Published in final edited form as:

J Neurosci Res. 2023 September ; 101(9): 1383–1392. doi:10.1002/jnr.25199.

Microglial inflammation modulates opioid analgesic tolerance

Priyanka Pahan,

Jennifer Yanhua Xie

Department of Basic Sciences, New York Institute of Technology College of Osteopathic Medicine at Arkansas State University, Arkansas, Jonesboro, USA

Abstract

As we all know, opioids are the drugs of choice for treating severe pain. However, very often, opioid use leads to tolerance, dependence, and hyperalgesia. Therefore, understanding the mechanisms underlying opioid tolerance and designing strategies for increasing the efficacy of opioids in chronic pain are important areas of research. Microglia are brain macrophages that remove debris and dead cells from the brain and participate in immune defense of the central nervous system during an insult or injury. However, recent studies indicate that microglial activation and generation of proinflammatory molecules (e.g., cytokines, nitric oxide, eicosanoids, etc.) in the brain may contribute to opioid tolerance and other side effects of opioid use. In this review, we will summarize the evidence and possible mechanisms by which proinflammatory molecules produced by activated microglia may antagonize the analgesic effect induced by opioids, and thus, lead to opioid tolerance. We will also delineate specific examples of studies that suggest therapeutic targets to counteract the development of tolerance clinically using suppressors of microglial inflammation.

Keywords

microglia; opioid analgesic tolerance; proinflammatory molecules

1 | INTRODUCTION

Although acute pain serves as a warning signal for our body from preventing injury and avoiding further aggravation, chronic pain often does not serve this protective role. In fact, it is an unwanted public health epidemic, which affects approximately 20% population worldwide (Cohen et al., 2021; Goldberg & McGee, 2011). On one hand, chronic pain is associated with injury, insults, and many human disorders, and on the other, chronic pain is also considered a separate disease in its own right that casts enormous impact on the quality of human life. Accordingly, multiple factors are known to influence the etiology of chronic pain (Fillingim et al., 2016; Mills et al., 2019). Even when there is a primary causing event

Correspondence Jennifer Yanhua Xie, Department of Basic Sciences, New York Institute of Technology College of Osteopathic Medicine at Arkansas State University, Jonesboro, AR 72401, USA. jennifer.xie@nyit.edu.

AUTHOR CONTRIBUTIONS

PP and JYX formed the idea, prepared and improved the manuscript together.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest.

in the origin of chronic pain (e.g., injury), a number of secondary events (e.g., sedentary lifestyle, as well as psychological, social, emotional, and physical states of the suffering individual) come in to promote pain chronicity. Despite intense investigations, effective pain management, especially for chronic pain, remains a challenge.

2 | CONTROLLING CHRONIC PAIN WITH OPIOIDS

Although there are severe side effects or even death caused by opioid intake, until now, opioids remain the mainstay for relieving pain. Opioid receptors are G-protein-coupled receptors present in the central nervous system (CNS). Opioids function pre-synaptically and post-synaptically by binding to their receptors on cell membranes. It is known that the binding of an opioid to the μ-opioid receptor (MOR) transduces receptor phosphorylation, facilitating the release of G-protein subunits and initiation of a cascade leading to reduction of adenylyl cyclase, decrease in intracellular cyclic adenosine monophosphate (cAMP) levels, and regulation of ion channels (Hines & Owings, 2021; Pepe et al., 2004). These signaling events inhibit neurotransmitter release to induce hyperpolarization of the cell membranes and modulate the activation of nociceptors, ultimately leading to analgesia. Morphine, codeine, hydrocodone (Vicodin), and oxycodone (OxyContin) are widely prescribed opioids for pain control (“Opioids for pain,” 2022).

3 | OPIOID TOLERANCE

Opioid pain relievers are very effective when taken for a short time and as prescribed by a doctor. But long-term use of opioids often diminishes their analgesic effects, and escalation of the dosage/frequency or switching to more efficacious drugs is required to maintain the same efficacy, that is, tolerance occurs. Moreover, because they produce euphoria in addition to pain relief, they can be misused (taken in a different way or in a larger quantity than prescribed, or taken for a long time without a doctor's prescription). Chronic opioid exposure may stimulate body's protection mechanism against the drug to reduce the body's responsiveness to the drug, thereby requiring dose escalation to exert the same effect leading to opioid tolerance (Morgan & Christie, 2011). Accordingly, efforts to treat and control chronic pain with opioids have been complicated by opioid tolerance, contributing to the widespread opioid overuse that has become a national crisis affecting public health as well as social and economic welfare (Shipton et al., 2018; Skolnick, 2018). The National Institutes of Health has also taken a new initiative “Helping to End Addiction Long-term (HEAL)” to promote research into pain and opioid disorders including opioid tolerance (Volkow & Koroshetz, 2019).

The development of opioid tolerance is related to modulation of opioid receptors such as post-translational modification, endocytosis, desensitization, down-regulation, and G-protein uncoupling (Allouche et al., 2014). In addition to the functional modulation of opioid receptors, it has been shown that chronic opioid exposure induces microglia activation indicated by their morphology change from ramified shape to activated amoeboid form, and accompanied by the increase in cell surface markers such as CD11b (Ferrini et al., 2013). These changes are similar to the microglia activation induced by inflammation or neuropathic pain (Gu et al., 2022; Loggia et al., 2015; Roberts et al., 2009). Activated

microglia release a variety of proinflammatory cytokines and chemokines to exacerbate pain, and chemokines may also induce desensitization of MOR in neuronal cells (Chen et al., 2018; Zhang et al., 2004).

4 | FUNCTIONS OF MICROGLIA

Microglia, which under normal conditions constitute 2%–5% of total CNS cells, are basically known as CNS resident macrophages (Harry, 2013). Although astrocytes are the major glial cells in the CNS providing structural and nutritional support (Mazaud et al., 2021), it is microglia that deliver first line of defense in the CNS against any insult and injury (Leng & Edison, 2021). In addition to providing neuroimmune defense, microglia also have an important repairing function through scavenging unwanted bodies in the CNS. However, upon activation, microglia produce a number of proinflammatory molecules including proinflammatory cytokines [e.g., tumor necrosis factor-α (TNFα), interleukin-1α (IL-1α), interleukin-1β (IL-1β), interleukin-6 (IL-6)], proinflammatory chemokines [e.g. macrophage inflammatory protein-1 alpha (MIP-1α), RANTES (regulated upon activation, normal T cell expressed and secreted), inducible protein-10 (IP-10)], nitric oxide (NO), reactive oxygen species (ROS), etc., which ultimately destroy the invading virus or bacteria (Barger & Harmon, 1997).

Traditionally, in proinflammatory state, microglia are termed M1 microglia (Pozzo et al., 2019; Zhang et al., 2018). Proinflammatory molecules released from M1 microglia are capable of damaging neurons and myelin-forming oligodendrocytes in the CNS (Brown & Vilalta, 2015; Harry, 2013). Therefore, multiple neurodegenerative (e.g., Alzheimer's disease, Parkinson's disease, HIV-associated neurocognitive disorders, Huntington's disease, amyotrophic lateral sclerosis, etc.) and neuroinflammatory (e.g., multiple sclerosis, optic neuritis, etc.) disorders are found to involve M1 microglial activation (Saijo et al., 2010).

On the other hand, the alternatively activated microglia (M2) phenotype, characterized by the production of anti-inflammatory molecules, such as IL-4, IL-10, and transforming growth factor-β (TGF-β), are considered to be anti-inflammatory and neuroprotective (Pozzo et al., 2019; Zhang et al., 2018).

This kind of dichotomy (M1 vs. M2, proinflammatory vs. anti-inflammatory) has been disputed by recent evidence since microglia are constantly changing their morphology and functions to sample the extracellular environment and respond to the changes [see review (Paolicelli et al., 2022)]. We will avoid using M1/M2 nomenclature in this manuscript. Rather, we will focus on the effects induced by different conditions.

5 | MICROGLIAL INFLAMMATION IN OPIOID TOLERANCE

5.1 | Opioid receptor expression in microglia

While activation of opioid receptors [μ (mu: MOR), δ (delta: DOR), κ (kappa: KOR), and the nociceptin/orphanin FQ peptide (NOP) receptor] in neurons leads to analgesia, microglia express MOR and possibly KOR, too, but not DOR (Eisenstein, 2019; Machelska & Celik, 2020; Mika et al., 2014).

