Scandinavian Journal of Pain 6 (2015) 3–6

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Topical review

# Perspectives in Pain Research 2014: Neuroinflammation and glial cell activation: The cause of transition from acute to chronic pain?

Brian E. Cairns[a,b], Lars Arendt-Nielsen[b,*], Paola Sacerdote[c]

[a] Faculty of Pharmaceutical Sciences, University of British Columbia, 2405 Wesbrook Mall, Vancouver, BC, Canada V6T 1Z3
[b] Center for Sensory-Motor Interaction, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Frederik Bajers Vej 7D3, 9220 Aalborg East, Denmark
[c] Dipartimento di Scienze farmacologiche e biomolecolari, Università degli Studi di Milano, Via Vanvitelli 32, 20129 Milano, Italy

## HIGHLIGHTS

- The immune system and the pain system are closely linked.
- Glial cells are activated in the dorsal root ganglion and at the spinal cord.
- Glia cells may cause contralateral spreading and possible widespread sensitisation.
- Opioids may stimulate microglia cells to produce proinflammatory cytokines.

## ARTICLE INFO

*Article history:*
Received 15 May 2014
Received in revised form 21 October 2014
Accepted 22 October 2014
Available online 24 November 2014

*Keywords:*
Neuroinflammation
Chronic pain
Widespread sensitisation
Glia
Cytokines

## ABSTRACT

**Background:** It is unknown why an acute pain condition under various circumstances can transition into a chronic pain condition.

There has been a shift towards neuroinflammation and hence glial cell activations specifically in the dorsal root ganglion and spinal cord as a mechanism possibly driving the transition to chronic pain. This has led to a focus on non-neuronal cells in the peripheral and central nervous system. Besides infiltrating macrophages, Schwann cells and satellite glial cells release cytokines and therefore important mechanisms in the maintenance of pain. Activated Schwann cells, satellite glial cells, microglia, and astrocytes may contribute to pain sensitivity by releasing cytokines leading to altered neuronal function in the direction of sensitisation.

**Aims of this perspective paper:** 1) Highlight the complex but important recent achievement in the area of neuroinflammation and pain at spinal cord level and in the dorsal root ganglion.

2) Encourage further research which hopefully may provide better understanding of new key elements driving the transition from acute to chronic pain.

**Recent results in the area of neuroinflammation and pain:** Following a sciatic nerve injury, local macrophages, and Schwann cells trigger an immune response immediately followed by recruitment of blood-derived immune cells. Schwann cells, active resident, and infiltrating macrophages release proinflammatory cytokines. Proinflammatory cytokines contribute to axonal damage and also stimulate spontaneous nociceptor activity. This results in activation of satellite glial cells leading to an immune response in the dorsal root ganglia driven by macrophages, lymphocytes and satellite cells. The anterograde signalling progresses centrally to activate spinal microglia with possible upregulation of glial-derived proinflammatory/pronociceptive mediators.

An important aspect is extrasegmental spreading sensitisation where bilateral elevations in TNF-α, IL-6, and IL-10 are found in dorsal root ganglion in neuropathic models. Similarly in inflammatory pain models, bilateral up regulation occurs for TNF-α, IL-1β, and p38 MAPK. Bilateral alterations in cytokine levels in the DRG and spinal cord may underlie the spread of pain to the uninjured side.

An important aspect is how the opioids may interact with immune cells as opioid receptors are expressed by peripheral immune cells and thus can induce immune signaling changes. Furthermore, opioids may stimulate microglia cells to produce proinflammatory cytokines such as IL-1.

DOI of refers to article: http://dx.doi.org/10.1016/j.sjpain.2014.10.004.
* Corresponding author. Tel.: +45 99408830.
*E-mail address:* LAN@hst.aau.dk (L. Arendt-Nielsen).

http://dx.doi.org/10.1016/j.sjpain.2014.10.002

**Conclusions:** The present perspective paper indicates that neuroinflammation and the associated release of pro-inflammatory cytokines in dorsal root ganglion and at the spinal cord contribute to the transition from acute to chronic pain. Neuroinflammatory changes have not only been identified in the spinal cord and brainstem, but more recently, in the sensory ganglia and in the nerves as well. The glial cell activation may be responsible for contralateral spreading and possible widespread sensitisation.
**Implications:** Communication between glia and neurons is proposed to be a critical component of neuroinflammatory changes that may lead to chronic pain. Sensory ganglia neurons are surrounded by satellite glial cells but how communication between the cells contributes to altered pain sensitivity is still unknown. Better understanding may lead to new possibilities for (1) preventing development of chronic pain and (2) better pain management.


