within the first 5-10 minutes after injection, followed by a period of rest (sensitization) of around 10 min and a second phase of nociceptive behavioural lasting 20-40 min. The first phase is related to the direct stimulation of nociceptors such as C fibers and mechanoreceptors and the positive regulation of substance P. The second phase involves both the inflammatory mechanisms and the central sensitization within the neurons of the dorsal horn with positive regulation of the bradykinin. serotonin, histamine, prostaglandin and NO [1-7].

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The several pain models used in the nociceptive tests allow us to obtain useful data at the preclinical level. The formalin test is a widely used inflammatory pain model since the chemical agent induces the release of inflammatory mediators that activate and sensitize the nociceptive system [8]. The method causes a biphasic pattern of pain behaviour, with an acute pain phase followed by an inflammatory pain phase.

3. Inflammatory pain

The release of inflammatory mediators by activated nociceptors or other non-neuronal cells from the injured area has been revised early by Basbaum (2009) and includes serotonin, histamine, glutamate, ATP, adenosine, substance P, calcitonin gene-related peptide (CGRP), bradykinin, eicosanoids, prostaglandins, thromboxanes, leukotrienes, endocannabinoids, nerve growth factor (NGF), proinflammatory cytokines (TNF-α, IL-1α, IL-1β, and IL-6), extracellular proteases and protons. The different mediators released bind to nociceptor receptors such as G-protein-coupled (GPCR), ionic receptors transient potential channel (TRP), acid-sensitive ion channels (ASICs), two-pore potassium channels (K2P), and receptor tyrosine kinases (RTK) [9].

Another area of intense research is the role of spinal microglia, which has been shown to modulate neuronal excitability after nerve injury and contribute to pathological pain. In such a way that the classic neuronal approach to pain has been joined by the contribution of the glia, especially the microglia and astrocytes, in their liberating function of pro-inflammatory pain mediators, as represented in Figure 1.

There is evidence that in the neural mechanisms of inflammatory pain, the mediator PGE2 contributes substantially to pain sensitization through activation of TRPV-1 and TTX-resistant Na + channels. In addition, the PGE2 produced by COX-2 at the spinal level is expressed by peripheral activation of pro-inflammatory cytokines, such as interleukins [10,11].

It is necessary to specify that the activation of mediators in the glia, such as the purinergic receptor P2X4R, in lymphocytes and macrophages, releases proalgogenic factors such as IL-6, IL-10, ROS together with the increase in the expression levels of phospholipase A2 (PLA2) and prostaglandin E2. (PGE2), which leads to the induction of inflammatory pain. Thus, the activation of P2X4R modifies neuronal excitability by increasing pain transmission, which represents a decisive factor, compared to other types of pain, in the genesis of pain. The previous antecedents demonstrate the importance of P2X4R in this type of pain and could constitute a potential promising new alternative for the treatment of inflammatory pain [12].

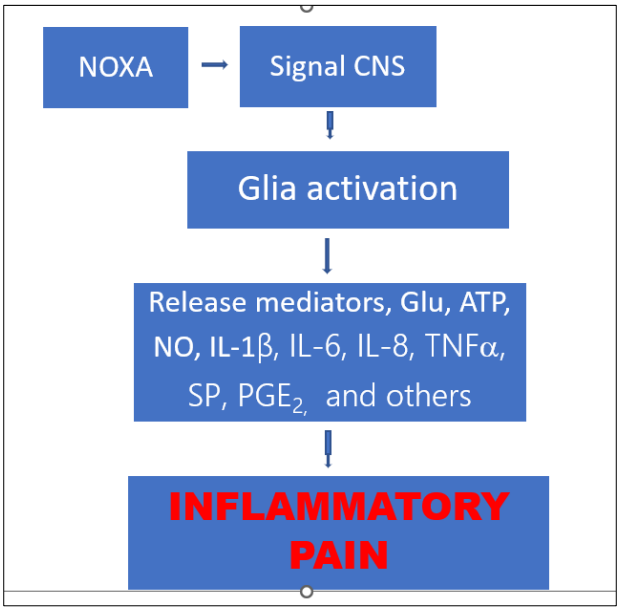

Figure 1 Suggested algorithm of the action of glia modulators in pain. glutamate (Glu), tumour necrosis factor α (TNFα), interleukin 1β (IL-1β), IL-6, IL-8, nitric oxide (NO), substance P (SP) and prostaglandin E2 (PGE2)

