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**Review**

# Modulation of microglia can attenuate neuropathic pain symptoms and enhance morphine effectiveness

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**Abstract:**

Microglia play a crucial role in the maintenance of neuronal homeostasis in the central nervous system, and microglia production of immune factors is believed to play an important role in nociceptive transmission. There is increasing evidence that uncontrolled activation of microglial cells under neuropathic pain conditions induces the release of proinflammatory cytokines (interleukin – IL-1 $\beta$ , IL-6, tumor necrosis factor – TNF- $\alpha$ ), complement components (C1q, C3, C4, C5, C5a) and other substances that facilitate pain transmission. Additionally, microglia activation can lead to altered activity of opioid systems and neuropathic pain is characterized by resistance to morphine. Pharmacological attenuation of glial activation represents a novel approach for controlling neuropathic pain. It has been found that propentofylline, pentoxifylline, fluorocitrate and minocycline decrease microglial activation and inhibit proinflammatory cytokines, thereby suppressing the development of neuropathic pain. The results of many studies support the idea that modulation of glial and neuroimmune activation may be a potential therapeutic mechanism for enhancement of morphine analgesia. Researchers and pharmacological companies have embarked on a new approach to the control of microglial activity, which is to search for substances that activate anti-inflammatory cytokines like IL-10. IL-10 is very interesting since it reduces allodynia and hyperalgesia by suppressing the production and activity of TNF- $\alpha$ , IL-1 $\beta$  and IL-6. Some glial inhibitors, which are safe and clinically well tolerated, are potential useful agents for treatment of neuropathic pain and for the prevention of tolerance to morphine analgesia. Targeting glial activation is a clinically promising method for treatment of neuropathic pain.

**Key words:**

neuropathic pain, morphine, glia, minocycline, pentoxifylline, interleukins, complement

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**Abbreviations:** C – complement, CNS – central nervous system, IL – interleukin, MAPK – mitogen-activated protein kinase, PKC – protein kinase C, TNF – tumor necrosis factor

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## Microglia under neuropathic pain

Researchers are working to characterize the changes in the nervous system that occur during the develop-

ment of neuropathic pain in animal models. An understanding of how neuropathic pain develops is necessary to guide development of new pain therapies. Recent evidence suggests that glia play a crucial role in the maintenance of neuronal homeostasis in the central nervous system [46, 74, 75, 107, 119]. Glial cells represent 70% of the cells in the central nervous system (CNS) under normal conditions, and microglia represent 5–10% of glia [124]. Microglial cells have a small soma bearing thin and branched processes un-

der normal conditions [124]. The most characteristic feature of microglia is their rapid activation in the CNS in response to pathological events, including trauma, ischemia, inflammation, hypoxia, neurodegeneration and viral or bacterial infection. After activation, microglia cells change morphology from a resting, ramified shape into an active, amoeboid shape [46, 75, 83, 107]. Activated microglia have dual regulatory functions in the maintenance and facilitation of tissue homeostasis in the CNS. They remove dead cells or dangerous debris by releasing toxic factors and phagocytosis, but they also repair injured cells by releasing neurotrophic factors [25, 74, 79, 89]. In contrast to neuronal processes, the phenomenon of microglial cell activation is multidirectional, and these cells dynamically modulate neuronal function under both normal and pathological conditions.

