



Topical review

Glial dysfunction and persistent neuropathic postsurgical pain

Linda Block^{a,b,*}^a Institute of Clinical Sciences at Sahlgrenska Academy, University of Gothenburg, Sweden^b Department of Anesthesiology and Intensive Care, Sahlgrenska University Hospital, Gothenburg, Sweden

HIGHLIGHTS

- Peripheral nerve injury can cause low-grade neuroinflammation.
- Low-grade neuroinflammation causes imbalance in the neuron–glia interaction.
- The disturbed neuron–glia interaction produces prolonged and exaggerated pain transmission.
- By targeting glial dysfunction instead of neurons, a new arena for the development of pharmacological agents is opened.

ARTICLE INFO

Article history:

Received 9 June 2015

Received in revised form 10 October 2015

Accepted 13 October 2015

Keywords:

Pain

Persistent postsurgical pain

Neuropathic pain

Neuroinflammation

Glial

ABSTRACT

Background: Acute pain in response to injury is an important mechanism that serves to protect living beings from harm. However, persistent pain remaining long after the injury has healed serves no useful purpose and is a disabling condition. Persistent postsurgical pain, which is pain that lasts more than 3 months after surgery, affects 10–50% of patients undergoing elective surgery. Many of these patients are affected by neuropathic pain which is characterised as a pain caused by lesion or disease in the somatosensory nervous system. When established, this type of pain is difficult to treat and new approaches for prevention and treatment are needed.

A possible contributing mechanism for the transition from acute physiological pain to persistent pain involves low-grade inflammation in the central nervous system (CNS), glial dysfunction and subsequently an imbalance in the neuron–glial interaction that causes enhanced and prolonged pain transmission.

Aim: This topical review aims to highlight the contribution that inflammatory activated glial cell dysfunction may have for the development of persistent pain.

Method: Relevant literature was searched for in PubMed.

Results: Immediately after an injury to a nerve ending in the periphery such as in surgery, the inflammatory cascade is activated and immunocompetent cells migrate to the site of injury. Macrophages infiltrate the injured nerve and cause an inflammatory reaction in the nerve cell. This reaction leads to microglia activation in the central nervous system and the release of pro-inflammatory cytokines that activate and alter astrocyte function. Once the astrocytes and microglia have become activated, they participate in the development, spread, and potentiation of low-grade neuroinflammation. The inflammatory activated glial cells exhibit cellular changes, and their communication to each other and to neurons is altered. This renders neurons more excitable and pain transmission is enhanced and prolonged.

Astrocyte dysfunction can be experimentally restored using the combined actions of a μ -opioid receptor agonist, a μ -opioid receptor antagonist, and an anti-epileptic agent. To find these agents we searched the literature for substances with possible anti-inflammatory properties that are usually used for other purposes in medicine. Inflammatory induced glial cell dysfunction is restorable in vitro by a combination of endomorphine-1, ultralow doses of naloxone and levetiracetam. Restoring inflammatory-activated glial cells, thereby restoring astrocyte–neuron interaction has the potential to affect pain transmission in neurons.

DOI of refers to article: <http://dx.doi.org/10.1016/j.sjpain.2015.10.001>.

* Corresponding author at: Anestesiexpeditionen, Blå Stråket 5, 41345 Gothenburg, Sweden. Tel.: +46 313428173/709955110.

E-mail address: Linda.block@vgregion.se

Conclusion: Surgery causes inflammation at the site of injury. Peripheral nerve injury can cause low-grade inflammation in the CNS known as neuroinflammation. Low-grade neuroinflammation can cause an imbalance in the glial–neuron interaction and communication. This renders neurons more excitable and pain transmission is enhanced and prolonged. Astrocytic dysfunction can be restored in vitro by a combination of endomorphin-1, ultralow doses of naloxone and levetiracetam. This restoration is essential for the interaction between astrocytes and neurons and hence also for modulation of synaptic pain transmission.