The presence of MOR in microglia has been shown at Oprm1 mRNA and protein levels in rodents and humans (Maduna et al., 2018; Rivat & Ballantyne, 2016). Conditional deletion of the MOR gene is able to deter the development of morphine analgesic tolerance, opioid-induced hyperalgesia, as well as dependence in mice (Reiss et al., 2022), highlighting the pivotal role of microglia in mediating opioid tolerance.

5.2 | How does activation of opioid receptors stimulate microglial inflammation?

Multiple studies report that agonism of opioid receptors, especially by the most clinically relevant opioids—MOR agonists (e.g., morphine and fentanyl), leads to microglial activation in the key areas involved with analgesia such as spinal cord and periaqueductal gray (Aceves et al., 2019; Liang et al., 2016; Matsushita et al., 2013; Merighi et al., 2013; Reiss et al., 2022; Yang et al., 2021). In cell culture experiments, morphine has been observed to stimulate the expression of IL-1β from primary mouse microglia (Liang et al., 2016) and mouse BV-2 microglial cells (Pan et al., 2016). In a mouse brain cell line, bEnd3 cells, morphine markedly induces the mRNA expression of TNFα and IL-6, although it does not increase the mRNA expression of IL-1β (Pan et al., 2016). Similarly, in a chronic constriction injury (CCI)-induced neuropathic pain model in rats, morphine treatment leads to the activation of NOD-like receptor protein 3 (NLRP3) inflammasomes and associated production of IL-1β in the spinal cord (Grace et al., 2016).

While investigating mechanisms, Wang et al. (2012) and Eidson and Murphy (2013) observed that morphine induces the expression of proinflammatory cytokines through binding to Toll-like receptor 4 (TLR4), inducing TLR4 signal transduction pathway and activation of downstream p38 mitogen-activated protein kinase (MAPK) and classical nuclear factor-κB (NF-κB) pathways (Figure 1). According to Merighi et al. (2013), morphine increases the level of TNFα, IL-1β, IL-6, and NO in microglial cells via MOR-mediated transduction of PKCε-ERK1/2 signaling pathway (Figure 1).

5.3 | Microglial cytokines in opioid analgesic tolerance

The critical role of microglial-secreted proinflammatory cytokines in the development of opioid analgesic tolerance has been demonstrated repeatedly. Proinflammatory cytokines are capable of enhancing the hyperactivity of dorsal horn neurons to counteract the anti-nociceptive effects of opioids, which manifests as tolerance to morphine (Taves et al., 2013). Intrathecal treatment of etanercept, a TNFα biological antagonist, suppresses microglial activation to inhibit morphine tolerance (Shen et al., 2011, 2012). In addition, suppression of IL-1/IL-1β signaling by either gene knockdown or physiological antagonist prevents the development of tolerance following chronic morphine treatment (Johnston et al., 2004; Shavit et al., 2005).

On the other hand, chronic morphine treatment has been reported to reduce the production of IL-10, an anti-inflammatory cytokine produced by activated microglia, further facilitating the overexpression of proinflammatory cytokines since the normal inhibition of the production of TNFα, IL-1β, and IL-6 by IL-10 is compromised (Johnston et al., 2004; Tu et al., 2021). Whether morphine treatment could interfere with the production of other anti-inflammatory mediators such as IL-4 or TGF-β by microglia remains to be elucidated.

The roles of pro- and anti-inflammatory cytokines produced by activated microglia in the development of morphine analgesic tolerance are summarized in Figure 2.

5.4 | ROS and NO in opioid analgesic tolerance

Several studies have demonstrated that receptor phosphorylation leading to internalization, desensitization, and/or uncoupling of the receptor complex from intracellular cascades regulates opioid tolerance (Qiu et al., 2003; Schulz et al., 2004; Williams et al., 2013). Although there is no report that microglia-derived proinflammatory cytokines are directly involved with the phosphorylation and desensitization of opioid receptors, activated microglia are known to release multiple oxygen radicals or ROS (Simpson & Oliver, 2020). It has been shown that ROS are capable of activating different protein kinases including Src tyrosine kinase (Chiarugi, 2008). According to Huang et al, proinflammatory cytokine IL-1β also induces the activation of Src in neurons via IL-1 receptor accessory protein (Huang et al., 2011). Interestingly, Src can phosphorylate MOR at Tyr 336, and this Src-dependent phosphorylation of MOR appears to be responsible for the development of opioid tolerance (L. Zhang et al., 2017) (Figure 3). TNFα and oxygen radicals can also induce the activation of protein kinase C (PKC), which catalyzes the phosphorylation of MOR at Thr 370 for promoting its internalization (Illing et al., 2014) (Figure 3).

Moreover, activated microglia produce NO, and proinflammatory cytokines can also trigger production of NO from microglia (Mitrovic et al., 1994). According to Santamarta et al, NO is directly involved in the desensitization of MOR in locus coeruleus neurons (Santamarta et al., 2014). Therefore, via activation of Src and PKC and employing NO, activated microglia can cause and/or influence the phosphorylation and desensitization of MOR in neurons.

5.5 | Chemokines in opioid analgesic tolerance

Monocyte chemoattractant protein (MCP-1), also known as the C-C motif chemokine ligand 2 (CCL2), plays an important role in neuroinflammation (Deshmane et al., 2009). Although the level of MCP-1 is very low in spinal cord under normal conditions, chronic morphine administration leads to marked increase in MCP-1 that mainly colocalizes with neurons, but not astrocytes and microglia (C. M. Zhao et al., 2012). Interestingly, intrathecal injection of functional blocking antibodies against MCP-1 reduces microglial activation in spinal cord and inhibits tolerance to morphine (Liu et al., 2017; C. M. Zhao et al., 2012), indicating a critical role of this chemokine in activation of microglia and opioid tolerance. Similarly, other chemokines such as C-X-C motif chemokine ligand 12 (CXCL12) and CXCL1 are also involved in microglial activation and opioid tolerance (Lin et al., 2015; Liu et al., 2019; Rivat et al., 2014). This has been confirmed in humans. Lin and Lu (2018) reported that the level of CXCL1 and CXCL12 in the cerebrospinal fluid increases significantly in opioid-tolerant patients compared to opioid-naive patients, and these changes correlate positively with the opioid dosage, providing direct evidence of neuroinflammation following chronic opioid exposure.

5.6 | Glutamate receptors in opioid analgesic tolerance

Glutamate receptors play critical roles in synaptic plasticity. Studies have shown that morphine sensitization is capable of increasing the mRNA expression of N-methyl D-

aspartate (NMDA) receptor subunits *in vivo* in the amygdala of rats (Sepehrizadeh et al., 2008). Similarly, TNFα, one of the major proinflammatory cytokines produced by activated microglia, enhances the expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Beattie et al., 2002). Activation of AMPA receptors leads to the depolarization of the cells to enable the activation of NMDA receptors by releasing their Mg^{2+} block, and thus, allow Ca^{2+} entry to mediate the long-term changes in synaptic strength (Huang et al., 2018). Antagonists of NMDA receptors or targeted disruption of NR2A or NR2B decreases opioid tolerance (Price et al., 2000; Y. L. Zhao et al., 2012), indicating that activation of NMDA receptors plays a role in the development of opioid tolerance (Figure 3).

6 | IS INHIBITION OF MICROGLIAL ACTIVATION A FEASIBLE APPROACH FOR MITIGATING OPIOID ANALGESIC TOLERANCE?

Although mechanisms of opioid tolerance are complex that encompass crosstalk among many factors, such as neural networks, G-protein-coupled receptors, and ion channels, recent evidence demonstrates that microglia play a critical role in the commencement and progression of opioid tolerance. Therefore, clampdown of neuroinflammation by reducing microglial activation and decreasing the production of proinflammatory molecules might be a meaningful strategy for improving the analgesic efficacy of opioids and attenuating opioid tolerance. Here, we provide some examples of therapeutic targets that have been studied to dampen microglial reactivity to interfere with/attenuate/modulate morphine analgesic tolerance.

1. Cannabinoids type 2 (CB2) receptor antagonists: Opioids and cannabinoids are distinct classes of drugs. CB2 receptors are expressed by glia and engage inhibitory G-proteins (Bie et al., 2018). It has been reported that activation of CB2 receptors decreases morphine-induced stimulation of IL-1β, IL-6, TNFα, and NO in microglia (Merighi et al., 2013), suggesting that agonists of CB2 receptor may be useful in reducing morphine-mediated microglial activation and hence morphine tolerance.