**Contents**



## 1. Introduction

Why does acute pain sometimes transition into a disabling chronic pain condition? This simple question continues to confound pain researchers. There has, however, been a gradual shift towards neuroinflammation and hence glial cell activations as key mechanisms that may favor the transition to chronic pain. This has led to a focus on the role of non-neuronal cells in the peripheral and central nervous system. Besides infiltrating macrophages, Schwann cells in the peripheral nerve, satellite glial cells, which are part of the peripheral nervous support system and are found in the dorsal root and trigeminal ganglia, and microglia, the endogenous immune cells of the central nervous system, can release cytokines thought to be an important mechanism in the maintenance of pain in conditions such as neuropathies and inflammatory pain. It is thought that activated Schwann cells, satellite glial cells, microglia, and astrocytes contribute to the maintenance of pain sensitivity by releasing a steady stream of cytokines that lead to altered neuronal function in the direction of sensitisation.

## 2. Neuroinflammation and neuropathic pain

In murine experimental models of neuropathic pain, it has been demonstrated that, following sciatic nerve injury, local macrophages and Schwann cells trigger an immune response immediately followed by recruitment of blood-derived immune cells. Schwann cells, active resident and infiltrating macrophages release proinflammatory cytokines, including the interleukins (IL)-1β, -6, -12 and tumor necrosis factor-α (TNF) as well as chemokines [1,2]. Proinflammatory cytokines contribute to axonal damage and they also stimulate spontaneous nociceptor activity. The load of inflammatory mediators at the site of nerve injury can provoke spontaneous action potential discharge in nociceptive fibers, causing an amplification of abnormal signals that reach dorsal root ganglion (DRG) sensory neurons and satellite glial cells. This results in activation of satellite glial cells, which leads to an immune response in the dorsal root ganglia that is driven by macrophages, lymphocytes and satellite cells. The anterograde signalling progresses centrally to activate spinal microglia with possible upregulation of glial-derived proinflammatory/pronociceptive mediators [3]. In particular, the increase in IL-1 in the DRG and spinal cord correlates well with the presence of both hyperalgesia and allodynia that is observed in these models [4,5]. However it is also well known that in the peripheral immune system antinflammatory cytokines, such as IL-10, act as endogenous feed-back inhibitors in order to maintain a balanced immune response. A significant alteration of IL-10 expression has been reported both in the peripheral and the central nervous system associated to neuropathic pain development [6]. Strategies aimed at enhancing IL-10 production have consistently resulted in prevention and reversal of pain hypersensitivity in models of neuropathy [7].

## 3. Bilateral pain spread

One important aspect associated with the development of chronic pain in humans is the contralateral spreading of sensitisation and later the widespread sensitisation. Most animal studies on localized experimental trauma have not systematically assessed ipsilateral and contralateral extraterritorial reactions and sensitisation in areas supplied by unaffected heteronymous nerves. For those that have studied this phenomenon, the predominant findings have been that peripheral inflammation or nerve lesions affect the non-inflamed or non-lesioned structures [8]. Although the underlying mechanisms are not fully understood, various models for the spreading have been implemented to study mechanisms such as up-regulation of neuro-inflammatory reaction (cytokine responses) and glial cell activation [9–12].

Bilateral elevation of TNF-α and IL-10 in dorsal root ganglion (DRG) associated with a unilateral injured spinal nerve has been found [13,14]. Interestingly, IL-10 may also prevent or reverse many pathological pain states, including pain induced by chronic constriction injury neuropathies [15]. Bilateral elevation of IL-6 protein in the DRG after spinal nerve injury has also been found [16]. Similarly in inflammatory pain models, bilateral changes occur; for example, TNF-α, IL-1β, and p38 MAPK expression are activated after hindpaw but not forepaw carrageenan injection, suggesting segmental mechanisms which so far are not known in detail [17]. These results obtained in inflammatory and neuropathic pain models suggest that bilateral alterations in cytokine levels in the DRG