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The Effect of Morphine on Glial Cells as a Potential Therapeutic Target for Pharmacological Development of Analgesic Drugs

Haroon Hameed · Mariam Hameed · Paul J. Christo

Abstract Opioids have played a critical role in achieving pain relief in both modern and ancient medicine. Yet, their clinical use can be limited secondary to unwanted side effects such as tolerance, dependence, reward, and behavioral changes. Identification of glial-mediated mechanisms inducing opioid side effects include cytokine receptors, κ-opioid receptors, *N*-methyl-D-aspartate receptors, and the recently elucidated Toll-like receptors. Newer agents targeting these receptors such as AV411, MK-801, AV333, and SLC022, and older agents used outside the United States or for other disease conditions, such as minocycline, pentoxifylline, and UV50488H, all show varied but promising profiles for providing significant relief from opioid side effects, while simultaneously potentiating opioid analgesia.

Keywords Toll-like receptor · Opioid receptor · Morphine · Dependence · Reward · Tolerance · NMDA · Ibudilast · Dizocilpine · Minocycline · Pentoxifylline · Propentofylline · Glial cell · Chronic pain · Analgesia · Pain relief

H. Hameed · M. Hameed
Department of Physical Medicine and Rehabilitation,
Johns Hopkins University School of Medicine,
600 North Wolfe Street, Phipps 160,
Baltimore, MD 21287, USA

H. Hameed
e-mail: hhameed1@jhmi.edu

M. Hameed
e-mail: mhameed1@jhmi.edu

P. J. Christo (✉)
Division of Pain Medicine, Department of Anesthesiology
and Critical Care Medicine,
Johns Hopkins University School of Medicine,
550 North Broadway, Suite 301,
Baltimore, MD 21205, USA
e-mail: pchristo@jhmi.edu

Introduction

Opioids have been used in the treatment of pain for thousands of years. Some date the use of opium poppy extracts for analgesia as far back as 3000 BC [1••]. Unfortunately, use of opioids for the treatment of pain has been associated with potential disadvantages, including development of tolerance, dependence, and undue side effects such as constipation, urinary retention, and mood and behavioral changes. Despite their side effects, opioids such as morphine, hydromorphone, oxycodone, and fentanyl continue to be widely prescribed due to their high efficacy in pain reduction.

The personal and social consequences of opioid use, such as addiction, have not only led doctors and patients to strive to limit opioid treatment, but there has also been an increasing trend toward tighter federal regulation of opioid prescriptions. For example, there currently is a US Food and Drug Administration motion to increase regulation of prescription of many opioids in the form of Risk Evaluation and Mitigation Strategies. Medications that soon may be included are generic and trade name versions of oral extended-release morphine and oxycodone, as well as extended-release transdermal fentanyl.

In addition to an increased interest in responsible opioid use, the current climate makes it more important to find methods to mitigate the unwanted side effects of opioids while preserving their qualities of highly effective pain relief. Many different mechanisms have been implicated in the genesis of opioid tolerance and dependence. This article reviews some of the different mechanisms involved, as well as specific glial-modifying agents that enhance opioid analgesia and mitigate tolerance.

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Glial Mechanisms of Pain, Opioid Tolerance, and Opioid Dependence