2. Metformin: It is an activator of 5′-adenosine monophosphate-activated protein kinase (AMPK) widely used as a first-line anti-diabetic medicine. It has been revealed that systemic administration of metformin suppresses morphine-induced activation of microglia in the spinal cord to attenuate the development of chronic morphine tolerance in mice (Pan et al., 2016). Moreover, studies have shown that metformin is capable of attenuating NF-κB activation in microglia (Abdi et al., 2021), a process that enables the transcription of different proinflammatory molecules in different cell types including microglia (Shabab et al., 2017), indicating an important mechanism by which metformin can control microglia-mediated inflammation.

3. Minocycline: It is a second-generation tetracycline, known to inhibit the production of proinflammatory molecules from activated microglia via suppression of NF-κB activation (Kobayashi et al., 2013). In addition, minocycline treatment also blocks the effects of proinflammatory chemokine

CCL2 on dorsal root-evoked currents in spinal cord slices induced by MOR agonist [D-Ala^2, N-Me-Phe^4, Gly^5-ol]-enkephalin (DAMGO) (Heles et al., 2021). Thus, minocycline has been used widely as a pan microglia activation blocker. It has been shown that minocycline and other glial inhibitors can significantly delay the development of morphine analgesic tolerance in both naive and neuropathic states in rodents (Mika et al., 2009; Zhang et al., 2015). However, it is unable to reverse the established opioid tolerance in rodents or opioid-maintained patients (Arout et al., 2019; Zhang et al., 2015).

4. Melatonin: It is a hormone in our body that is released by the pineal gland to promote sleep and maintain circadian rhythms (Miranda-Riestra et al., 2022). As expected, chronic morphine infusion elicits anti-nociceptive tolerance and increases the level of heat shock protein 27 (HSP27) in the dorsal horn of the rat spinal cord (Lin et al., 2016; van Noort, 2008). HSP27 is selectively expressed in reactive glia. It has been suggested to play a pivotal role in mediating inflammation (van Noort, 2008). Treatment with melatonin partially restores morphine's anti-nociceptive effect in morphine-tolerant rats and reverses morphine-induced HSP27 upregulation (Lin et al., 2016). It is likely that melatonin exhibits these functions via suppression of microglial activation.

5. Signal transducer and activator of transcription (STAT) inhibitors: STAT proteins play an important role in the activation of microglia (Jain et al., 2021). Pinocembrin (5,7-dihydroxyflavanone), a natural flavonoid present in a wide variety of plants, exhibits anti-inflammatory, anti-cancer, and apoptotic effects (Rasul et al., 2013). It has been shown that pinocembrin effectively prevents and alleviates chronic morphine tolerance in mice through inhibition of STAT3-mediated microglia activation and neuroinflammation (Han et al., 2022).

6. Epidermal growth factor receptor (EGFR) inhibitors: Yang et al. (2021) have described that EGFR inhibitors mitigated morphine-induced production of proinflammatory cytokines in microglia in a dose- and time-dependent manner, revealing the importance of EGFR in this process. Thus, blockade of EGFR signaling pathway may represent a pharmacological strategy to reduce morphine tolerance through attenuation of microglial activation.

7. TLR4/TLR2 blockers: Consistent with the finding that morphine requires TLR4 for activating microglia (Figure 1), blockade of TLR4 is shown to decrease morphine tolerance and enable the analgesic properties of morphine (Eidson & Murphy, 2013). On the other hand, Zhang et al. (2011) have shown that mice deficient in TLR2 have blunted production of microglial proinflammatory cytokines induced by morphine. TLR2-deficient mice also exhibit reduced symptoms of morphine withdrawal (Zhang et al., 2011). Therefore, it is possible that inhibitors of both TLR2 and TLR4 are beneficial for reducing morphine tolerance.

8. Lidocaine: Although lidocaine is a local anesthetic that is known to prevent pain by blocking Na-channel activation at the nerve endings, one recent study has shown that it is capable of decreasing microglial activation and the levels

of proinflammatory cytokines in the spinal cord via stimulation of the AMPK-SOCS3 signaling pathway, and thus, reducing morphine tolerance (Y. Zhang et al., 2017).

9. Resveratrol: It is a natural phenol mostly found in grapes and grape products. Interestingly, Han et al. have found that resveratrol can reduce morphine tolerance by inhibiting microglial activation via upregulation of AMPK signaling (Han et al., 2014).

10. TNFα inhibitors: Since TNFα is readily produced by morphine-stimulated microglia, TNFα antagonist, etanercept, has also been found to restore the anti-nociceptive effect of morphine via suppressing spinal neuroinflammation in morphine-tolerant rats (Shen et al., 2011).

11. IL-1 receptor antagonists (IL-1Ra): Similar to TNFα, morphine-activated microglia also release IL-1β/IL-1β (Merighi et al., 2013). The IL-1Ra, encoded by the *IL1RN* gene, is known to compete with IL-1α and IL-1β while binding to IL-1R, thereby reducing inflammatory signaling (Steinkasserer et al., 1992). Johnston et al. (2004) have delineated that intrathecal administration of IL-1Ra is capable of reducing morphine tolerance in rats.

12. Nitric oxide (NO) inhibitors: NO, an important biomolecule, acts as a double-edged sword depending on its concentration in the microenvironment(Colasanti & Suzuki, 2000). Activated microglia express inducible NO synthase (iNOS) to produce excessive NO in the CNS and cause neuroinflammation (Brown & Vilalta, 2015; Parkinson et al., 1997). Majeed et al. have shown that administration of NOS inhibitor (e.g., L-N^G-Nitro arginine methyl ester or L-NAME) along with morphine blocks the development of tolerance to morphine, and also decreases some signs of morphine dependence in mice (Majeed et al., 1994). Moreover, locus coeruleus neurons express opioid receptors and exhibit tolerance to chronic administration of opioids in rats (Highfield & Grant, 1998). Interestingly, inhibition of NO decreases the development of tolerance to morphine in locus coeruleus neurons (Highfield & Grant, 1998). These results suggest that either inhibitors of iNOS or scavengers of NO may reduce tolerance to morphine.

13. Fractalkine receptor (CX3CR1) antagonists: Fractalkine is also known as CX3C motif chemokine receptor 1 (CX3CR1) (Johnston et al., 2004). CX3C motif is a chemokine that signals through the G-protein-coupled chemokine receptor CX3CR1 (Pawelec et al., 2020). It has been demonstrated to reduce microglial inflammation via suppression of NF-κB activation (Jiang et al., 2022). Interestingly, fractalkine is also seen to modulate opioid tolerance as co-administration of morphine with intrathecal neutralizing antibody against CX3CR1 stimulated acute morphine analgesia and reduced the development of tolerance (Johnston et al., 2004).

14. P2X7/P2X4 antagonists: ATP-gated purinergic receptors such as P2X7 and P2X4 receptors modulate opioid-activated microglial functions (Horvath et al., 2010;

Leduc-Pessah et al., 2017). Morphine treatment enhances the expression of P2X7 and P2X4 receptors in microglia (Horvath & DeLeo, 2009; Zhou et al., 2010). Chen et al. (2012) have shown that blockade of P2X7 receptors by either P2X7 antagonist or small interfering RNA (siRNA) is capable of decreasing morphine analgesic tolerance in the pain behavioral test and spinal extracellular recordings *in vivo* and whole-cell recording of the spinal cord slices *in vitro*. In *in vitro* cultures, morphine enhances P2X4 receptor-mediated microglia migration via MOR activation (Horvath & DeLeo, 2009). Intrathecal administration of P2X4 receptor antisense oligonucleotide successfully blocked the development of morphine anti-nociceptive tolerance in rats (Horvath et al., 2010). In addition to the spinal effects, more recent evidence indicates that antagonizing P2X7 and P2X4 receptors in the medial prefrontal cortex enhances morphine analgesia in tolerant mice (Zeng et al., 2021). Therefore, blockade of purinergic P2X7 and P2X4 receptors may represent additional viable targets for reduction of morphine analgesic tolerance through inhibition of microglial activities.

