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Editorial comment

Neuroinflammation explains aspects of chronic pain and opens new avenues for therapeutic interventions

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In this issue of the Scandinavian Journal of Pain Elisabeth Hansson reviews the processes behind neuroinflammation in the CNS and possible causal relationship to the development of chronic pain [1]. This is an important issue, with large amount of basic neuroscience evidence, not well known to pain clinicians. This developing field should be studied also by clinicians who are struggling with management of patients in chronic pain. Current drugs for chronic pain, which exclusively target neuronal mechanisms, are only partly effective, at best, and new strategies to manipulate neuron–glia interactions in pain processing hold considerable promise [2]. In fact, Costigan et al. [3] stated recently that inhibition of immune function represents a major avenue for therapeutic intervention for neuropathic pain.

Peripheral nerve injuries can cause low-grade inflammation in the dorsal horn of the spinal cord and along the pain pathways to the thalamus and the parietal cortex [4]. This neuroinflammation is due to activation of glial cells. Microglia, which are the macrophages of the CNS, release substances to the blood, increasing permeability of the tight junctions of the capillary endothelial cells (the blood–brain-barrier) and blood cells pass into the CNS [5]. These cells are transformed into reactive microglia, which in turn may activate astrocytes.

Astrocytes are coupled into networks that occupy strategic positions between the vasculature and the synapses, monitoring neuronal activity and transmitter release [1]. Eventually the activated astrocyte network leads to formation of new synapses. New neuronal contacts are formed that maintain and spread neurosignals, with the pain-sensation-mediating astrocytic networks acting as bridges [1,6,7]. These processes, in which activated glia cells play important parts, may contribute to the explanation of how acute or sub-acute pain sensations can become long-term and how they can be experienced in other parts of the body than where the original injury occurred [1,2,8,9].

In animal models of neuropathic pain, proinflammatory immunological processes involving activation of microglia and astrocytes are involved [10]. Glucocorticoids are immunosuppressive agents [11]. Thus, methylprednisolone reduced the activation of the spinal cord microglia and prevented development of neuropathic pain signs after nerve injury in rats [10,12]. In clinical studies, the somatosensory changes after surgery were significantly diminished by methylprednisolone given i.v. before incision for mammoplasty [13]. Specific somatosensory changes around the surgical wound appear to be predictors of chronic neuropathic pain after augmentation mammoplasty [14].

The changes that occur due to longstanding activation of microglia and the astrocyte networks may become irreversible, in part due to death of neurones in the spinal cord from apoptosis and excitotoxic processes [1]. It may therefore be too much to hope for that immunosuppressive therapy will have any effect at in late stages of chronic complex pain conditions. Multiple other mechanisms will also have been involved in neuropathic pain that has lasted for years [3]

Still, repeated intrathecal injections of methylprednisolone significantly reduced chronic neuropathic pain after herpes zoster [15].

With the well documented neuroinflammation and its sequelae in animal models, it is time to look closer at the preventive effects of glucocorticoids and other inhibitors of immune functions given at an earlier stage, maybe not later than when abnormal signs of sub-acute neuropathic type pain is developing after tissue trauma or surgery [1,13]. Immunosuppressive drugs that cross the blood–brain-barrier more readily than glucocorticoids should be studied. Other immunosuppressive drugs, e.g., minocycline, have been suggested by Kehlet et al. [16] in order to prevent microglial activation and transition of acute pain to chronic postoperative pain.

References

[1] Hansson E. Long-term pain, neuroinflammation and glial activation. Scand J Pain 2010;1:67–72.
[2] Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. Nature Re Neurosci 2009;10:23–36.
[3] Costigan M, Scholtz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci 2009;32:1–32.
[4] Saadé NE, Jabbur SJ. Nociceptive behaviour in animal models for peripheral neuropathy: spinal and supraspinal mechanisms. Progr Neurobiol 2008;86:22–47.

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[5] Gordh T, Chu H, Sharma HS. Spinal nerve lesion alters the blood–spinal cord barrier function and activates astrocytes in the rat. Pain 2006;124:211–21.
[6] Hansson E, Rönnbäck L. Glial neuronal signalling in the central nervous system. FASEB J 2003;17:341–8.
[7] Hansson E. Could chronic pain and spread of pain sensation be induced and maintained by glial activation? Acta Physiol 2006;187:321–7.
[8] Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. Nat Rev Neurosci 2005;6:521–32.
[9] Scholtz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. Nat Neurosci 2007;10:1361–8.
[10] Takeda K, Sawamura S, Sekiyama H, Tamai H, Hanaoka K. Effect of methylprednisolone on neuropathic pain and spinal glial activation. Anesthesiology 2004;100:1249–57.
[11] Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids – new mechanisms for old drugs. N Engl J Med 2005;353:1711–23.
[12] Takeda K, Sawamura S, Tamai H, Sekiyama H, Hanaoka K. Role for cyclooxygenase 2 in the development and maintenance of neuropathic pain and spinal glial activation. Anesthesiology 2005;103:837–44.
[13] Romundstad L, Breivik H, Roald H, Skolleborg K, Romundstad PR, Stubhaug A. Chronic pain and sensory changes after augmentation mammoplasty. Long term effects of preincisional administration of methylprednisolone. Pain 2006;124:92–9.
[14] Kaasa T, Romundstad L, Stubhaug A. Hyperesthesia one year after breast augmentation surgery increases the odds for persisting pain at four years. A prospective four year follow up study. Scand J Pain 2010;1:75–81.
[15] Kotani N, Kushikata T, Hashimoto H, Kimura F, Muraoka M, Yodono M, et al. Intrathecal methylprednisolone for intractable postherpetic neuralgia. N Engl J Med 2000;343:1514–9.
[16] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618–25.