Glial cells appear to have a prominent role in the development of neuropathic pain syndromes such as complex regional pain syndrome, herpes zoster, diabetic neuropathy, AIDS, and tumors [2, 3]. These cells (astrocytes and microglia) make up 70% of cells found within the central nervous system (CNS). They act as neuronal support cells and immune cells in the CNS and have many important functions including maintaining neuronal homeostasis, impulse propagation, immune response, waste removal, and neuronal repair [4]. They surround synapses and lie in apposition to neuronal cell bodies [5]. Further, glia appear to play a central role in neuropathic pain perception development and maintenance by modulating neuronal signal transmission and excitability [6, 7], as well as development of opioid tolerance and dependence. These cells become upregulated in chronic pain states, as evidenced by an increase of their markers, glial fibrillary acid protein (GFAP), and cell surface receptors (OX-42 and CD11b) [7, 8]. Glial cells can be activated by noxious stimuli–like trauma, hypoxia, ischemia, inflammation, infection, or neuronal degeneration. More specifically, activation occurs through the binding of various neurotransmitter receptors, such as substance P, glutamate, *N*-methyl-D-aspartate (NMDA), and purinergic receptors. Continuous nociceptive input results in high levels of glutamate within synapses leading to dysregulation of glutamate transporters (GLT1 and GLAST), which are critical for removal of this excitatory neurotransmitter, further enhancing prolonged glial activation. After astrocytic receptor activation, the mitogen-activated protein kinase (MAPK) intracellular signaling pathways become activated. The MAPK family has three main members: the extracellular signal-regulated kinase, c-Jun N-terminal kinase (JNK), and p38 [9], each of which can activate the transcription factor, nuclear factor-κB (NF-κB), ultimately resulting in increased production of many substances such as proinflammatory cytokines and chemokines, neurotrophic factors, prostaglandins, nitric oxide, complement proteins, free radicals, neurotoxins, and excitatory amino acids [10, 11]. Important cytokines in the generation of pain include interleukin (IL)-1α, IL-1β, IL-6, tumor necrosis factor (TNF)-α, and IL-10 and are discussed below. These spinal cytokines have also been shown to oppose acute and chronic opioid analgesia [12].

Cytokines

IL-1α and IL-1β, the IL-1 type-1 receptor and its accessory protein, appear to be important in the generation of neuropathic pain. This is evidenced by research showing that intrathecal IL-1β injection can induce allodynia and hyperalgesia [13, 14••, 15]. Also, experiments have shown that IL-1β induces apoptosis by phosphorylation of p38 of MAPK, leading to the apoptotic caspace cascade by activation of caspace-3 [14••]. p38 MAPK has also been linked to morphine tolerance in spinal microglia by a mechanism of upregulation of p38 MAPK positive cells after chronic morphine administration [14••]. The mechanisms in which IL-1β induces sensory neuronal sensitization to pain through IL-1 receptor type-1 activation is thought to involve tyrosine kinases as well as protein kinase C [14••]. On the contrary, intrathecal IL-1α administration has been shown to dose dependently relieve neuropathic pain symptoms [14••]. IL-1—related cascades are well studied and appear to be of high importance, especially in conjunction with other receptors in activating the processes that lead to negative glia-mediated opioid sequelae as described later.

IL-6 has also been linked to the etiology of many neurological disorders as mentioned above. Studies have shown increased ipsilateral expression of IL-6 in the dorsal root ganglion after nociceptive stimulation [14••]. Interestingly, in contrast to the pain promoting effects of IL-1, intrathecal IL-6 injection has been shown to have an inhibitory effect on neuropathic pain [16].

Among the studied cytokines, IL-10 has been shown to possess the most potent anti-inflammatory action, and its release downregulates the expression of other cytokines, namely IL-1β, IL-6, and TNF-α [17]. IL-10 has also been shown in experimental animals to reduce chronic pain over 2 months duration after administration of a single dose [18]. It acts by downregulating proinflammatory genes, which leads to decreased expression of the above mentioned cytokines and their receptors and upregulation of their functional antagonists [19, 20]. IL-10 upregulation is currently a promising new target for glia-modifying medications, and we expect much research regarding such Il-10—modifying agents in the coming years.

TNF-α is another potent cytokine associated with the induction of inflammation in the CNS as well as in peripheral tissues. In the CNS, it is also produced by microglial cells and has been shown to be released after injury [21]. It appears to have dual action. Although its proinflammatory destructive effects are mediated through the p55 TNF-α receptor-1 [22], interestingly, TNF-α also plays a neuroprotective role. This is demonstrated by its ability to encourage expression of antiapoptotic and antioxidative proteins via the p75 TNF-α receptor-2 [22]. Both of these effects through different receptor mechanisms may provide targets for future glia-modifying medications (Table 1).