7 | CONCLUSION

As once an English Physician (Dr. Thomas Sydenham) wrote, “Among the remedies which it has pleased almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.” Until now, opioids remain unbeatable in its pain-alleviating effects. Accordingly, a sharp increase in prescription of almost all types of opioid medications has been seen in the last 20 years for taking care of pain and stimulation of the pleasure component. As a result, opioid tolerance has also increased, exacerbating opioid overuse. Recent studies indicate that opioid-mediated microglial activation and production of different proinflammatory molecules may contribute to opioid tolerance (Du et al., 2020; Han et al., 2014; Zhang et al., 2011; Y. Zhang et al., 2017). Therefore, the challenge is to maintain the pain-relieving effect of opioids while minimizing microglial activation in an effort to mitigate opioid tolerance and hyperalgesia in patients (Figure 1). In these conditions, specific targeting of opioid-sensitive signaling pathways that are responsible for microglial inflammation by blood–brain barrier-penetrable non-toxic drugs may be a valid option. Fortunately, as described above, many such options (e.g., CB2 agonists, metformin, minocycline, melatonin, blockers of TLR2 and TLR4, lidocaine, resveratrol, pinocembrin, TNFα antagonists, IL-1Ra, inhibitors of iNOS, fractalkine receptor antagonists, P2X7/P2X4 receptor antagonists, etc.) are available to suppress opioid-induced microglial inflammation. Although many of these studies have been performed with rodents and rodent results are not always translated to human settings, randomized clinical trials could be employed based on these preclinical studies to establish whether different inhibitors of microglial inflammation have any therapeutic value in mitigating opioid tolerance.

REFERENCES

Abdi M, Pasbakhsh P, Shabani M, Nekoonam S, Sadeghi A, Fathi F, Abouzaripour M, Mohamed W, Zibara K, Kashani IR, & Zendedel A (2021). Metformin therapy attenuates proinflammatory microglia by inhibiting NF-kappaB in cuprizone demyelinating mouse model of multiple sclerosis. Neurotoxicity Research, 39(6), 1732–1746. 10.1007/s12640-021-00417-y [PubMed: 34570348]

Aceves M, Terminel MN, Okoreeh A, Aceves AR, Gong YM, Polanco A, Sohrabji F, & Hook MA (2019). Morphine increases macrophages at the lesion site following spinal cord injury: Protective effects of minocycline. Brain, Behavior, and Immunity Health, 79, 125–138. 10.1016/j.bbi.2019.01.023

Allouche S, Noble F, & Marie N (2014). Opioid receptor desensitization: Mechanisms and its link to tolerance. Frontiers in Pharmacology, 5, 280. 10.3389/fphar.2014.00280 [PubMed: 25566076]

Arout CA, Waters AJ, MacLean RR, Compton P, & Sofuoglu M (2019). Minocycline does not affect experimental pain or addiction-related outcomes in opioid maintained patients. Psychopharmacology, 236(10), 2857–2866. 10.1007/s00213-018-5146-7 [PubMed: 30564869]

Barger SW, & Harmon AD (1997). Microglial activation by Alzheimer amyloid precursor protein and modulation by apolipoprotein E. Nature, 388(6645), 878–881. 10.1038/42257 [PubMed: 9278049]

Beattie EC, Stellwagen D, Morishita W, Bresnahan JC, Ha BK, von Zastrow M, Beattie MS, & Malenka RC (2002). Control of synaptic strength by glial TNFalpha. Science, 295(5563), 2282–2285. 10.1126/science.1067859 [PubMed: 11910117]

Bie B, Wu J, Foss JF, & Naguib M (2018). An overview of the cannabinoid type 2 receptor system and its therapeutic potential. Current Opinion in Anaesthesiology, 31(4), 407–414. 10.1097/ACO.0000000000000616 [PubMed: 29794855]

Brown GC, & Vilalta A (2015). How microglia kill neurons. Brain Research, 1628(Pt B), 288–297. 10.1016/j.brainres.2015.08.031 [PubMed: 26341532]

Chen G, Zhang YQ, Qadri YJ, Serhan CN, & Ji RR (2018). Microglia in pain: Detrimental and protective roles in pathogenesis and resolution of pain. Neuron, 100(6), 1292–1311. 10.1016/j.neuron.2018.11.009 [PubMed: 30571942]

Chen ML, Cao H, Chu YX, Cheng LZ, Liang LL, Zhang YQ, & Zhao ZQ (2012). Role of P2X7 receptor-mediated IL-18/IL-18R signaling in morphine tolerance: Multiple glial-neuronal dialogues in the rat spinal cord. The Journal of Pain, 13(10), 945–958. 10.1016/j.jpain.2012.06.007 [PubMed: 22968128]

Chiarugi P. (2008). Src redox regulation: There is more than meets the eye. Molecules and Cells, 26(4), 329–337. [PubMed: 18772619]

Cohen SP, Vase L, & Hooten WM (2021). Chronic pain: An update on burden, best practices, and new advances. Lancet, 397(10289), 2082–2097. 10.1016/S0140-6736(21)00393-7 [PubMed: 34062143]

Colasanti M, & Suzuki H (2000). The dual personality of NO. Trends in Pharmacological Sciences, 21(7), 249–252. 10.1016/s0165-6147(00)01499-1 [PubMed: 10979862]

Deshmane SL, Kremlev S, Amini S, & Sawaya BE (2009). Monocyte chemoattractant protein-1 (MCP-1): An overview. Journal of Interferon & Cytokine Research, 29(6), 313–326. 10.1089/jir.2008.0027 [PubMed: 19441883]

Du ER, Fan RP, Rong LL, Xie Z, & Xu CS (2020). Regulatory mechanisms and therapeutic potential of microglial inhibitors in neuropathic pain and morphine tolerance. Journal of Zhejiang University. Science. B, 21(3), 204–217. 10.1631/jzus.B1900425 [PubMed: 32133798]

Eidson LN, & Murphy AZ (2013). Blockade of Toll-like receptor 4 attenuates morphine tolerance and facilitates the pain relieving properties of morphine. The Journal of Neuroscience, 33(40), 15952–15963. 10.1523/JNEUROSCI.1609-13.2013 [PubMed: 24089500]

Eisenstein TK (2019). The role of opioid receptors in immune system function. Frontiers in Immunology, 10, 2904. 10.3389/fimmu.2019.02904 [PubMed: 31921165]

Ferrini F, Trang T, Mattioli TA, Laffray S, del'Guidice T, Lorenzo LE, Castonguay A, Doyon N, Zhang W, Godin AG, Mohr D, Beggs S, Vandal K, Beaulieu JM, Cahill CM, Salter MW, & de Koninck Y (2013). Morphine hyperalgesia gated through microglia-mediated disruption of neuronal Cl(−) homeostasis. Nature Neuroscience, 16(2), 183–192. 10.1038/nn.3295 [PubMed: 23292683]

Fillingim RB, Loeser JD, Baron R, & Edwards RR (2016). Assessment of chronic pain: Domains, methods, and mechanisms. The Journal of Pain, 17(9 Suppl), T10–T20. 10.1016/j.jpain.2015.08.010 [PubMed: 27586827]

Goldberg DS, & McGee SJ (2011). Pain as a global public health priority. BMC Public Health, 11, 770. 10.1186/1471-2458-11-770 [PubMed: 21978149]

Grace PM, Strand KA, Galer EL, Urban DJ, Wang X, Baratta MV, Fabisiak TJ, Anderson ND, Cheng K, Greene LI, Berkelhammer D, Zhang Y, Ellis AL, Yin HH, Campeau S, Rice KC, Roth BL, Maier SF, & Watkins LR (2016). Morphine paradoxically prolongs neuropathic pain in rats by amplifying spinal NLRP3 inflammasome activation. Proceedings of the National Academy of Sciences of the United States of America, 113(24), E3441–E3450. 10.1073/pnas.1602070113 [PubMed: 27247388]

Gu N, Yi MH, Murugan M, Xie M, Parusel S, Peng J, Eyo UB, Hunt CL, Dong H, & Wu LJ (2022). Spinal microglia contribute to sustained inflammatory pain via amplifying neuronal activity. Molecular Brain, 15(1), 86. 10.1186/s13041-022-00970-3 [PubMed: 36289499]

Han D, Dong W, & Jiang W (2022). Pinocembrin alleviates chronic morphine-induced analgesic tolerance and hyperalgesia by inhibiting microglial activation. Neurological Research, 44(10), 946–955. 10.1080/01616412.2022.2075656 [PubMed: 35574904]

Han Y, Jiang C, Tang J, Wang C, Wu P, Zhang G, Liu W, Jamangulova N, Wu X, & Song X (2014). Resveratrol reduces morphine tolerance by inhibiting microglial activation via AMPK signalling. European Journal of Pain, 18(10), 1458–1470. 10.1002/ejp.511 [PubMed: 24756886]

Harry GJ (2013). Microglia during development and aging. Pharmacology & Therapeutics, 139(3), 313–326. 10.1016/j.pharmthera.2013.04.013 [PubMed: 23644076]