Clinical neuropathic pain syndrome can develop as a result of damage to nerves due to tumors, diabetic neuropathy, herpes zoster, complex regional pain syndrome, AIDS, sclerosis multiplex, hypoxia, or stroke [15, 60]. Studies in recent years have suggested an important role for microglial activation observed during neuropathic pain [13]. However, the role of glia in the cellular mechanisms underlying the symptoms of neuropathic pain, such as hyperalgesia or allodynia, is not clear [26, 126, 129]. Microglial cells secrete a large variety of substances, including growth factors, cytokines, complement components, lipid mediators, extracellular matrix components, enzymes, free radicals, neurotoxins, nitric oxide and prostaglandins [68]. Indeed, it seems that activation of glia in the CNS is a driving force behind pain [13, 26, 34, 46, 75, 107, 124]. Some proinflammatory cytokines derived from microglia are already known to be common mediators of allodynia and hyperalgesia [7, 13, 15, 18, 93, 124, 125]. Glial activation enhances neuronal nociceptive transmission, but the mechanism of this phenomenon is poorly understood. Production of various immune factors, including cytokines interleukin (IL)-1 $\alpha$ , IL-1 $\beta$ , IL-10, IL-6 and tumor necrosis factor (TNF)- $\alpha$  as well as complement components C1q, and C5a, is believed to play an important role in nervous system inflammation and may lead to abnormal processing of pain signals [13, 15, 18, 63, 124].

## Immune factors in neuropathic pain conditions

### Cytokines

**The interleukin-1 (IL-1) family** includes IL-1 $\alpha$  and IL-1 $\beta$ , which bind to the IL-1-type 1 receptor and the IL-1 receptor accessory protein. Microglia and macrophages have been identified as the major source of IL-1 $\beta$  [29, 117], which is known as one of the principal pro-inflammatory cytokines released in response to damage [37, 73, 95]. Accumulating evidence indicates a potential relationship between IL-1 $\beta$ , neuronal apoptosis and neuropathic pain [19, 93, 111, 121, 124, 128]. It is known, for instance, that intrathecal administration of IL-1 $\beta$  induces allodynia and hyperalgesia in rats [57, 63, 77, 78, 80]. Recently, Wang et al. [121] provided evidence that IL-1 $\beta$  serves as an external apoptosis-triggering signal, mediated by phosphorylation of p38 mitogen activated protein kinase (MAPK) and subsequent activation of caspase-3. In accordance with this idea, intrathecal administration of an IL-1 receptor antagonist prevented neuronal apoptosis and consequently diminished the development of neuropathic pain symptoms [63, 94, 111]. Interestingly, intrathecal administration of IL-1 $\alpha$ , in contrast to IL-1 $\beta$ , dose-dependently attenuated symptoms of neuropathic pain after nerve injury [63], similar way as IL-1 receptor antagonist did. This is particularly interesting because both IL-1 $\alpha$  and IL-1 $\beta$  bind to the IL-1 receptor type I, a specific cell surface receptor that is present in the spinal cord and in dorsal root ganglion (DRG) neurons [77]. The mechanism by which IL-1 $\beta$  induces rapid effects in sensory neurons after IL-1 receptor type I activation is not well established. It was suggested by Obreja et al. [77] that tyrosine kinases and protein kinase C, which are activated by IL-1 $\beta$  could be involved. The exact role of IL-1 $\alpha$  and IL-1 $\beta$  in the CNS have not been clarified, but the presence of IL-1 receptor type 1 on sensory neurons suggests that these cytokines may directly influence nociceptive transmission after nerve injury [77, 78, 80]. It is intriguing that IL-1 $\alpha$  and IL-1 $\beta$ , acting through the same receptor, can differentially influence nociceptive transmission and the neuropathic pain response [63].

**Interleukin-6 (IL-6)** is a multifunctional cytokine involved in many neuroimmunological processes. IL-6 is known as an important mediator of inflammatory and immune responses in the periphery. How-

ever, recent studies indicate that IL-6 is also produced in the CNS and may play an important role in a variety of functions such as cell-to-cell signaling, coordination of neuroimmune response, protection of neurons from insult, as well as in neuronal differentiation, growth, and survival [32, 46, 67]. IL-6 may also contribute to the etiology of neuropathological disorders, including AIDS, dementia complex, Alzheimer's disease, multiple sclerosis, systemic lupus erythematosus, CNS trauma and meningitis [28, 32]. Recently, a strong increase in ipsilateral to the sciatic nerve injury IL-6 gene expression was observed in regions important for nociceptive transmission, such as the spinal cord and DRG [63]. Interestingly, the induction of IL-6 mRNA was more pronounced in the DRG than in the spinal cord [51, 63]. Flatters et al. [23] suggested that spinal administration of IL-6 following nerve injury elicited antinociceptive effects. The inhibitory effects of IL-6 on neuronal hyperexcitability after injury suggest IL-6 to be a potential modulator of neuropathic pain [23]. IL-6<sup>-/-</sup> mice developed a lower level of hyperalgesia after carrageenan injection than wild-type mice [132]. Together, these data suggest that IL-6 plays an important role in nociceptive transmission that is still not well recognized.