Table 1 Highly relevant cytokines

Cytokines	Mechanism of action	Effects
IL-1β	IL-1 receptor type 1 activation, tyrosine kinases, protein kinase C	Neuropathic pain
	Phosphorylation of p38	Apoptosis
TNF-α	p55 TNF-α receptor-1	Neuropathic pain
	p75 TNF-α receptor-2	Neuroprotective role
IL-10	Downregulation of proinflammatory cytokine expression with upregulation of functional antagonists	Relieves neuropathic pain

IL interleukin, *TNF* tumor necrosis factor

Toll-like Receptors

A very exciting discovery has been elaboration of the Toll-like receptor (TLR) and how it relates to glial activation. TLRs are a group of pattern recognition receptors found on astrocytes and mainly microglia that can be activated by exogenous (pathogenic proteins) and endogenous (IL-1β, TNF-α) molecules; when activated, they produce an immune response resulting in the release of cytokines. TLR activation has been positively linked to the development of opioid tolerance and other side effects, decreased opioid efficacy, and the development and maintenance of neuropathic pain [1••]. TLRs are composed of 10 different transmembrane receptors that bind a wide variety of exogenous and endogenous substances, which are inherently immunoreactive. Exogenous TLR-activating substances, which have been well characterized, include lipopolysaccharides (LPS), such as gram-negative bacteria, and endogenous substances that include cell membrane components, DNA and RNA, plasma proteins, and heat shock proteins [23, 24]. TLRs that have received the most attention with respect to mediating neuropathic pain include TLR2 and TLR4.

TLRs appear to activate very similar signaling pathways to IL-1, and some researchers now refer to this pathway as the TLR-IL1 signaling pathway [25]. That is, TLRs work through activation of an adapter protein known as myeloid differentiation factor 88 (MyD88). This factor leads to activation of the IL-1 receptor—associated kinases (IRAKs) and TNF receptor—associated factor-6 (TRAF6), which finally culminates in activation of NF-κB [26••]. Other TLR-associated pathways include the JNK and interferon (IFN) pathways [27]. Both TLR2 and TLR4 are important in recognizing endogenous pain-mediating signals such as those mentioned above. These studies have shown a highly interconnected web of pathways involving TLRs and other well-defined proinflammatory pathways previously known to be associated with neuropathic pain, glial activation, and opioid side effects; they provide a convincing platform of evidence in favor of the central role of the TLRs. Further, various knockout and knockdown studies of TLR2 and TLR4 that show suppression of nerve injury—induced allodynia strengthen this viewpoint [23, 24].

Toll-like Receptors and Neuropathic Pain

TLRs offer a convincing body of evidence of their role in neuropathic pain. Among these, TLR4 appears to be the most significant, with TLR2 and TLR3 playing minor roles. TLR4 is normally expressed on microglia, but its expression can also be induced on astrocytes in response to inflammation [27]. The CNS microglial response to inflammation includes activation of the TLR4-related pathways, leading to increased IFN-γ, IL-1β, and TNF-α. This TLR4-related cascade has been explained using the well-defined effect of bacterial LPS on the CNS. After binding the LPS-binding protein, LPS is delivered to cluster determinant 14 (CD14) on the microglial cell membrane, causing activation of intracellular sphingomyelinase, which cleaves to form ceramide. Ceramide causes production of a "lipid raft" containing the coreceptor myeloid differentiation factor 2 (MyD2), TLR4, and heat shock proteins 70 and 90, in addition to others. Further heterodimerization and homodimerization of MyD2-TLR4 pairs occurs after LPS presentation by CD14 to MyD2. Finally, proinflammatory cytokine production results from the NF-κB MAPK pathways [28••].

Prior studies have also shown direct links between TLR4 and neuropathic pain models. One study showed TLR4 was important in initiation of nerve injury-induced hypersensitivity, and correspondingly, TLR4 mRNA has been shown to be increased in spinal microglia post-L5 nerve transection [26••]. TLR4 knockout animals do not develop allodynia, which is likely due to reduction of glial activation and cytokine expression; TLR4 antisense nucleotide therapy results in reduced spinal proinflammatory cytokine production and reduced microglial activation, with resultant decreased centrally mediated neuropathic pain [23]. These effects may be mediated through decreased binding of TLRs to heat shock proteins (HSPs), especially HSP70 and HSP90, with resultant decreased induction of TNF-α and IL-6 release [29]. Moreover, decreased activation of TLR4 results in decreased induction of its ligand fibronectin, which has been shown to be upregulated in neuropathic pain, and is responsible for P2X4 ATP-receptor activation post nerve injury [26••]. This P2X4 downregulation is thought to be closely linked to a decrease in development of allodynia [30]. P2X4 is also closely related to microglial migration, which plays a role in the development and maintenance of neuropathic pain [31].