Heles M, Mrozkova P, Sulcova D, Adamek P, Spicarova D, & Palecek J (2021). Chemokine CCL2 prevents opioid-induced inhibition of nociceptive synaptic transmission in spinal cord dorsal horn. Journal of Neuroinflammation, 18(1), 279. 10.1186/s12974-021-02335-4 [PubMed: 34857006]

Highfield DA, & Grant S (1998). Ng-nitro-L-arginine, an NOS inhibitor, reduces tolerance to morphine in the rat locus coeruleus. Synapse, 29(3), 233–239. 10.1002/(SICI)1098-2396(199807)29:3<233::AID-SYN5>3.0.CO;2-7 [PubMed: 9635893]

Hines CB, & Owings CR (2021). Opioids: Understanding how acute actions impact chronic consequences. Dimensions of Critical Care Nursing, 40(5), 268–274. 10.1097/DCC.0000000000000487 [PubMed: 34398562]

Horvath RJ, & DeLeo JA (2009). Morphine enhances microglial migration through modulation of P2X4 receptor signaling. The Journal of Neuroscience, 29(4), 998–1005. 10.1523/JNEUROSCI.4595-08.2009 [PubMed: 19176808]

Horvath RJ, Romero-Sandoval EA, & De Leo JA (2010). Inhibition of microglial P2X4 receptors attenuates morphine tolerance, Iba1, GFAP and mu opioid receptor protein expression while enhancing perivascular microglial ED2. Pain, 150(3), 401–413. 10.1016/j.pain.2010.02.042 [PubMed: 20573450]

Huang S, Chen L, Bladen C, Stys PK, & Zamponi GW (2018). Differential modulation of NMDA and AMPA receptors by cellular prion protein and copper ions. Molecular Brain, 11(1), 62. 10.1186/s13041-018-0406-3 [PubMed: 30359282]

Huang Y, Smith DE, Ibanez-Sandoval O, Sims JE, & Friedman WJ (2011). Neuron-specific effects of interleukin-1beta are mediated by a novel isoform of the IL-1 receptor accessory protein. The Journal of Neuroscience, 31(49), 18048–18059. 10.1523/JNEUROSCI.4067-11.2011 [PubMed: 22159118]

Illing S, Mann A, & Schulz S (2014). Heterologous regulation of agonist-independent mu-opioid receptor phosphorylation by protein kinase C. British Journal of Pharmacology, 171(5), 1330–1340. 10.1111/bph.12546 [PubMed: 24308893]

Jain M, Singh MK, Shyam H, Mishra A, Kumar S, Kumar A, & Kushwaha J (2021). Role of JAK/STAT in the neuroinflammation and its association with neurological disorders. Annals of Neurosciences, 28(3–4), 191–200. 10.1177/09727531211070532 [PubMed: 35341232]

Jiang M, Xie H, Zhang C, Wang T, Tian H, Lu L, Xu JY, Xu GT, Liu L, & Zhang J (2022). Enhancing fractalkine/CX3CR1 signalling pathway can reduce neuroinflammation by attenuating microglia activation in experimental diabetic retinopathy. Journal of Medicine and Biochemistry, 26(4), 1229–1244. 10.1111/jcmm.17179

Johnston IN, Milligan ED, Wieseler-Frank J, Frank MG, Zapata V, Campisi J, Langer S, Martin D, Green P, Fleshner M, Leinwand L, Maier SF, & Watkins LR (2004). A role for proinflammatory cytokines and fractalkine in analgesia, tolerance, and subsequent pain facilitation induced by chronic intrathecal morphine. Rapid Communications, 24(33), 7353–7365. 10.1523/JNEUROSCI.1850-04.2004

Kobayashi K, Imagama S, Ohgomori T, Hirano K, Uchimura K, Sakamoto K, Hirakawa A, Takeuchi H, Suzumura A, Ishiguro N, & Kadomatsu K (2013). Minocycline selectively inhibits M1 polarization of microglia. Cell Death and Disease, 4(3), e525. 10.1038/cddis.2013.54 [PubMed: 23470532]

Leduc-Pessah H, Weilinger NL, Fan CY, Burma NE, Thompson RJ, & Trang T (2017). Site-specific regulation of P2X7 receptor function in microglia gates morphine analgesic tolerance. The Journal of Neuroscience, 37(42), 10154–10172. 10.1523/JNEUROSCI.0852-17.2017 [PubMed: 28924009]

Leng F, & Edison P (2021). Neuroinflammation and microglial activation in Alzheimer disease: Where do we go from here? Nature Reviews. Neurology, 17(3), 157–172. 10.1038/s41582-020-00435-y [PubMed: 33318676]

Liang Y, Chu H, Jiang Y, & Yuan L (2016). Morphine enhances IL-1beta release through Toll-like receptor 4-mediated endocytic pathway in microglia. Purinergic Signalling, 12(4), 637–645. 10.1007/s11302-016-9525-4 [PubMed: 27506813]

Lin CP Kang KH, Lin TH, Wu MY, Liou HC, Chuang WJ, Sun WZ, & Fu WM (2015). Role of spinal CXCL1 (GROalpha) in opioid tolerance: A human-to-rodent translational study. Anesthesiology, 122(3), 666–676. 10.1097/ALN.0000000000000523 [PubMed: 25383568]

Lin CP, & Lu DH (2018). Role of neuroinflammation in opioid tolerance: Translational evidence from human-to-rodent studies. Advances in Experimental Medicine and Biology, 1099, 125–139. 10.1007/978-981-13-1756-9_11 [PubMed: 30306520]

Lin SH, Huang YN, Kao JH, Tien LT, Tsai RY, & Wong CS (2016). Melatonin reverses morphine tolerance by inhibiting microglia activation and HSP27 expression. Life Sciences, 152, 38–43. 10.1016/j.lfs.2016.03.032 [PubMed: 27012766]

Liu DQ, Zhou YQ, & Gao F (2019). Targeting cytokines for morphine tolerance: A narrative review. Current Neuropharmacology, 17(4), 366–376. 10.2174/1570159X15666171128144441 [PubMed: 29189168]

Liu L, Gao XJ, Ren CG, Hu JH, Liu XW, Zhang P, Zhang ZW, & Fu ZJ (2017). Monocyte chemoattractant protein-1 contributes to morphine tolerance in rats with cancer-induced bone pain. Experimental and Therapeutic Medicine, 13(2), 461–466. 10.3892/etm.2016.3979 [PubMed: 28352316]

Loggia ML, Chonde DB, Akeju O, Arabasz G, Catana C, Edwards RR, Hill E, Hsu S, Izquierdo-Garcia D, Ji RR, Riley M, Wasan AD, Zürcher NR, Albrecht DS, Vangel MG, Rosen BR, Napadow V, & Hooker JM (2015). Evidence for brain glial activation in chronic pain patients. Brain Communications, 138(Pt 3), 604–615. 10.1093/brain/awu377

Machelska H, & Celik MO (2020). Opioid receptors in immune and glial cells-implications for pain control. Frontiers in Immunology, 11, 300. 10.3389/fimmu.2020.00300 [PubMed: 32194554]

Maduna T, Audouard E, Dembele D, Mouzaoui N, Reiss D, Massotte D, & Gaveriaux-Ruff C (2018). Microglia express mu opioid receptor: Insights from transcriptomics and fluorescent reporter mice. Frontiers in Psychiatry/Frontiers Research Foundation, 9, 726. 10.3389/fpsyt.2018.00726

Majeed NH, Przewlocka B, Machelska H, & Przewlocki R (1994). Inhibition of nitric oxide synthase attenuates the development of morphine tolerance and dependence in mice. Neuropharmacology, 33(2), 189–192. 10.1016/0028-3908(94)90006-x [PubMed: 7518573]

Matsushita Y, Omotuyi IO, Mukae T, & Ueda H (2013). Microglia activation precedes the anti-opioid BDNF and NMDA receptor mechanisms underlying morphine analgesic tolerance. Current Pharmaceutical Design, 19(42), 7355–7361. 10.2174/13816128194214010516173 [PubMed: 23448475]

Mazaud D, Capano A, & Rouach N (2021). The many ways astroglial connexins regulate neurotransmission and behavior. Glia, 69, 2527–2545. 10.1002/glia.24040 [PubMed: 34101261]