Implications: Larger studies in clinical settings are needed before these findings can be applied in a clinical context. Potentially, by targeting inflammatory activated glial cells and not only neurons, a new arena for development of pharmacological agents for persistent pain is opened.

© 2015 The Author. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

1. Introduction: the clinical problem of persistent pain after surgery	75
1.1. Neuropathic pain conditions in persistent postsurgical pain (PPP)	75
1.2. Objectives of this review	76
2. Methods	76
3. Peripheral injuries can cause low-grade neuroinflammation	76
3.1. Blood–brain barrier made permeable by cytokines	76
3.2. Microglia and astrocytes' function are altered by neuroinflammation	76
4. Microglia and astrocytes' important role in development of neuropathic pain	76
4.1. Microglia initiates neuroinflammation	76
4.2. Astrocytes can modify neuronal activity	76
4.2.1. Astrocytic calcium (Ca^{2+}) signalling	76
4.2.2. Gap junction coupling	77
4.2.3. Glutamate–glutamine cycle	77
5. Astrocytic cellular dysfunction in inflammatory conditions	77
5.1. Toll like receptor-4 is a pro-inflammatory receptor	77
5.2. Astrocytes communicate with Ca^{2+} waves	77
5.3. Na^+/K^+ ATPase modulates Ca^{2+} signalling	77
5.4. An intact cytoskeleton is needed for Ca^{2+} signalling	78
5.5. Pro-inflammatory cytokine IL-1 β closes gap junctions	78
5.6. Inflammation disrupts astrocytes' communication	78
6. Reversing glial dysfunction (Fig. 3)	78
6.1. Endomorphin-1 stimulates the μ -opioid receptor and Na^+/K^+ ATPase	78
6.2. Naloxone inhibits the excitatory second messenger protein G_s and restores actin filaments	78
6.3. Levetiracetam opens blocked gap junctions	78
6.4. Experimental studies of the combination endomorphin-1, naloxone and levetiracetam	79
7. Clinical applications	79
8. Conclusions	79
9. Implications	79
Conflicts of interest	80
Acknowledgements	80
References	80

1. Introduction: the clinical problem of persistent pain after surgery

Acute pain in response to injury is an important mechanism that serves to protect living beings from harm. The pain signals transmitted from the site of injury to the brain cause us to avoid harmful, noxious stimuli. However, severe pain that is sustained for a long time after the injury has healed serves no useful purpose and is a disabling condition. Persistent pain is devastating for individuals and causes substantial health impairment and significant social, financial, and work-related difficulties [1–3]. From a social point of view, persistent pain is a large burden and results in the use of extensive resources for sick leave, disability retirement, and rehabilitation.

Persistent postsurgical pain, which is often defined as pain that remains for 3 months or more after surgery, is the second most common cause of chronic pain after degenerative disease [4]. Recent reports regarding persistent postsurgical pain confirm that it is a complex and highly significant clinical problem [5–8]. A study that

included 2043 patients [9] demonstrated that 12% of patients who underwent an elective, mixed type of surgery developed moderate persistent postsurgical pain and 7% developed severe persistent postsurgical pain. Persistent postsurgical pain after a number of surgical procedures has been described, the prevalence of persistent postsurgical pain varies with the type of surgery, ranging from 50% for limb amputation, 30% for breast surgery, and 10% for hernia repair [5,10,11].

1.1. Neuropathic pain conditions in persistent postsurgical pain (PPP)

Persistent postsurgical pain is strongly associated with neuropathic pain [12,13]. Depending on the type of surgery, neuropathic pain is experienced by 3% (laparoscopic surgery) to 68% (breast surgery) of patients with persistent postsurgical pain. Neuropathic pain is characterised by lesion to or disease of the somatosensory nervous system [14,15]. It is recognised by pain that is distributed

Download English Version:

<https://daneshyari.com/en/article/8623561>

Download Persian Version:

<https://daneshyari.com/article/8623561>

[Daneshyari.com](https://daneshyari.com)