**Interleukin-10** (IL-10) is considered to be the most powerful anti-inflammatory cytokine, potently down-regulating TNF- $\alpha$ , IL-1 $\beta$  and IL-6 production and release [71]. We observed that IL-10 mRNA levels in the ipsilateral DRG and spinal cord increased after sciatic nerve injury [63]. Recently, Ledebuer et al. [48] demonstrated that IL-10, when injected in a region of the spinal cord where activated glial cells are present, dramatically reversed the pain state in animal models of chronic pain. Additionally, studies in animal models have shown that IL-10 prevents or reverses every pathological pain state examined, including pain induced by spinal inflammation, traumatic neuropathy and spinal trauma, without altering normal sensation [5]. Although, the precise functions of IL-10 in the CNS require further clarification, IL-10 is well known as an important negative regulator of proinflammatory gene expression [33, 96]. It can down-regulate the expression of receptors for proinflammatory cytokines [96] and up-regulates endogenous functional antagonists of proinflammatory cytokines such as the IL-1 receptor antagonist [39]. It has been shown by Milligan et al. [66] that intrathecal administration of a novel AAV2-IL-10 vector in rodents prevented and reversed neuropathic pain.

Furthermore, the Avigen company has also published that AV333, a plasmid that drives the production of IL-10, can reverse neuropathic pain symptoms when injected intrathecally. Animal models have shown that AV333 is well tolerated and completely reverses neuropathic pain symptoms for up to 90 days from a single course of treatment [5]. As yet, however, drugs directly influencing IL-10 biosynthesis are unavailable [125].

**Tumor necrosis factor  $\alpha$**  (TNF- $\alpha$ ) is a proinflammatory cytokine produced by microglia in the CNS [36, 108]. This cytokine is released in response to various insults or injury [62] and it has been shown that injection of a neutralizing TNF- $\alpha$  antibody into lesion sites may significantly reduce experimental ischemic injury [6, 61]. Although, TNF- $\alpha$  has been implicated in the acceleration of injury, current studies suggest that TNF- $\alpha$  may also serve a protective role [3, 24]. Further evidences indicate that TNF- $\alpha$  can provide protection to neurons because it is able to encourage the expression of antiapoptotic and antioxidative proteins [24]. Moreover, it was also shown that TNF- $\alpha$  plays a role in both, the long-term behavioral recovery and the histological repair of tissues in TNF- $\alpha$ -deficient mice, and on the other hand, has a deleterious effect during the acute response that occurs in a traumatized brain [98]. Some recent reports indicate that such dual action of TNF- $\alpha$  is mediated *via* different receptors, with the p55 TNF- $\alpha$  receptor 1 and the p75 TNF- $\alpha$  receptor 2 responsible for neurotoxic and neuroprotective effects, respectively [24, 133].

### Complement components

The activation of microglial cells under neuropathic pain also appears to involve complement proteins, an innate humoral immune defense system. Complement mediates a large variety of cellular and humoral interactions in the immune response, including neuronal cell death, cell adhesion, B- and T-cell differentiation, phagocytosis and chemotaxis [10, 72, 100]. There is also emerging evidence that uncontrolled activation of complement biosynthesis can lead to inflammation with a resulting loss of neurons and oligodendrocytes, ultimately inducing profound tissue damage [104]. Increased biosynthesis of various complement factors in the CNS has also been reported in animal models, e.g., after peripheral and central axotomy [30, 40, 41, 82, 110], excitotoxic kainic acid lesions [30, 82] and global brain ischemia [97]. Recently, microarray expression profiles have shown substantial changes in