Merighi S, Gessi S, Varani K, Fazzi D, Stefanelli A, & Borea PA (2013). Morphine mediates a proinflammatory phenotype via muopioid receptor-PKCvarepsilon-Akt-ERK1/2 signaling pathway in activated microglial cells. Biochemical Pharmacology, 86(4), 487–496. 10.1016/j.bcp.2013.05.027 [PubMed: 23796752]

Mika J, Popiolek-Barczyk K, Rojewska E, Makuch W, Starowicz K, & Przewlocka B (2014). Delta-opioid receptor analgesia is independent of microglial activation in a rat model of neuropathic pain. PLoS One, 9(8), e104420. 10.1371/journal.pone.0104420 [PubMed: 25105291]

Mika J, Wawrzczak-Bargiela A, Osikowicz M, Makuch W, & Przewlocka B (2009). Attenuation of morphine tolerance by minocycline and pentoxifylline in naive and neuropathic mice. Brain, Behavior, and Immunity, 23(1), 75–84. 10.1016/j.bbi.2008.07.005 [PubMed: 18684397]

Mills SEE, Nicolson KP, & Smith BH (2019). Chronic pain: A review of its epidemiology and associated factors in population-based studies. British Journal of Anaesthesia, 123(2), e273–e283. 10.1016/j.bja.2019.03.023 [PubMed: 31079836]

Miranda-Riestra A, Estrada-Reyes R, Torres-Sanchez ED, Carreno-Garcia S, Ortiz GG, & Benitez-King G (2022). Melatonin: A neurotrophic factor? Molecules, 27(22), 7742. 10.3390/molecules27227742 [PubMed: 36431847]

Mitrovic B, St Pierre BA, Mackenzie-Graham AJ, & Merrill JE (1994). The role of nitric oxide in glial pathology. Annals of the New York Academy of Sciences, 738, 436–446. 10.1111/j.1749-6632.1994.tb21835.x [PubMed: 7832453]

Morgan MM, & Christie MJ (2011). Analysis of opioid efficacy, tolerance, addiction and dependence from cell culture to human. British Journal of Pharmacology, 164(4), 1322–1334. 10.1111/j.1476-5381.2011.01335.x [PubMed: 21434879]

Pan Y, Sun X, Jiang L, Hu L, Kong H, Han Y, Qian C, Song C, Qian Y, & Liu W (2016). Metformin reduces morphine tolerance by inhibiting microglial-mediated neuroinflammation. Journal of Neuroinflammation, 13(1), 294. 10.1186/s12974-016-0754-9 [PubMed: 27855689]

Paolicelli RC, Sierra A, Stevens B, Tremblay ME, Aguzzi A, Ajami B, Amit I, Audinat E, Bechmann I, Bennett M, Bennett F, Bessis A, Biber K, Bilbo S, Blurton-Jones M, Boddeke E, Brites D, Brône B, Brown GC, … Wyss-Coray T (2022). Microglia states and nomenclature: A field at its cross-roads. Neuron, 110(21), 3458–3483. 10.1016/j.neuron.2022.10.020 [PubMed: 36327895]

Parkinson JF, Mitrovic B, & Merrill JE (1997). The role of nitric oxide in multiple sclerosis. Journal of Molecular Medicine (Berlin, Germany), 75(3), 174–186. 10.1007/s001090050102 [PubMed: 9106074]

Pawelec P, Ziemka-Nalecz M, Sypecka J, & Zalewska T (2020). The impact of the CX3CL1/CX3CR1 axis in neurological disorders. Cell, 9(10), 2277. 10.3390/cells9102277

Pepe S, van den Brink OW, Lakatta EG, & Xiao RP (2004). Cross-talk of opioid peptide receptor and beta-adrenergic receptor signalling in the heart. Cardiovascular Research, 63(3), 414–422. 10.1016/j.cardiores.2004.04.022 [PubMed: 15276466]

Pozzo ED, Tremolanti C, Costa B, Giacomelli C, Milenkovic VM, Bader S, Wetzel CH, Rupprecht R, Taliani S, Settimo FD, & Martini C (2019). Microglial pro-inflammatory and anti-inflammatory phenotypes are modulated by translocator protein activation. IJMS, 20(18), 4467. 10.3390/ijms20184467 [PubMed: 31510070]

Price DD, Mayer DJ, Mao J, & Caruso FS (2000). NMDA-receptor antagonists and opioid receptor interactions as related to analgesia and tolerance. Journal of Pain and Symptom Management, 19(1 Suppl), S7–S11. 10.1016/s0885-3924(99)00121-9 [PubMed: 10687332]

Qiu Y, Law PY, & Loh HH (2003). Mu-opioid receptor desensitization: Role of receptor phosphorylation, internalization, and representation. The Journal of Biological Chemistry, 278(38), 36733–36739. 10.1074/jbc.M305857200 [PubMed: 12860981]

Rasul A, Millimouno FM, Ali Eltayb W, Ali M, Li J, & Li X (2013). Pinocembrin: A novel natural compound with versatile pharmacological and biological activities. BioMed Research International, 2013, 379850. 10.1155/2013/379850 [PubMed: 23984355]

Reiss D, Maduna T, Maurin H, Audouard E, & Gaveriaux-Ruff C (2022). Mu opioid receptor in microglia contributes to morphine analgesic tolerance, hyperalgesia, and withdrawal in mice. Journal of Neuroscience Research, 100(1), 203–219. 10.1002/jnr.24626 [PubMed: 32253777]

Rivat C, & Ballantyne J (2016). The dark side of opioids in pain management: Basic science explains clinical observation. Pain Reports, 1(2), e570. 10.1097/PR9.0000000000000570 [PubMed: 29392193]

Rivat C, Sebaihi S, van Steenwinckel J, Fouquet S, Kitabgi P, Pohl M, Melik Parsadaniantz S, & Reaux-le Goazigo A (2014). Src family kinases involved in CXCL12-induced loss of acute morphine analgesia. Brain, Behavior, and Immunity Health, 38, 38–52. 10.1016/j.bbi.2013.11.010

Roberts J, Ossipov MH, & Porreca F (2009). Glial activation in the rostroventromedial medulla promotes descending facilitation to mediate inflammatory hypersensitivity. The European Journal of Neuroscience, 30(2), 229–241. 10.1111/j.1460-9568.2009.06813.x [PubMed: 19614984]

Saijo K, Crotti A, & Glass CK (2010). Nuclear receptors, inflammation, and neurodegenerative diseases. Advances in Immunology, 106, 21–59. 10.1016/S0065-2776(10)06002-5 [PubMed: 20728023]

Santamarta MT, Llorente J, Mendiguren A, & Pineda J (2014). Involvement of neuronal nitric oxide synthase in desensitisation of micro-opioid receptors in the rat locus coeruleus. Journal of Psychopharmacology, 28(10), 903–914. 10.1177/0269881114538542 [PubMed: 24961237]

Schulz S, Mayer D, Pfeiffer M, Stumm R, Koch T, & Hollt V (2004). Morphine induces terminal micro-opioid receptor desensitization by sustained phosphorylation of serine-375. The EMBO Journal, 23(16), 3282–3289. 10.1038/sj.emboj.7600334 [PubMed: 15272312]

Sepehrizadeh Z, Sahebgharani M, Ahmadi S, Shapourabadi MB, Bozchlou SH, & Zarrindast MR (2008). Morphine-induced behavioral sensitization increased the mRNA expression of NMDA receptor subunits in the rat amygdala. Pharmacology, 81(4), 333–343. 10.1159/000122959 [PubMed: 18391508]

Shabab T, Khanabdali R, Moghadamtousi SZ, Kadir HA, & Mohan G (2017). Neuroinflammation pathways: A general review. The International Journal of Neuroscience, 127(7), 624–633. 10.1080/00207454.2016.1212854 [PubMed: 27412492]

Shavit Y, Wolf G, Goshen I, Livshits D, & Yirmiya R (2005). Interleukin-1 antagonizes morphine analgesia and underlies morphine tolerance. Pain, 115(1–2), 50–59. 10.1016/j.pain.2005.02.003 [PubMed: 15836969]

Shen CH, Tsai RY, Shih MS, Lin SL, Tai YH, Chien CC, & Wong CS (2011). Etanercept restores the antinociceptive effect of morphine and suppresses spinal neuroinflammation in morphine-tolerant rats. Anesthesia and Analgesia, 112(2), 454–459. 10.1213/ANE.0b013e3182025b15 [PubMed: 21081778]

Shen CH, Tsai RY, & Wong CS (2012). Role of neuroinflammation in morphine tolerance: Effect of tumor necrosis factor-alpha. Acta Anaesthesiologica Taiwanica, 50(4), 178–182. 10.1016/j.aat.2012.12.004 [PubMed: 23385041]