4. Morphine

Among the different therapeutic regimens for pain, opioids are frequently used for the treatment of acute pain, taking into account their effectiveness and availability, however, there are few reviews that provide complete and detailed information on their use, especially in pain inflammatory. The expression of opioid receptors in the glia has been little investigated and the findings, primarily concentrated in MOR receptors, have been contradictory. In rodents, no MOR RNA was detected, in microglia and astrocytes of the spinal cord or nucleus accumbens, using different techniques (in situ hybridization, quantitative polymerase chain reaction, transcriptomic profile of microglia, double immunofluorescence) [13]. In divergence, other studies have identified MOR receptors in human and rodent microglia. However, with double labelling of glial cell antibodies and MOR receptors, MOR receptors were detected in rodents, but without convincing staining specificity. The evaluation of the presence, in the glia, of MOR receptors such as DOR, KOR and NOR, requires further studies. [14-15]. It is known that opioids bind and potently activate all opioid receptor subtypes, associated with which actions appear that alter the activity of glial cells associating with other receptors such as purinergic receptors, the toll-like receptor 4 (TLR4) [16,17].

It is widely known that opioids are the drugs of choice for the treatment of acute and chronic pain, despite the severe adverse reactions caused by prolonged use. One of the drugs most used clinically in pain therapy is morphine, which is the paradigmatic agonist of MOR, but which also has activity in DOR and KOR as well as in other receptors. In addition, it is frequently used as a point of comparison for other analgesic drugs. Activation of MOR not only induces analgesia, but also side effects such as constipation, bradycardia, nausea, vomiting, urinary retention, itching, respiratory depression, muscle stiffness, miosis, dysphoria, and others that produce abuse [18,19]. Opioid receptors are essential in the induction of analgesia and present the following distribution in the spinal cord of rodents, around 75% MOR, 25% DOR and 5% KOR. Similar distribution has been suggested in man. MOR, DOR, and KOR opioid receptor agonists reduce, at supraspinal, spinal, and peripheral levels, the release of various mediators that contribute to the transmission of inflammatory pain. Consequently, it is accepted that opioids produce analgesia by reducing central and peripheral sensitization [20].

The analgesic efficacy of opioids, especially morphine, in experimental inflammatory pain has not been extensively investigated. One reason could be that there are no suitable models that can potentially mimic all the symptoms of human inflammatory pain. Here are some findings, obtained with morphine, in a preclinical animal model of tonic pain induced by a chemical stimulus, the formalin test, since it has been demonstrated that the assay is sensitivity to central analgesic drugs [21].

It is possible to evidence a vast number of preclinical trials related to the use of formalin, related to its pharmacokinetic and pharmacodynamic topics and carried out predominantly in rodents. Among them, in addition to the contributions summarized in [1,2,3], mention should be made of the standardization of the evaluation of analgesics in the test [22] and a similar validation of the test in mice [23]. The demonstration that both phases of the formalin test depend on the activation of primary afferents and that the second phase cannot be mediated by central sensitization alone [24]. The results indicate that the two phases of the formalin test have different properties. They suggest modulation by substance P and bradykinin for phase I and for phase II the participation of PGs, histamine, and 5-HT [25]. Also, it was shown that in the formalin test there is an increase in plasma levels of ACTH, beta-endorphin, corticosterone, and IL-6 [26]. At the same time, the use of the formalin test in the orofacial route was reported [27]. In addition, it was reported that ssubcutaneous injection of formalin on the dorsal surface of the hind paw was shown to produce biphasic pain in which NSAIDs have a powerful effect on the nociceptive process. Furthermore, the ultrashort-acting opioid, remifentanil was suggested to activate peripheral opioid receptors to prevent the synthesis and / or release of formalin-evoked pro-inflammatory compounds [28].

Morphine is an opioid frequently used in the therapy of both moderate and severe pain. However, its use in the treatment of inflammatory pain is controversial, mainly due to its safety, its effectiveness and its side effects. The present study analyses the effect of an opioid, morphine in a preclinical model of pain, the inflammatory one induced by the administration of formalin where Phase I is considered as acute nociceptive and phase II as inflammatory [29].