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gene expression in the ipsilateral dorsal horn of the spinal cord in response to peripheral nerve injury, the animal model of neuropathic pain. Many of the commonly regulated transcripts were complement components, such as C1q, C3 and C4, and were found in CNS to be expressed only by spinal microglia [31]. Interestingly, the biggest up-regulation was observed for C1q. Activation of C1q may lead to increased levels of functionally active C1 complexes, thus driving local activation of the classical complement activation cascade [10], or may instead trigger cellular responses by binding to C1q receptors [9, 10]. The induction of oxygen or nitrogen intermediates by C1q may play an important role in the pathogenesis of CNS diseases [115]. Additionally, membrane-bound C1q is thought to play an important role in the adhesion of macrophages to the extracellular matrix and in cell-to-cell interactions between macrophages and other cell types, the processes involved in neurodegeneration [8]. In addition, Griffin et al. [31] found that the complement component C5 and C5a receptor are also up-regulated in spinal microglia after peripheral nerve injury. Interestingly, mice null for C5 had reduced neuropathic pain sensitivity and C5a receptor peptide antagonist reduces allodynia in neuropathic pain models [31]. The results of many studies indicate that the induction of the complement cascade in spinal microglia after peripheral nerve injury contributes to neuropathic pain, which suggests the potential benefits of using complement inhibitors as a novel therapeutic approach in the treatment of inflammatory and degenerative neurological diseases also highlighted by the report of Huang et al. [31, 38].

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### Glial inhibition influences neuropathic pain development

Activated microglial cells in the spinal cord may release proinflammatory cytokines and other substances thought to facilitate pain transmission [12, 13, 15, 22, 54, 120, 124, 125]. Therefore, pharmacological attenuation of glial activation represents a novel approach for controlling neuropathic pain [125]. It seems that microglia might be responsible for the initiation of neuropathic pain states [22, 46, 58]. Recent studies indicate that preemptive treatment with glial inhibitors seems to be more effective than their administration only after glial cells have already been

activated [21, 50, 91]. Many current studies aim to find substances inhibiting the biosynthesis of proinflammatory cytokines. It has been found that propentofylline, pentoxifylline, minocycline and ibudilast inhibit cytokines and lower astroglia and microglia activation, thereby suppressing the development of neuropathic pain [49, 56, 64, 76, 91, 92, 112].

**Propentofylline**, is a methylxanthine derivative, previously found to attenuate astrocytic activation in a rodent ischemia model [18]. In ischemia, propentofylline has been shown to be neuroprotective through a multitude of actions, including inhibition of glutamate release [2, 69] and increased nerve growth factor secretion [101]. *In vitro* studies revealed that propentofylline maintains astrocytic glutamate uptake and inhibits potentially neurotoxic functions adopted by microglia upon pathological activation [99]. In formalin-induced pain in rats, the local injection of propentofylline reduced the pain behavior by decreasing TNF- $\alpha$  [21]. In a rodent model of neuropathic pain, systemic application of propentofylline produces a decrease in mechanical allodynia [114]. The antiallodynic activity of propentofylline by suppression of astroglial and microglial activity supports the concept that modulation of glial activation may be therapeutically promising in the treatment or prevention of neuropathic pain [91, 114].

**Pentoxifylline** is a non-specific cytokine inhibitor and an inhibitor of phosphodiesterase, which can inhibit the synthesis of TNF- $\alpha$ , IL-1 $\beta$  and IL-6 [53, 56, 76]. The local injection of pentoxifylline reduced inflammatory pain by decreasing TNF- $\alpha$  [21]. Some studies have demonstrated that pentoxifylline influences the development of neuropathic pain behavior in rats and mice [53, 64], and that when injected in a preemptive analgesia schema, it reduces postoperative pain in patients [20, 113, 130]. The antinociceptive effects of pentoxifylline are correlated with the reduction of the production of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 through inhibition of nuclear factor- $\kappa$ B, and stimulation of IL-10 expression in the spinal cord and brain [53, 118]. However, the therapeutic effects of pentoxifylline on developed neuropathic pain remain to be determined by future studies.