Shipton EA, Shipton EE, & Shipton AJ (2018). A review of the opioid epidemic: What do we do about it? Pain and Therapy, 7(1), 23–36. 10.1007/s40122-018-0096-7 [PubMed: 29623667]

Simpson DSA, & Oliver PL (2020). ROS generation in microglia: Understanding oxidative stress and inflammation in neurodegenerative disease. Antioxidants (Basel), 9(8), 743. 10.3390/antiox9080743 [PubMed: 32823544]

Skolnick P. (2018). The opioid epidemic: Crisis and solutions. Annual Review of Pharmacology and Toxicology, 58, 143–159. 10.1146/annurev-pharmtox-010617-052534

Steinkasserer A, Spurr NK, Cox S, Jeggo P, & Sim RB (1992). The human IL-1 receptor antagonist gene (IL1RN) maps to chromosome 2q14-q21, in the region of the IL-1 alpha and IL-1 beta loci. Genomics, 13(3), 654–657. 10.1016/0888-7543(92)90137-h [PubMed: 1386337]

Taves S, Berta T, Chen G, & Ji RR (2013). Microglia and spinal cord synaptic plasticity in persistent pain. Neural Plasticity, 2013, 753656. 10.1155/2013/753656 [PubMed: 24024042]

. (2022). Opioids for pain. The Medical Letter on Drugs and Therapeutics, 64(1665), 193–200. [PubMed: 36541938]

Tu H, Chu H, Guan S, Hao F, Xu N, Zhao Z, & Liang Y (2021). The role of the M1/M2 microglia in the process from cancer pain to morphine tolerance. Tissue & Cell, 68, 101438. 10.1016/j.tice.2020.101438 [PubMed: 33220596]

van Noort JM (2008). Stress proteins in CNS inflammation. The Journal of Pathology, 214(2), 267–275. 10.1002/path.2273 [PubMed: 18161755]

Volkow ND, & Koroshetz WJ (2019). The role of neurologists in tackling the opioid epidemic. Nature Reviews. Neurology, 15(5), 301–305. 10.1038/s41582-019-0146-8 [PubMed: 30792513]

Wang X, Loram LC, Ramos K, de Jesus AJ, Thomas J, Cheng K, Reddy A, Somogyi AA, Hutchinson MR, Watkins LR, & Yin H (2012). Morphine activates neuroinflammation in a manner parallel to endotoxin. Proceedings of the National Academy of Sciences of the United States of America, 109(16), 6325–6330. 10.1073/pnas.1200130109 [PubMed: 22474354]

Williams JT, Ingram SL, Henderson G, Chavkin C, von Zastrow M, Schulz S, Koch T, Evans CJ, & Christie MJ (2013). Regulation of mu-opioid receptors: Desensitization, phosphorylation, internalization, and tolerance. Pharmacological Reviews, 65(1), 223–254. 10.1124/pr.112.005942 [PubMed: 23321159]

Yang Y, Sun Y, Hu R, Yan J, Wang Z, Li W, & Jiang H (2021). Morphine promotes microglial activation by upregulating the EGFR/ERK signaling pathway. PLoS One, 16(9), e0256870. 10.1371/journal.pone.0256870 [PubMed: 34520454]

Zeng Y, Luo H, Gao Z, Zhu X, Shen Y, Li Y, Hu J, & Yang J (2021). Reduction of prefrontal purinergic signaling is necessary for the analgesic effect of morphine. iScience, 24(3), 102213. 10.1016/j.isci.2021.102213 [PubMed: 33733073]

Zhang L, Kibaly C, Wang YJ, Xu C, Song KY, McGarrah PW, Loh HH, Liu JG, & Law PY (2017). Src-dependent phosphorylation of mu-opioid receptor at Tyr(336) modulates opiate withdrawal. EMBO Molecular Medicine, 9(11), 1521–1536. 10.15252/emmm.201607324 [PubMed: 28818835]

Zhang L, Zhang J, & You Z (2018). Switching of the microglial activation phenotype is a possible treatment for depression disorder. Frontiers in Cellular Neuroscience, 12, 306. 10.3389/fncel.2018.00306 [PubMed: 30459555]

Zhang N, Rogers TJ, Caterina M, & Oppenheim JJ (2004). Proinflammatory chemokines, such as C-C chemokine ligand 3, desensitize mu-opioid receptors on dorsal root ganglia neurons. Journal of Immunology, 173(1), 594–599. 10.4049/jimmunol.173.1.594

Zhang X, Wang J, Yu T, Du D, & Jiang W (2015). Minocycline can delay the development of morphine tolerance, but cannot reverse existing tolerance in the maintenance period of neuropathic pain in rats. Clinical and Experimental Pharmacology & Physiology, 42(1), 94–101. 10.1111/1440-1681.12316 [PubMed: 25311407]

Zhang Y, Li H, Li Y, Sun X, Zhu M, Hanley G, Lesage G, & Yin D (2011). Essential role of Toll-like receptor 2 in morphine-induced microglia activation in mice. Neuroscience Letters Supplement, 489(1), 43–47. 10.1016/j.neulet.2010.11.063

Zhang Y, Tao GJ, Hu L, Qu J, Han Y, Zhang G, Qian Y, Jiang CY, & Liu WT (2017). Lidocaine alleviates morphine tolerance via AMPK-SOCS3-dependent neuroinflammation suppression in the spinal cord. Journal of Neuroinflammation, 14(1), 211. 10.1186/s12974-017-0983-6 [PubMed: 29096659]

Zhao CM, Guo RX, Hu F, Meng JL, Mo LQ, Chen PX, Liao XX, Cui Y, & Feng JQ (2012). Spinal MCP-1 contributes to the development of morphine antinociceptive tolerance in rats. The American Journal of the Medical Sciences, 344(6), 473–479. 10.1097/MAJ.0b013e31826a82ce [PubMed: 23187120]

Zhao YL, Chen SR, Chen H, & Pan HL (2012). Chronic opioid potentiates presynaptic but impairs postsynaptic N-methyl-D-aspartic acid receptor activity in spinal cords: Implications for opioid hyperalgesia and tolerance. The Journal of Biological Chemistry, 287(30), 25073–25085. 10.1074/jbc.M112.378737 [PubMed: 22679016]

Zhou D, Chen ML, Zhang YQ, & Zhao ZQ (2010). Involvement of spinal microglial P2X7 receptor in generation of tolerance to morphine analgesia in rats. The Journal of Neuroscience, 30(23), 8042–8047. 10.1523/JNEURQSCI.5377-09.2010 [PubMed: 20534852]

Significance

We have summarized the evidence supporting the important role of microglia activation in modulating opioid analgesic tolerance. Thus, microglial inhibitors may represent an effective strategy to mitigate opioid tolerance.

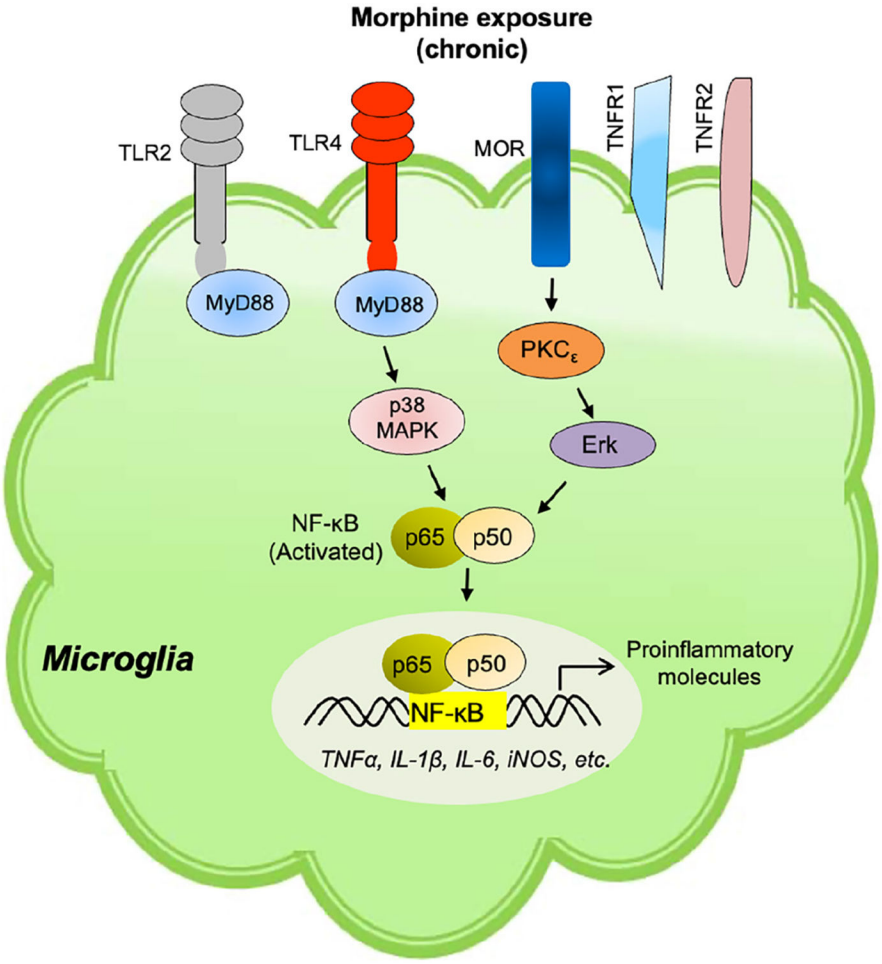

FIGURE 1.