Toll-like Receptors and Inflammatory Pain

Although direct evidence is lacking, tissue damage and subsequent release of endogenous proinflammatory products and factors as well exogenous substances, such as bacterial endotoxins, can lead to inflammatory pain. Levels of inflammatory pain correlate with microglial activation. Secondary to this, some propose a concept that microglial activation is necessary to states involving facilitated pain, which include inflammatory pain in addition to neuropathic pain [32]. This correlates with data reporting increased upregulation of microglial activation markers following administration of LPS and polyinosinic:polycytidylic acid, a viral infection simulator [26••]. In addition, in a model of Freund's adjuvant-induced chronic inflammatory pain, increased expression of TLR4 and inflammatory cytokines has been described. These data contribute to the validity of a relationship between inflammatory pain and TLR activation.

Toll-like Receptors and Opioid Tolerance and Dependence

For some time, researchers have postulated that an independent mechanism is responsible for tolerance, hyperalgesia, physical dependence, reward, and respiratory depression than those effects mediated by classical opioid receptors such as μ, κ, and δ receptors.

In a recent study, the induction of opioid-induced hyperalgesia in triple receptor knockout mice suggests that opioids also act through different mechanisms separate from the classic opioid receptors on neurons. It has been shown that opioids can bind to TLR-4 receptors on glial cells leading to their activation and synthesis of nociceptive cytokines, thus enhancing neuropathic pain and counteracting opioid analgesic effects [5]. Opioid receptor-independent opioid effects were corroborated by the development of opioid-induced hyperalgesia in triple opioid receptor knockout animals that were administered morphine. Further experiments have shown that intrathecal morphine analgesia can be prolonged when coadministered with LPS variants, which are TLR4 competitive receptor antagonists, and with TLR1/IL-1 receptor domain adapter protein inhibitors. Interestingly, concomitant intrathecal-intrathecal, systemic-systemic, and systemic-intrathecal administration of morphine with naloxone, respectively, have all been shown to prolong acute morphine analgesia. The simultaneous and continuous administration of naloxone and morphine intrathecally has been shown to attenuate morphine-induced hyperalgesia, which occurs after prolonged morphine administration. Further, this dual administration significantly decreased withdrawal after opioid administration was terminated. All these effects are thought to be related to previously proven effects showing that positive and negative isomers of naloxone block TLR4 [33••, 34].

Other studies have shown potentiation of analgesia after morphine administration in TLR4 knockout mice, although there was no difference in initial pain thresholds between the TLR4 knockouts and wild-type mice. This further supports the role of TLR4 in antagonizing morphine-induced analgesia. Moreover, naloxone administered concomitantly with morphine potentiated analgesia in the wild-type mice but not in the TLR4 knockouts [33••].

NMDA Receptors

NMDA-positive glutamate receptors have also been shown to be important in the modulation of morphine tolerance. A great deal of research has helped explain the details of enhancement of NMDA activity after morphine administration. This effort was inspired by studies showing that MK-801, an NMDA-receptor antagonist, could attenuate morphine tolerance and dependence, whereas other studies show that ketamine and dextromethorphan could decrease opioid requirements when administered with morphine [35]. It was subsequently shown that after chronic opioid administration, there is downregulation of the glutamate transporter (GLAST) in astrocytes, which likely causes an increase in glutamate in the synaptic cleft, as well as an upregulation of D-serine, thereby potentiating NMDA-receptor signaling. In addition, morphine has been shown to upregulate brain-derived neurotrophic factor (BDNF) in cultured microglia. This, coupled with the finding that BDNF upregulates the antiopioid subunit of the NMDA receptor subtype known as GluRepsilon1 (NR2A), led researchers to believe that the NR2A receptor may be the site of morphine-induced NMDA receptor-dependent antiopioid activity [36••]. This concept is further corroborated by the enhancement of morphine analgesia in NR2A knockout animals [36••].