**Minocycline**, a semisynthetic second-generation tetracycline with adequate penetration into the brain and cerebrospinal fluid [4, 14, 131], has emerged as a potent inhibitor of microglial activation and proliferation, without any known direct action on astrocytes or neurons [1, 116]. The effects of minocycline are me-



diated by microglial cells and are distinct from the antimicrobial actions of this drug [35, 45]. Administration of minocycline either systemically or intrathecally attenuated hyperalgesia in rat models of neuropathy. The effect is associated with an inhibition of spinal microglial activation and attenuation of expression of proinflammatory cytokines [50, 64, 91]. The authors emphasized that minocycline attenuated the development of behavioral hypersensitivity in the rat model of neuropathic pain when the inhibitor was injected preemptively [50, 91]. The beneficial effects of minocycline are associated with reduction of inducible nitric oxide synthase and cyclooxygenase-2 expression, a decrease in cytokine and prostaglandin release, and a decrease in the induction of IL-1 $\beta$ -converting enzyme in microglia [134, 135]. Other authors showed that the analgesic effects of minocycline in a rat model of neuropathic pain result from attenuation of expression of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IL-1 $\beta$ -converting enzyme, TNF- $\alpha$ -converting enzyme, IL-1 receptor antagonist and IL-10 in the lumbar dorsal spinal cord [50, 136].

**AV411 (ibudilast)** is a relatively nonselective phosphodiesterase inhibitor that suppresses glial activation [44, 47, 49, 109]. In activated glial cells *in vitro*, ibudilast suppresses, in a concentration-dependent manner, the production of proinflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$ . It also increases the production of the anti-inflammatory cytokine IL-10 [70, 109]. Recently, Ledebuer et al. [47, 49] showed that ibudilast might be effective in the treatment of neuropathic pain and may attenuate sciatic nerve injury-induced allodynia in rats. Since AV411 is effective in animal models of neuropathic pain and has been in long use in Japan to treat bronchial asthma [43, 44], it seems likely to be a promising potential therapeutic agent [43, 44, 47, 49].

**The plasmid AV333** has proven effective in inducing the potent anti-inflammatory cytokine IL-10 after intrathecal injection and appears to reverse neuropathic pain through attenuation of glial cell activity [5].

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### Glial inhibitors enhance morphine effectiveness in neuropathic pain

Many studies indicate that neuropathic hyperalgesia leads to lowered morphine efficacy and quicker de-

velopment of morphine tolerance [59, 64, 65, 81, 85] and some authors have suggested that uncontrolled activation of microglial cells after nerve injury can lead to altered activities of opioid systems or opioid-specific signaling [104, 122, 123]. The impairment of opioidergic transmission may diminish the antinociceptive potency of morphine after nerve injury as a consequence of reduced presynaptic opioid receptors induced by loss of neurons [81, 85, 87, 88, 104]. It is already known that microglia release neuroexcitatory substances in response to morphine, thereby opposing its effects [19, 122, 123, 124]. This raises an older hypothesis that suppression of glial activation and the resulting blockade of proinflammatory cytokine synthesis can improve morphine efficacy [90, 103, 123].

Recently, some behavioral studies have shown restoration of the analgesic activity of morphine by propentofylline or pentoxifylline treatment in animal models of neuropathic pain [21, 56, 64, 76, 90, 92, 112]. Furthermore, preemptive administration of pentoxifylline influenced morphine intake in the postoperative period in several patient groups [113, 130]. In rats and mice, minocycline has been shown to be an effective neuroprotective agent [52, 64, 106] that potentiates the effects of single morphine administration under neuropathic pain conditions [64].