Pain control by morphine opioid analgesia is a complex system that is mediated by neural pathways, receptors and mediators, being the activation of MOR opioid receptors at multiple sites, in the CNS and PNS, responsible for analgesia, although the exact sites of the MORs and the circuits responsible for this effect are not entirely clear. However, various studies have shown that morphine-activated receptors on primary sensory neurons are essential for inflammatory pain. Besides, it was found that the analgesia of MOR-induced inflammatory pain is mediated by vesicular glutamate transporter 2 (VgluT2) neurons but not GABAergic. [30]. In addition, it has been reported that among the various pharmacological actions, morphine, by activating the MOR receptors of microglial cells, increases the release of pro-

inflammatory cytokines, IL-1β, TNF-α, IL-6 and also NO [31]. An analytical study of the various effects of morphine in the formalin assay demonstrated a significant separation between the doses that induce analgesic effects (40 mg/kg) and affective effects (10 mg / kg). The results suggest different mechanisms involved in the effects of morphine [32].

On the other side, cannabinoid receptors are grouped into 2 families, CB1R, located mainly centrally and CB2R, it is expressed in peripheral tissues and regulates inflammatory responses. Later, through an isobolographic analysis study between a CB2R agonist and morphine, it was established that the CB2R receptor modulates the analgesia produced by the activation of the MOR receptor in the formalin assay [33-35].

There is information that the administration of morphine produces the analgesic effect in the formalin test involving the mesencephalic serotonergic system through the $5HT_{1A}$ receptor [36]. It is important to consider that there are certain stress factors generated in morphine-induced analgesia such as the generation of nitric oxide (NO) and oxidative stress (OS).

The explanation for the adverse effects of morphine analgesia is related to the opioid-induced modulation of the TRPM2 channel, a Ca^{+2} permeable cation channels, sensitive to oxidative stress and highly expressed in microglial cells. The findings confirmed that TRPM2 inhibition can modulate morphine-induced neurodegeneration of pro-inflammatory mediators [37].

In addition, it has been shown that morphine induces the activation of microglia through the toll-like receptor 4 (TLR4), which is a mediator of danger signals or damage-associated molecular patterns (DAMPs) that produce an adequate or efficient biological response [16].

It has been described that the sigma-1 receptor, of the endoplasmic reticulum, which regulates calcium function, has an important role in the control of morphine analgesia, both in nociceptive and inflammatory pain [38].

Venlafaxine is an antidepressant from the group of selective serotonin and norepinephrine reuptake inhibitors (SSRIs). Coadministration of venlafaxine with morphine reduced levels of TNF-α, IL-1β, IL-6, NO, and MDA in mouse brain tissue. These results suggest the possibility of using venlafaxine as a coadjuvant or co-analgesic to morphine in inflammatory pain [39].

A surprisingly dissimilar point among the effect of morphine activation on microglia is the one described above that by activating the MOR receptors of microglial cells, it increases the release of pro-inflammatory cytokines, IL-1β, TNF-α, IL-6, and also NO [31]. The fact that morphine could directly activate the TRL4 receptor for the production of pro-inflammatory cytokines is reflected in the maintenance of inflammation and decreased analgesia. The results indicate a significant difference of morphine in cytokine production between the CNS and the periphery. They also collaborate with the explanation of the passage from acute to chronic pain [40,41].

5. Conclusion

The complex mechanisms underlying pain have been characterized, in their different degrees of modulation, with the help of receptors, mediators, and pathways. These advances in the sensitivity of nociceptive neurons are expressed in this work associated with inflammatory pain and its relationship with morphine. The morphine interactions described in this review are closely associated with the known release of inflammatory mediators from cells damaged by a pain stimulus. They can occur to one or more levels of cellular function with the participation of receptors, ion channels, cytokines, or others. These interactions would be dependent on the local concentration of morphine and the concentration of applied formalin.

Morphine has antinociceptive efficacy so it can provide pain relief and this study presents evidence of an effective action to relieve inflammatory pain.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

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Authors' contributions

All authors contributed equally in preparing all parts of the work and approved the version submitted for revision.

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