Opioid Receptors: κ Subtype

κ-Opioid receptors (KORs) are a type of opioid receptor with a somewhat different mechanism of action from the classic μ receptor. For example, they have been shown to be activated by dynorphins after partial sciatic nerve ligation. In turn, this has led to glial proliferation in contrast to μ receptors, which decrease glial proliferation [37]. Further, they have shown promise in the attenuation of morphine tolerance [35]. Unfortunately, it has been difficult to locate agents that possess these positive KOR agonist effects of diminishing tolerance while lacking the negative KOR agonist effects such as dysphoria and psychomimetic effects [35].

Specific Medications With Potential for Use as Opioid Adjuncts

Ibudilast (AV411)

AV411 (Avigen, Inc., Alameda, CA) is a blood-brain permeable, nonspecific phosphodiesterase inhibitor that acts centrally by way of attenuation of glial cell activation and reduction of proinflammatory activating factors, such as cytokines (TNF-α, IL-1β), nitric oxide, and chemokines such as monocyte chemo-attractant protein-1 and fractalkines; it increases production of anti-inflammatory IL-10 [18, 38•]. It was initially used to treat bronchial asthma and poststroke dizziness, which has been attributed to its ability to reduce inflammation and cause vasodilatation [39]. In a recent study, AV411 was shown to reduce mechanical allodynia caused by neuropathic pain as well as noxious neuropathy induced by chemotherapeutic agents (paclitaxel and vincristine); it was also shown to reduce morphine tolerance.

When administered systemically, AV411 was shown to be distributed to the spinal cord and to attenuate morphine-induced glial cell activation in certain brain regions. AV411 has also been shown to inhibit peripheral inflammatory cells [40, 41], which has been suggested as a possible cause of reduced pain perception peripherally. Other recent published data demonstrate that AV411 reduced spontaneous opioid withdrawal, protected naloxone-induced morphine withdrawal when given during the period of development of morphine dependence, and simultaneously enhanced analgesic effects (three to five times increases in acute potency), even in situations in which opioid dependence had already been established [33••]. These effects were seen with both morphine and oxycodone, with no changes in plasma morphine levels. Another study shows that AV411 decreases a morphine-induced increase of dopamine in the nucleus accumbens, a nucleus known to be associated with morphine-induced drug reward as well as withdrawal [42, 43•], thus further illustrating the beneficial role of AV411 in regulation of drug reward and dependence.

Dizocilpine (MK-801)

MK-801 is an NMDA-positive glutamate receptor noncompetitive antagonist that has been shown to attenuate opioid tolerance and does not influence the antinociceptive effects of morphine. When injected intrathecally, it has been shown to decrease morphine tolerance at the spinal level [44]. Proteomic studies have shown there is upregulation of GFAP in those animal models with morphine tolerance, whereas MK-801 was shown to reduce the GFAP levels in these animals. Interestingly, similar to minocycline, MK-801 is not able to decrease morphine tolerance once it has developed [35].

A recent study attributed a part of MK-801's ability to reduce opioid tolerance to an inhibition of the NMDA receptor-dependent activation of spinal JNK; this kinase has been shown to be involved in the development of morphine analgesic tolerance [45]. Interestingly, MK-801 injection in the ventral periaqueductal gray area increased the acute analgesic action when coadministered with morphine but did not affect nociception when administered alone, suggesting that different tolerance mechanisms occur in the spinal cord compared with the periaqueductal gray area [46]. It should be noted that despite having antinociceptive effects in chronic pain models, MK-801 has been shown to have the opposite effect in acute pain models causing hyperalgesia [47].

Propentofylline (SLC022)

SLC022 (Solace Pharmaceuticals, Canterbury, Kent, United Kingdom) is an orally available, blood-brain permeable, methylxanthine derivative that acts as a glial inhibitor and has been shown to attenuate neuropathic pain states as well as chemotherapy-induced painful neuropathy [48]. Studies have shown that it decreases allodynia, possibly through altering γ-aminobutyric acid (GABA)ergic tone through modulation of glutamic acid decarboxylase in the spinal cord after injury, as well as reducing an injury-induced increased expression of GFAP [49].

