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OBM Integrative and Complementary Medicine

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Editorial

Neuroinflammation in Chronic Pain, Treatment with Topical and Nontraditional Therapies

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Special Issue: Topical Treatment of Pain: Perspectives on Complementary, Traditional, and Plant Medicine

OBM Integrative and Complementary Medicine
2025, volume 10, issue 1
doi:10.21926/obm.icm.2501010

Received: February 09, 2025
Accepted: February 09, 2025
Published: February 10, 2025

Abstract

Medicines used in pain and chronic pain are aimed at relieving neuroinflammation. This neuroinflammation can occur in the brain, brain stem, dorsal root ganglion and other sites. What causes neuroinflammation? Why does this neuroinflammation last for years? Are there cures for neuroinflammation?

1. Introduction

The brain and brain stem participate in chronic pain. Neuroinflammation in the brain and brain stem have been extensively studied in models of chronic pain [1]. Usually, an initial painful stimulus leads to chronic pain. Although depression is associated with pain that may not have an initial painful insult to the body. Chronic pain can be, in part, a learned experience when patients learn how to be in pain all the time [2]. Epigenetic mechanisms appear to cause or promote neuroinflammation and chronic pain [3]. Microglia and astrocytes become activated in the brain and brain stem [1]. Activation causes them to release cytokines and chemokines that promote widespread pain. What causes this activation that leads to neuroinflammation?

Chemokines are proteins released by many types of cells that act as chemotactic proteins to attract neutrophils, macrophages and other cells [4]. Chemokines also have an important role in pain [5], since they depolarize sensory neurons in the skin, dorsal root ganglion and transactivate transient receptor potential cation channels (TRPs). The chemokine MCP-1 (monocyte chemoattractant protein-1) and its receptor CCR2 are important in pain and chronic pain [6]. Monocytes express cyclooxygenase-2 that makes prostaglandins involved in pain and secrete chemokines that contribute to pain and inflammation [7]. Chemokine receptors are expressed on astrocytes, microglia and neurons in the brain [8]. Stimulation of these brain receptors may cause neuroinflammation and the pain chemokine cycle to be discussed.

2. The Skin during Chronic Pain

An initial painful stimulus usually occurs in the skin and involves activation of sensory neurons and their TRPs in the skin [9, 10]. Sensory neurons also release chemokines following stimulation that attract inflammatory cells such as macrophages and neutrophils to the skin [6]. Macrophages release prostaglandins that induce the phosphorylation of TRPs which enhances and prolongs pain [11]. Damaged keratinocytes release bradykinin that interacts with bradykinin receptors on sensory neurons to increase pain [12]. Bradykinin receptors on macrophages stimulate chemokine release that transactivates TRPs on sensory neurons. Neutrophils are stimulated by chemokines to make more chemokines. Neutrophils also release leukotrienes that induce long term pain by TRP channel activation [13]. Skin resident T cells are stimulated by chemokines to release IL-17 that induces more chemokine production [14]. Chronic pain is caused by the pain chemokine cycle where prostaglandins, bradykinin and chemokines produce pain that induces more chemokine release from neurons, neutrophils and macrophages. Chemokines and IL-17 enhance and prolong pain. Sensory neurons also release neurokinins that induce pain and inflammation at distant sites including the brain [5, 15].

Damage to skin keratinocytes causes these cells to release IL-1β [16]. In addition, TNFα is released by damaged keratinocytes and mast cells [17]. These two factors, IL-1β and TNFα released by skin cells, stimulate astrocytes in the brain to become reactive [18]. This activation initiates the pain chemokine cycle in the brain that can last for years and is the basis of chronic pain.

3. Medications and Pain

The major purpose of opioids, nonsteroidal anti-inflammatory drugs and other pain medicines is to treat pain in the brain and brain stem. This may be a more focused approach than treating the entire skin. None of these medicines cures chronic pain. In fact, they induce chemokine production that exacerbates pain and chronic pain [19], such as opioid induced hyperalgesia [20]. Opioid peptides made in the skin and secreted by immune cells induce chemokine and chemokine receptor synthesis [19]. Nonsteroidal anti-inflammatory drugs also induce chemokine synthesis [21-23]. This is why long-term use of these oral pain medicines enhances chronic pain. These dangerous medicines kill over 150,000 people in the US every year from respiratory depression, seizures, ulcers, heart attacks and strokes.

4. Cures for Chronic Pain

4.1 Exercise

Exercise has been found to diminish and even cure chronic pain [24, 25]. Cure means the pain is gone and does not return, unless a new injury occurs. Regular, daily exercise decreases inflammation and chemokine production [24, 25]. Regular exercise also retrains brain circuits [26] which can cure chronic pain, but not arthritis pain. Exercise, when done regularly, without damaging the body, can inhibit the pain chemokine cycle and stop chronic pain.

4.2 Acupuncture

Acupuncture for arthritis does not cure arthritis, but diminishes the chronic pain associated with arthritis. Acupuncture can cure opioid induced hyperalgesia [27]. Acupuncture inhibits the synthesis and release of some chemokines, such as C-C motif chemokine ligand 2 (CCL2), a chemokine that activates brain microglia [28]. Acupuncture, when administered daily over several weeks, might cure chronic pain by decreasing chemokines and inhibiting neuroinflammation. This should be examined in clinical trials.

4.3 Medicines

A number of medicines have been tested in chronic pain conditions [1]. Etanercept, a TNF deactivator, provided pain relief for several weeks after one injection. Etanercept decreases blood chemokine levels [29]. Naltrexone decreases microglial activation and is effective against fibromyalgia. Naltrexone downregulates the expression of chemokine receptors in the skin [30] and may cure chronic pain. Anakinra, an IL-1 receptor antagonist, decreases chronic pain in an animal model.

The topical application of mixtures of monoterpenoids with or without diterpenoids cures chronic pain in fibromyalgia, whiplash, chronic back pain and bursitis patients [31]. Monoterpenoid application to the skin requires about 5 weeks to cure chronic pain. Applying diterpenoids and monoterpenoids to the skin can cure chronic pain in one week. The chemicals inhibit the production of chemokines in the skin, that are released into the blood and cause neuroinflammation. Pain causes chemokine release which causes more pain, the pain chemokine cycle. This is the basis of chronic pain and can be cured by topical monoterpenoids and diterpenoids [31].

5. Future

Exercise regimens should be designed to cure chronic pain. Doctors should prescribe these regimens and work with physical therapists to train patients to exercise safely and daily. Not every patient will be able to exercise daily, perhaps due to the long-term effects of injuries. For these patients, topical mixtures of monoterpenoids and diterpenoids should be tested in clinical trials until effective mixtures are found that cure chronic pain. These mixtures are safe since the compounds penetrate into the skin, are effective, then evaporate from the skin. They also inhibit the pain chemokine cycle. Acupuncture is very safe and should be tested in long term clinical trials to see if it cures chronic pain. Etanercept and naltrexone may be of interest also but suffer from toxicity problems.

Author Contributions

The author did all the research work for this study.

Competing Interests

The author has declared that no competing interests exist.

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