Chronic pain in the Skin and Neurogenic Inflammation

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Abstract

The treatment of any pain with oral preparations is dangerous and should be replaced by topical preparations or acupuncture. Pain is sensed in the skin, is most effectively and safely treated with topical preparations. Chronic pain is exacerbated in the skin by the pain chemokine cycle. Neurogenic inflammation comes from pain sensed in the skin and increases inflammation throughout the body. Inhibition of skin sensory neuron pain receptors relieves pain and inflammation.

Keywords: Chronic pain; Neurogenic inflammation; Pain; Pain chemokine cycle

Introduction

Most pain is sensed in the skin, even pain from broken bones, cancer, kidney stones and other internal causes [1,2]. This is because internal pain transmitting neurons communicate with pain sensing neurons in the skin that communicate with the brainstem [1,2]. Chronic pain involves a number of inter-related mechanisms in the skin and other areas [3,4]. Many receptors on skin sensory neurons are responsible for sensing pain and prolonging pain, especially Transient Receptor Potential (TRP) cation channels. Many different TRP channels exist on skin sensory neurons. Populations of specific TRP channels are found on different neurons. The pain chemokine cycle in the skin prolongs and worsens chronic pain [5,6].

Damage to or activation of a sensory neuron in the skin causes the release of chemokines that attract neutrophils and macrophages (Figure 1) into the skin [5,6]. Neutrophils secrete leukotrienes that activate TRP channels on skin sensory neurons causing pain [7]. Leukotrienes can have long half-lives, perhaps allowing them to induce pain in many neighboring neurons over a long period of time.

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Sexual Differences in Chronic Pain

There are clear differences in male and female skin, including thickness, response to hormones and macronutrients [9,10]. These differences may be, in part, responsible for the differences reported in acute pain sensation and responses to acute pain between men and women [11]. However, differences in chronic pain between men and women in relation to skin differences have not been adequately explored.

Neurogenic Inflammation

When TRP channels are activated, it causes the release of inflammatory proteins from sensory neurons in the skin, such as Calcitonin Gene-Related Peptide (CGRP), high Mobility Group Box 1 protein (HMGB1), neurokinin A and substance P [12]. This is the basis of neurogenic inflammation. The skin is important in inflammatory diseases such as arthritis and asthma [13].
CGRP released from skin sensory neurons is found at high levels in the synovial fluids of arthritis patients [14]. It is clear that CGRP contributes to the inflammatory process in arthritis. Monoterpenoids that inhibit skin TRP channels may decrease CGRP levels in synovial fluids and may be anti-inflammatory [14]. CGRP also induces pain, contributes to the pain that arthritis patients experience and contributes to chronic pain, which is induced by the pain chemokine cycle [15].

CGRP binds to a G protein coupled receptor called calcitonin receptor-like receptor (CLR) [14]. CLR activity may be greatly magnified by interactions of the receptor with receptor activity modifying protein (RAMP) [14] which contributes to the pain and inflammation induced by CGRP.

HMGB1 is secreted by activated macrophages, such as the monocytes/macrophages attracted to the skin by chemokines during the pain chemokine cycle [16]. HMGB1 interacts with Receptor for Advanced Glycation End products (RAGE), and Toll Like Receptors (TLR2 and 4), to induce the secretion of inflammatory cytokines [17]. Tumor necrosis factor α is a cytokine/adipokine that is involved in the induction of inflammation in arthritis. HMGB1 increases the secretion of tumor necrosis factor α from macrophages [18]. Tumor necrosis factor α can travel to remote sites, such as synovial tissues, to increase inflammation.

Neurokinin A is released by skin sensory neurons and enhances pain and inflammation [19]. There are several neurokinin receptors, NK1R, NK2R and NK3R, which are all G protein coupled receptors [20]. Substance P is another kinin that is released from skin sensory neurons [21]. Substance P also interacts with NK1R, NK2R and NK3R to induce pain and inflammation [21]. It is clear that both neurokinin A and substance P are released from the skin, travel to remote sites and are involved in arthritis and other inflammatory conditions [21].

Conclusion

Chronic pain and chronic inflammation are linked by the process of neurogenic inflammation. An initial inflammation results in skin sensory neuron activation and the release of inflammatory proteins from the neurons that can exacerbate inflammation. Chronic inflammation probably leads to chronic pain and more inflammation. On the other hand, an initial pain can cause the release of inflammatory proteins that may induce inflammation in the body. Chronic pain may cause the chronic release of inflammatory proteins that enhance pain in other sensory neurons and may lead to chronic inflammation.

Osteoarthritis can be caused by adipokine secretion by visceral adipocytes [22]. The adipokines visfatin, leptin, resistin in and tumor necrosis factor α are involved in causing cartilage and bone degradation in osteoarthritis. This degradation leads to pain that is sensed in the skin and establishes the pain chemokine cycle leading to neurogenic inflammation that exacerbates osteoarthritis [3,4].

Treating pain in the skin by inhibiting TRP channels is anti-inflammatory, as has been noted in several case reports [23,24]. Inhibiting skin TRP channels stops the pain chemokine cycle and stops neurogenic inflammation [25]. Effective pain therapy requires a topical preparation that is powerful enough to inhibit a large population of different TRP channels on many different sensory neurons.

References


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