Apart from its advantageous role in pain reduction, propentofylline has also been shown to modulate drug reward. In vivo studies have shown that intraperitoneal injections of propentofylline attenuated condition-placed preference, a measure of drug reward in animals that were dependent on methamphetamine and morphine; this attenuation is thought to be caused by astrocytic activation [50]. Propentofylline has also been shown to act as a neuroprotective agent in ischemia models [51].

Aconiti Tuber Extract (U50488H)

An extract of the tuber of Ranunculaceae Aconitum carmichaeli Debeaux—referred to as PAT or U50488H—has been found to possess KOR agonist activity, without any significant adverse effects [35]. U50488H has been used in China and Japan to treat chronic pain without adverse effects for some time and has shown to be effective not only in attenuating morphine tolerance when administered initially, but also reversing morphine tolerance after it developed. Some studies have shown greater effectiveness of U50488H over MK-801 because U50488H can potentiate the thermal antinociceptive effect of morphine and can reverse morphine tolerance once it has developed [35].

AV333

AV333 (Avigen, Inc., Alameda, CA) is a plasmid that has been shown to be a well-tolerated and effective antineuropathic agent when injected intrathecally. It functions as a glial cell inhibitor and promotes an increase in the amount of the anti-inflammatory cytokine IL-10 in the spinal cord. Experimental studies have shown that a single course of therapy entirely diminishes neuropathic pain symptoms for 90 days [18]. We expect to learn more about this agent's effectiveness in the near future.

Minocycline

Minocycline is a semisynthetic, second-generation broad spectrum, blood-brain barrier permeable tetracycline that has been historically used for its antimicrobial properties. However, it has also been reported to possess neuroprotective effects with reported benefits in experimental models of neurodegenerative disease, traumatic brain injury, and cerebral ischemia. Minocycline's protective role occurs by suppression of the mitochondrial permeability transition, inhibition of caspace-1 and -3 expression, and inhibition of microglial activation and proliferation [52] via antihyperalgesic and antiallodynic effects [53, 54]. The latter effects occur by reducing proinflammatory factor-mediated nociceptive transmission. This is achieved by decreasing mRNA expression for IL-1β, TNF-α, each of their converting enzymes, and IL-10 in the dorsal spinal cord; reducing IL-1β and TNF-α in cerebrospinal fluid; and decreasing serum IL-6 [54, 55]. Inhibition of microglial cells is thought to partly occur by suppressing p38 MAPK [56, 57], which has also shown to reduce tolerance to morphine.

Minocycline also affects neuropathic pain. For instance, minocycline enhances the effects of morphine in neuropathic pain models and diminishes the development of morphine tolerance. In a recent study by Mika et al. [51], minocycline delayed the development of morphine tolerance in normal and neuropathic pain conditions, and was associated with decreasing the morphine-induced increase in CD11b/c protein expression in microglial cells without inhibiting astroglial cells. Minocycline inhibits the activation of microglial cells, which are thought to initiate neuropathic pain, thus preventing development of neuropathic pain in animal models. However, once these cells are activated, minocycline does not seem to be as effective in reducing pain states [54].

Although minocycline enhances the analgesic efficacy of opioids, it may also increase undesirable effects of opioids such as respiratory depression and drug dependence. Minocycline is a p-glycoprotein (p-gp) inhibitor, and inhibition of p-gp can cause altered pharmacokinetics of opioids, thus leading to increased bioavailability and ultimately an increase in adverse effects. However, in a recent study, minocycline was shown to reduce the morphine-induced decrease in respiratory parameters such as tidal volume, minute volume, inspiratory force, expiratory force, and blood oxygen saturations. Minocycline did not affect the morphine-induced depression in respiratory rate. These data, in concert with some studies reporting the unsuccessful disruption of morphine tolerance [54], do not