Activation of microglia by morphine exposure. Microglia harbor different surface receptors including Toll-like receptor 2 (TLR2), TLR4, mu-opioid receptor (MOR), TNFα receptor 1 (TNFR1), TNFR2, etc. Chronic morphine exposure activates the TLR4 signaling pathway, leading to its association with adaptor protein myeloid differentiation primary response 88 (MyD88), transduction of downstream p38 mitogen-activated protein kinase (p38MAPK), and activation of nuclear factor-κB (NF-κB) pathway in microglia. Morphine also engages MOR to activate extracellular signal-regulated kinase (ERK), a classical MAP kinase, via protein kinase Cε (PKCε), for the activation of NF-κB in the cytoplasm. Activated NF-κB then translocates into the nucleus, and binds to NF-κB-binding sites present in the promoter region of the genes encoding different proinflammatory molecules, causing transcription of TNFα, IL-1β, inducible nitric oxide synthase (iNOS), and other proinflammatory molecules in microglia.

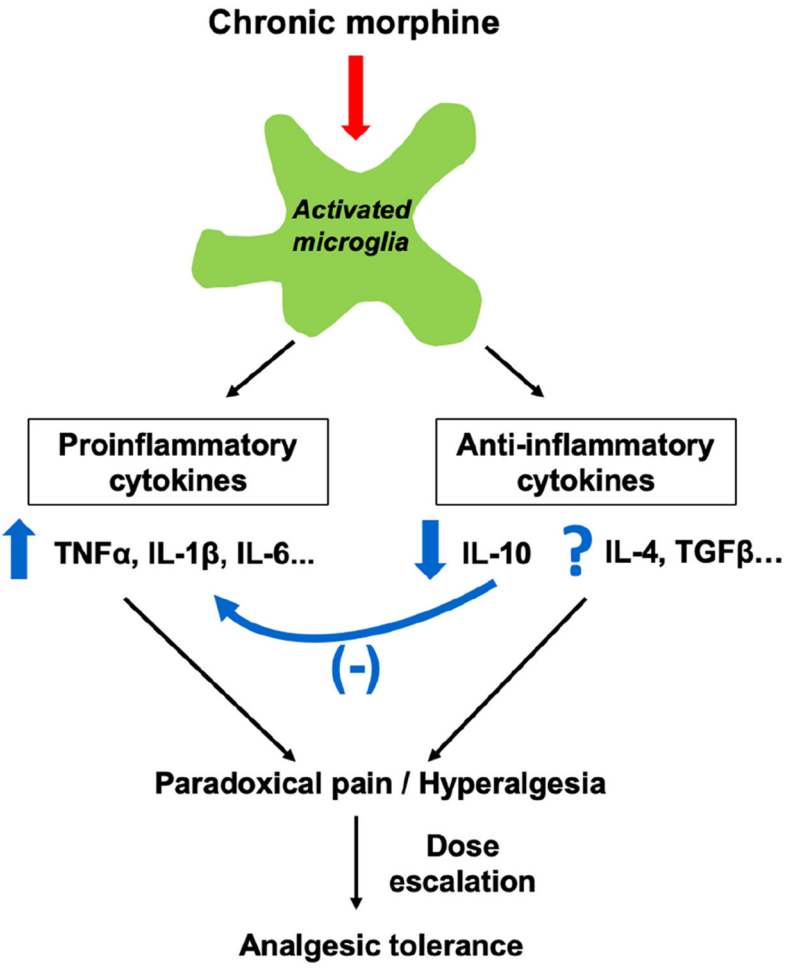

FIGURE 2.

Summary of the change in cytokines following chronic morphine exposure. Chronic morphine exposure activates microglia to release a battery of proinflammatory cytokines (TNFα, IL-1β, and IL-6) and suppress the expression of anti-inflammatory cytokines (IL-10, and possibly IL-4 and TGFβ). IL-10 has been shown to inhibit the production of proinflammatory cytokines. Thus, reduction of IL-10 may further increase the production of proinflammatory cytokines. Collectively, these changes promote morphine-induced paradoxical pain and hyperalgesia, leading to dose escalation of morphine and finally, tolerance.

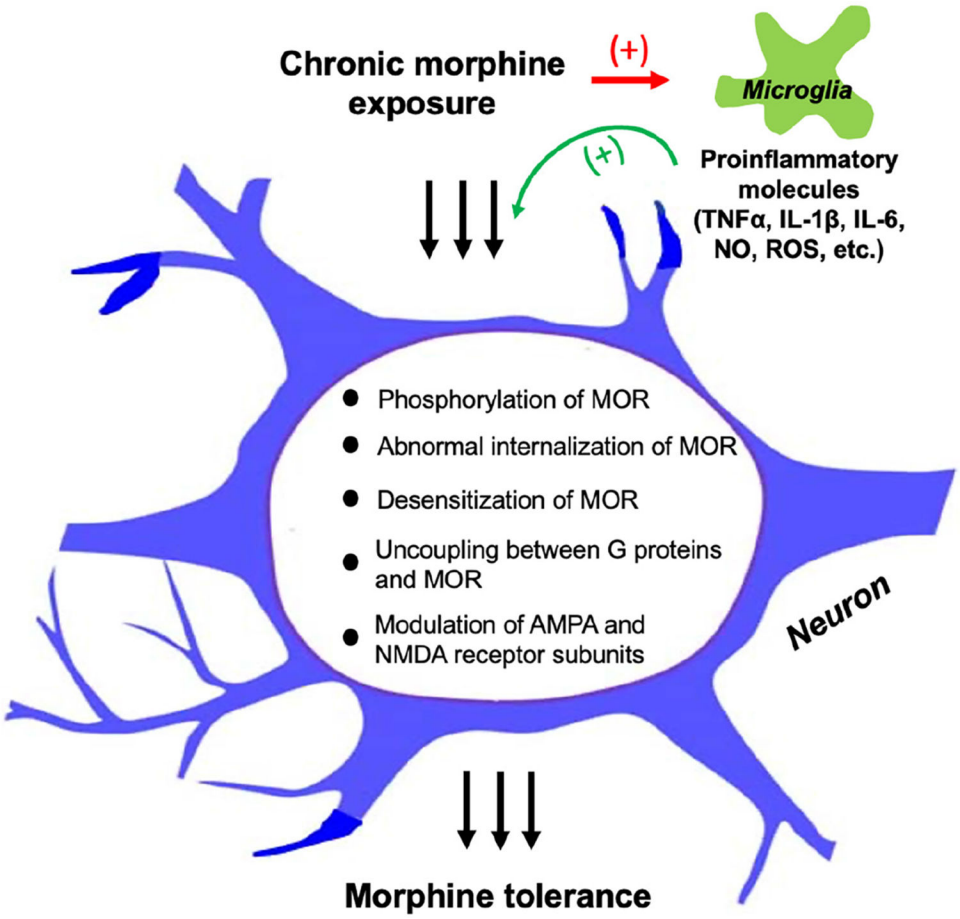

FIGURE 3.

Possible mechanisms of modulation of morphine tolerance by microglia-derived proinflammatory molecules. Chronic morphine exposure can directly act on neurons or modulate neuronal functions by activating microglia to produce a host of proinflammatory molecules and cause phosphorylation and desensitization of MOR and modulation of AMPA and NMDA receptor subunits in neurons, ultimately leading to tolerance to morphine.