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### Glial inhibitors influence the development of morphine tolerance

Both, opioid tolerance and neuropathic pain conditions share features of diminished morphine analgesia, leading to suggestions of a common mechanism [59]. Chronic morphine treatment activates spinal and cortical glial cells and induces the development of tolerance [16, 17, 103]. The mechanism underlying the involvement of glial cells in morphine tolerance is unclear. It is possible that morphine can act directly on glial cells triggering alterations in their morphology and functions [42, 90, 92, 105, 122]. However, some indirect pathways may also exist by which glial cells regulate neural plasticity, e.g. they are responsible for uptake of amino acid neurotransmitters such as glutamate that are also important factors in the development of tolerance [90, 92, 122]. Additionally, some authors indicate that activation of glial metabotropic glutamate receptors by glutamate can regu-

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late glial function and may be involved in the interaction between glia and neurons [127]. Glial cells are also considered to be crucial sources of nitric oxide (NO), cytokines and cyclooxygenase products that influence synaptic transmission in the CNS. Inhibition of these factors may delay morphine tolerance [86]. The altered expression of glial receptors may play a role in producing critical changes in glia-neuron communication in neuropathic pain, as well as in opioid tolerance [59, 127]. The first report linking glia to morphine tolerance demonstrated that chronic systemic morphine increased glia activation in the spinal cord [103]. Other authors have also shown that chronic morphine administration activates astroglia and microglia [16, 90]. The presence of opioid receptors on glia and the ability of morphine to prime microglia for enhanced production of proinflammatory cytokines suggests a possible direct interaction of morphine with glial cells [11]. The chronic morphine-induced activation of glial proinflammatory immune responses could activate the MAPK and protein kinase C (PKC) pathways, which are key players in the intracellular signaling cascade leading to the development of morphine tolerance [27, 59, 90, 92, 102, 124].

Administration of the glial metabolic inhibitor fluorocitrate has been found to attenuate the development of morphine tolerance [103]. In our study [63], pentoxifylline significantly blocked the development of morphine tolerance in naive mice, as well as in a model of neuropathic pain. Wordliczek et al. [130] have shown that pentoxifylline provides beneficial postoperative analgesic effects in patients undergoing cholecystectomy by diminishing the production of IL-6 and TNF $\alpha$ . Similarly, Lu et al. [55] showed that patients who received pentoxifylline exhibited longer patient-controlled analgesia trigger times, required less morphine consumption, and showed a faster return of bowel function. The effect seems to be due to both central and peripheral effects by attenuating the production of IL-6 and TNF- $\alpha$  in the perioperative period [55, 130]. Cui et al. [17] have provided evidence that intrathecal pretreatment with minocycline attenuates not only the development of morphine antinociceptive tolerance, but also the activities of spinal microglia and astrocytes induced by chronic morphine treatment. This further confirms the role of spinal glia in the development of tolerance to morphine analgesia. In our experiments, preemptive and repeated systemic administration of minocycline significantly blocked development of tolerance to anal-

gesic effects of morphine in naive mice as well as in mice after sciatic nerve injury, as measured in tail-flick, von Frey and cold plate tests [63]. The beneficial effects of minocycline are associated with a reduction of inducible nitric oxide synthase and cyclooxygenase-2 expression and a decrease in cytokine and prostaglandin release in microglia [134, 135]. Further studies have shown that minocycline reduced microglial activation by inhibiting p38 MAPK in microglia, and in this way delayed morphine tolerance [16, 17, 84]. It was also suggested that AV411 (ibudilast) may counteract opioid tolerance by blocking the activation of glial cells in the spinal cord in rodents. In preclinical studies, AV411 is now being examined and initial results have been promising in humans [5].

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## Conclusions

The results of many studies provide strong support for the idea that glial inhibitors, which are safe and clinically well tolerated, are potentially useful agents for preventing tolerance to morphine analgesia. It seems that microglia are important for the generation of neuropathic pain and that modulation of microglial cells, and thus neuroimmune activation may provide a strong therapeutic mechanism to increase morphine efficiency and prevent morphine tolerance during neuropathic pain. Targeting glial activation is a novel and clinically promising method for the treatment of neuropathic pain.

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