Chronic pain is a major health issue in our society that clearly impacts quality of life. Thirty to forty percent of the population in the United States suffer from chronic pain and its total cost has been estimated at 560-635 billion dollars annually. Even if research progresses to develop novel analgesics, opioids remain the gold standard to treat pain. However, opioid treatment is associated with several adverse side effects including analgesic tolerance and opioid-induced hyperalgesia (OIH). OIH is of major importance and the use of morphine continues to increase. Analgesia tolerance corresponds to a progressive decrease of analgesia produced by a given dose of opioid upon chronic administration, resulting in the need to increase the dosage in order to maintain the initial analgesic effect. OIH usually clinically presents itself as the development of hypersensitivity to painful stimuli. OIH is well established in humans in different types of pain such as post-surgical pain, cancer pain and musculoskeletal pain. Hence, clinicians face a dilemma to decide to either treat or not treat chronic pain with opioids which the knowledge of the patient developing pain hypersensitivity that may develop into opioid dependence. OIH is not yet completely understood and different mechanisms have been identified for this adaptive process to occur following opioid administration. These included the sensitization of primary afferent neurons and enhanced release of glutamate, hyperexcitability of second order neurons to excitatory neurotransmitters. However, more recently glial cells have been shown to play an important role in OIH. Receptors expressed in both microglia and
astrocytes become activated in OIH.\cite{5}

Long-term potentiation (LTP) is a sensitization of synapse (homo- and heterosynaptic) that enhances the strength of the synapse and its signal transduction. Increase LTP can cause hypersensitivity and may lead to hyperalgesia and has been shown to be involved in OIH.\cite{6} In addition to glutamate-NMDA receptor mediated LTP in OIH, glial cells and released pro-inflammatory mediator have also been implicated in LTP in OIH. For example, cytokines interleukin-1beta (IL-1β) and tumor necrosis factor-α (TNF-α) can enhance post-synaptic potentials leading to neuronal excitation in the spinal cord. Cytokines in the central nervous system act mostly through the activation of glial cells to induce the release of other mediators that trigger LTP and hyperexcitability or neurons that leads to OIH.\cite{7} The pro-inflammatory cytokine, IL-1β plays a major role in host defense and inflammation and is associated with inflammatory pain and opioid analgesia. In rodent models, peripheral administration of IL-1β produced hyperalgesia and reduced morphine analgesia while contributing to morphine tolerance.\cite{8,9}

At the molecular level, the interaction of IL-1β and the opioid system is shown by the finding that IL-1β increased the levels of mu opioid receptor (MOR) mRNA in primary astrocytes, neurons and in neural microvascular endothelial cells.\cite{10-12} Other cytokines, including IFNα, TNFα, IL-4 and IL-6, also increase the expression of MOR in neuroblastoma cells and peripheral immune cells.\cite{13-15} These results and others show that cytokines interact with endogenous opioid systems but explicit molecular mechanisms remain elusive. Interleukin-1beta mediates its effects through the interleukin-1 receptor type 1 (IL1R1) protein, which is a member of the Toll-like/IL-1R1 (TIR) domain family of membrane receptors.\cite{16} Like the Toll-like receptors, the IL1R1 receptor signals through a complex of accessory proteins and downstream signaling events including activation of the JAK-STAT, MAPK, and NF-κB pathways.\cite{17} Functional studies in cell lines show that transcription factors from the JAK-STAT, MAPK and NF-κB signaling pathways alter MOR gene transcription after cytokine stimulation.\cite{10,18,19}

The NOD-like receptor protein 3 (NLRP3) inflammasome and downstream release of IL-1β are involved in pain conditions such as post-operative pain, post-herpetic neuralgia, diabetic peripheral neuropathy and spinal cord injury and if not controlled can lead to neuropathic pain.\cite{20} In these and other forms of pain conditions, opioid such as morphine remains the gold standard analgesic and opioid use for pain management has dramatically increased, with little assessment of the pathological consequences on the primary pain condition. Recent data has shown that prolonged treatment with morphine doubled the duration of pain associate with nerve injury independent of opioid-receptor selectivity.\cite{21} Morphine-mediated persistence of pain was attenuated following co-administration with the IL-1 receptor antagonist (IL-1ra).\cite{21} Prolonged morphine use can activate glial toll-like receptors such as the toll-like receptor 4 (TLR4) which following priming ensures neurotoxicity, immune mediated amplification of nociceptive signaling in the spinal cord.\cite{6,21-23} Evidence has also shown that morphine can directly compromise opioid-induced analgesia by promoting proinflammation via a TLR4 dependent mechanism and can potentiate mechanical allodynia.\cite{24,25}

Reactive microglia has been implicated in playing a key role in morphine-mediated persistent pain conditions as demonstrated with the use of glial cell blockers.\cite{20-29} It is noteworthy that while there are many reports that have described the importance of neuroinflammation in analgesic tolerance, since 2002 only a dozen few have focused on immune mechanism for OIH with four of the studies showing that the blockade of IL-1β reduced OIH.\cite{30-33} In astrocytes, morphine exposure has shown to trigger astrocytes activation and lead to the upregulation of IL-1β.\cite{34} Also, more recently, ultra-low dose morphine induced OIH was found to selectively activate astrocytes.\cite{35} Together, this indicates that concurrent activation of microglia and astrocytes are involved in OIH.

In conclusion, my hypothesis is that opioid tolerance is a consequence of OIH. The increase in pain sensitivity caused by OIH masks opioid analgesia and if this continues would lead to opioid tolerance. At the molecular level, increased, chronic use of opioids would cause a decrease in MOR expression contributing to a loss of any analgesia mediated by opioids. Therefore, in the future it would be key to determine the cellular chronological order involved in increasing synaptic activity (i.e. LTP), which is normally mediated by increased levels of glutamate in the synaptic cleft and is removed by astrocytes. Current research shows that the common thread that may lead to OIH is the pro-inflammatory cytokine, IL-1β. Morphine alone can increase the expression and release of IL-1β from activated microglia and this increase may disrupt glutamate homeostasis. Recent evidence has shown that IL-1β can down-regulate the expression of GLT-1 and directly elevate the levels of glutamate and trigger the release of ATP from glia.\cite{21} Increased glutamate, ATP and reactive oxygen species may contribute to excitotoxicity and chronic inflammatory and therefore the cycle may continue until morphine is discontinued. Current and previous data supports the
rationale to further examine whether the management of pain with opioids such as morphine contributes to a neuroinflammatory challenge that then leads to opioid tolerance and other pain comorbidities.

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