Table 2 Glial-modifying agents

Medication	Mechanism of action	Effects
AV411 (ibudilast)	Attenuates glial cell activation; increases IL-10; phosphodiesterase inhibitor	Reduction of proinflammatory cytokines; attenuates morphine tolerance; beneficial in chemotherapeutic-induced neuropathy, poststroke dizziness, and bronchial asthma
MK-801	NMDA-glutamate receptor noncompetitive antagonist	Diminishes morphine tolerance through reduced c-JNK activation
Propentofylline (SLC022)	Glial cell inhibition	Antineuropathic agent; modulates drug reward; neuroprotective role in ischemia models
Aconiti tuber extract (U50488H)	Selective KOR agonist	Attenuates morphine tolerance when given initially or after tolerance has developed
Pentoxifylline	Glial cell activation inhibitor; phosphodiesterase inhibitor; inhibits activation of NF-κB	Reduction of proinflammatory cytokines; may diminish opioid tolerance and reward by potentially reducing NO and adenosine production
Minocycline	Suppression of mitochondrial permeablity transition; inhibition of caspace-1 and -3 expression; inhibition of microglial activation and proliferation	Diminishes morphine tolerance and reward; neuroprotective effects through inhibition of apoptosis
AV333	Glial cell inhibitor; increases IL-10	Antineuropathic agent

c-JNK c-Jun N-terminal kinase, *IL* interleukin, *KOR* κ-Opioid receptor, *NF-κB* nuclear factor-κB, *NMDA N*-methyl-D-aspartate, *NO* nitric oxide

support the theory of increased bioavailability of opioids by minocycline administration. In fact, minocycline was also shown to suppress morphine reward as measured by conditioned place preference, which is a widely accepted measure of morphine reward, as mentioned previously. Of note, this study used naive animal models, in which glial cells were not activated; thus, it is not known whether minocycline would continue to have similar effects in neuropathic pain states, and should be studied further. In conclusion, minocycline suppresses microglial cells, which can lead to attenuation of neuropathic pain, enhance morphine analgesia, decrease certain undesired opioid effects, and delay the development of morphine tolerance in normal and neuropathic pain conditions.

Pentoxifylline

Pentoxifylline is an inhibitor of glial activation, nonspecific cytokine synthesis, and phosphodiesterase (PDE) [1••]. Pentoxifylline has been shown to inhibit the production of mRNA and protein levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, which were associated with reduced neuropathic pain [58] and inflammatory pain [59]. Along with reduction of these cytokines through inhibition of NK-κB, attenuation of pain symptoms has also been shown to be associated with elevated levels of the anti-inflammatory cytokine, IL-10, in the CNS [60]. In prior studies, pentoxifylline was also shown to reduce postoperative pain and formalin-induced pain behavior in animal models [59].

Similar to AV411's inhibition of PDE, pentoxifylline reduces cyclic adenosine monophosphate (cAMP) levels, and this in turn results in decreased TNF-α and IL1-β production by microglia. These cytokines cause upregulation of nitric oxide synthase, which increases nitric oxide (NO) levels. NO is known to affect dopamine levels in the mesolimbic system, where increased dopamine levels are associated with opioid reward. Thus, these PDE inhibitors can potentially modulate drug reward and dependence [43•]. Another suggested mechanism of attenuating morphine reward relates to a reduced production of adenosine by limited cAMP hydrolization. Adenosine causes inhibition of the inhibitory GABA pathways, which modulate pathways in the ventral tegmental area (VTA) of the mesolimbic system. The VTA contains cells that project to the nucleus accumbens and are a source of dopamine. Therefore, with reduced adenosine levels by PDE inhibitors, there may be attenuation of morphine reward through decreased dopamine in the nucleus accumbens and activation of cells in the VTA as well as glial cells [43•]. In conclusion, pentoxifylline has been shown to attenuate neuropathic pain states and may also contribute to reduction of morphine-induced tolerance and reward (Table 2).

Conclusions

There are a number of exciting directions for the use of glial-modifying agents as opioid adjuncts for the treatment of acute and chronic pain. Important targets include cytokine receptors, TLRs, NMDA-positive glutamate receptors, and the κ-opioid receptors. It appears that basic and clinical research involving both previously discovered agents such as minocycline, pentoxifylline, and U50488H, as well as newer agents such as MK-801, AV411, and SLC022, may introduce a new era of improved opioid efficacy and reduced sequelae.

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