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Editorial comment

Neuroinflammation and glial cell activation in pathogenesis of chronic pain

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In this issue of the *Scandinavian Journal of Pain* Lars Arendt-Nielsen and his co-authors [1] publish an important study in which they discuss why acute pain can transit into a disabling long-term pain condition via neuroinflammatory processes in the dorsal root ganglion and spinal cord. This problem and the mechanisms behind have been studied for a long time [2]. It is an important task to clarify the mechanisms behind these phenomena: why do some conditions lead to an inflammation in the nervous system, a neuroinflammation, that results in increased neuronal excitability with intense signalling-traffic along the pain tracts of the spinal cord to the brain. The present review helps us to understand this conundrum better [1].

The review by Lars Arendt-Nielsen and his co-authors highlights that the immune system and the pain system are closely linked together, that glial cells are activated at least in the dorsal root ganglion and spinal cord, that glial cells may cause a contralateral spreading of pain, and that opioids stimulate the microglia to produce pro-inflammatory cytokines. At a tissue injury local macrophages trigger an immune response followed by recruitment of blood-derived cells, and these cells release pro-inflammatory cytokines, such as IL-1β, TNF-α, IL-6 and chemokines, which stimulate nociceptor activity. Satellite glial cells and Schwann cells together with microglia activate an immune response in the dorsal root ganglia and spinal cord. In order to maintain a balanced immune response, anti-inflammatory cytokines, such as IL-10, act as feed-back inhibitors.

The communication between glial cells and neurons seems to be a critical component of neuroinflammatory changes. It is proposed that satellite glial cells express glutamate transporters and release glutamate [1]. They also discuss the research findings that document that opioids interact with the immune cells [1]. Opioid receptors are expressed by peripheral immune cells as well as on cells in the central nervous system (CNS). Interactions between opioid receptors and the inflammatory Toll like receptors (TLRs) may induce immune signalling changes, which may be of importance in neuroinflammation and long-term pain.

Changes in pro- and anti-inflammatory cytokines may underlie the spread of the neuroinflammation and pain to the uninjured side. The glial cells are documented to take part in activation and the contralateral spreading causing widespread sensitization of pain modulating neuronal networks [3].

A common underlying mechanism of persistent pain is the presence of a low-grade inflammation at the site of the damaged or affected peripheral nerve(s). Pain activating substances are released from neurons located in the spinal cord and brain, leading to an over-activation [4]. Resting microglia cells react and release cytokines. At the injured region substances are released to the blood, which influence the blood–brain barrier and give rise to an increased permeability of the tight junctions of the capillary endothelial cells, leading to passage of blood cells into the CNS both at the spinal cord level and in the brain. The blood cells transform into microglia [5]. The low-grade inflammation can turn into a pathological process, and then the astrocytes also are activated [5,6].

The resulting increased neuronal excitability at the spinal cord level and in the brain leads to increased glutamate release. Astrocyte uptake of excessive extracellular glutamate by membrane-bound glutamate transporters plays a critical role in preventing glutamate excitotoxicity [7]. After an injury followed by neuroinflammation, the glutamate transporter activities are inhibited [8].

Regulation of Ca^{2+} dynamics by transmitters and other soluble factors is a possible mechanism by which the astrocyte networks, at the spinal cord level and in the brain, detect changes in the CNS microenvironment [9]. Brain activities such as inflammatory processes can be recognized by these networks. Inflammatory receptors are influenced with increased expression of some receptors, for example the TLR4 [10], and changed in the sensitivity or responses of others, for example the opioid receptors [11,12]. There are also down-regulations of sodium-transporters, and disruption of the cytoskeleton, which abolishes the Ca^{2+} signalling by changing the balance between the Ca^{2+} regulating processes [13]. The inflammatory induced dysfunction of glial cells can lead to pathogenic chronic neuroinflammation.

In the inflammatory state, TLR4 activity is increased in microglia and astrocytes and it is proposed that TLRs drive inflammation that

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gives rise to symptoms and increased production and release of IL-1β [10]. The classical opioid system is also important in modulating the immune system and releasing Ca^{2+} from intracellular stores. These effects are mediated by G protein-coupled opioid receptors, which can be activated by inflammatory stimuli. The endogenous opioids are involved in nociceptive information processing through μ-opioid receptors. During chronic morphine administration the μ-receptor, normally coupled to $G_{i/o}$ protein is decreased, and the μ-receptor coupling to the G_s protein is increased [14]. This switch in G protein coupling can be one explanation and a proposed underlying mechanism for development of opioid tolerance. Ultralow concentrations of the μ-opioid antagonist naloxone can inhibit the G_s protein, and thereby switch the coupling back to $G_{i/o}$ protein. This has been shown in dorsal root ganglia and astrocytes, that an increase in the analgesic effects of opioids in long-term pain conditions has been observed [15]. In the clinic there are observations that indicate that ultralow doses of naloxone can increase the antinociceptive effects of opioids, for references see [15–17]

Arendt-Nielsen and co-authors [1] interestingly propose a relationship between opioid receptors, opioid agonists and antagonists, and TLR4, and further experimental studies may tell us if it is a possible way to attenuate neuroinflammation and thereby be novel targets for new drugs that can ameliorate chronic pain.

Conflict of interest

The author has no conflict of interest concerning this editorial comment.

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