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REVIEW

NLRs and inflammasome signaling in opioid-induced hyperalgesia and tolerance

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Abstract

We investigated the role that innate immunological signaling pathways, principally nod-like receptors (NLRs) and inflammasomes, in the manifestation of the contradictory outcomes associated with opioids, namely hyperalgesia, and tolerance. The utilization of opioids for pain management is prevalent; nonetheless, it frequently leads to an increased sensitivity to pain (hyperalgesia) and reduced efficacy of the medication (tolerance) over an extended period. This, therefore, represents a major challenge in the area of chronic pain treatment. Recent studies indicate that the aforementioned negative consequences are partially influenced by the stimulation of NLRs, specifically the NLRP3 inflammasome, and the subsequent assembly of the inflammasome. This process ultimately results in the generation of inflammatory cytokines and the occurrence of neuroinflammation and the pathogenesis of hyperalgesia. We also explored the putative downstream signaling cascades activated by NOD-like receptors (NLRs) and inflammasomes in response to opioid stimuli. Furthermore, we probed potential therapeutic targets for modifying opioid-induced hyperalgesia, with explicit emphasis on the activation of the NLRP3 inflammasome. Ultimately, our findings underscore the significance of conducting additional research in this area that includes an examination of the involvement of various NLRs, immune cells, and genetic variables in the development of opioid-induced hyperalgesia and tolerance. The present review provides substantial insight into the possible pathways contributing to the occurrence of hyperalgesia and tolerance in individuals taking opioids.

Keywords Inflammasome · Hyperalgesia · Opioids · NLRPs · Tolerance

Introduction

Opioids are pharmacological agents frequently used in anesthesia and acute pain treatment due to their dual properties. Opioid-induced hyperalgesia (OIH) and tolerance are two negative consequences that can arise from long-term opioid use (Roeckel et al. 2016). OIH is a paradoxical increase in pain sensitivity that can occur when pain is treated with opioids. More amounts of opioids are required to treat pain because tolerance reduces the response to their pain-relieving properties (Williams et al. 2013). The mechanisms underlying the development of tolerance and OIH are intricate and poorly understood. Recent studies suggest that these processes are driven to a significant extent by neuroinflammation and activation of innate immune pathways (Grace et al. 2014).

A class of intracellular pattern-recognizing receptors (PRRs) known as nod-like receptors (NLRs) is critical for both innate immunity responses and the activation of inflammatory pathways (Ting et al. 2008). When the NLR family recognizes pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), they can be assembled to multiprotein complexes called inflammasomes. These complexes drive caspase-1 to become activated, which causes the production and release of pro-inflammatory cytokines, including IL-1 and IL-18 (Swanson et al. 2019). A growing body of research suggests that NLRs and inflammasome activation have a role in many types of pain, such as neuropathy or inflammation-related pain (Ji et al. 2014). However, the specific functions of diverse NOD-like

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receptors (NLRs) and inflammasomes in these biological processes remain unclear.

Our aim was to provide a proper review of the existing knowledge regarding the roles of NOD-like receptors (NLRs) and inflammasomes in opioid tolerance and opioid-induced hyperalgesia (OIH). This study delved into the intricate molecular mechanisms by which opioids modulate the activation of nuclear receptors and the assembly of inflammasomes. Furthermore, we highlighted potential therapeutic strategies targeting these pathways to ameliorate or prevent the adverse effects associated with opioid medications.

Opioids family and opioids receptors

Pain, reward, addiction, stress, inflammation, and many other physiological processes are regulated by opioid receptors i.e., GPCRs that bind to opioids. While opioids are beneficial in the treatment of severe acute and chronic pain, they also have side effects such as constipation, respiratory depression, tolerance, addiction, and dependence (Zöllner and Stein 2007), (Kiyatkin 2019).

Distinct categories of opioids are distinguished based on their chemical composition, place of origin and pharmacological characteristics. These families comprise opiates, i.e., natural alkaloids derived from the opium poppy plant (*Papaver somniferum*), including morphine, codeine and thebaine; semi-synthetic opioids, i.e., modified forms of opiates like heroin, oxycodone, hydrocodone and buprenorphine; Synthetic opioids: these are opioids that are produced entirely in a laboratory, including fentanyl, methadone, tramadol, and tapentadol; endogenous opioids are peptides that the body produces naturally. Endorphins, enkephalins, dynorphins, and endomorphins are some of the examples (Zöllner and Stein 2007), (Corder et al. 2018), (Shang and Filizola 2015). In addition, opioids are categorized as agonists (such as morphine and fentanyl), partial agonists (such as buprenorphine), antagonists (such as naloxone), and mixed agonist-antagonists (such as nalbuphine) on the basis of their receptor affinity and effect. Opioids differ in their onset of action, duration of action, potency, efficacy, and safety due to differences in their pharmacokinetic and pharmacodynamic properties (Wardhan and Chelly 2017).

Opioid receptors, which exhibit diverse pharmacological properties, distinct anatomical distributions, specific functional roles, and unique molecular structures, are systematically categorized into four major subtypes. Mu (μ)-opioid receptors are the most widespread and abundant opioid receptors in the central nervous system (CNS) and peripheral nervous system (PNS). The predominant impacts of opioids on pleasure, sedation, pain relief, respiratory depression, and addiction are facilitated by these agents. Opioid receptors influence immunological and inflammatory responses. Among these receptors, there are three subtypes of μ-opioid receptors: μ1, μ2, and μ3. In addition, delta (δ)-opioid receptors are predominantly localized in the central nervous system (CNS), particularly in regions such as the limbic system and the spinal cord. They affect learning and memory processes and moderate some of the effects of opioids for pain relief, antidepressants, anxiolytics, and anticonvulsants. Delta opioid receptors have two distinct subtypes: δ1 and δ2. Kappa (κ) opioid receptors, which are predominantly localized in the central nervous system (CNS), demonstrate their highest concentration in regions such as the hypothalamus, brainstem, and spinal cord. Some of the effects of opioids in pain treatment, anticonvulsants, diuretics, and neuroprotection are mediated through them. They also cause stress reactions, sedation, hallucinations, and dysphoria. There are three subtypes of kappa opioid receptors: κ1, κ2, and κ3. Nociceptin/orphanin FQ peptide receptors (NOPs) are mainly located in the CNS, mainly in the cortex, hippocampus, amygdala, and cerebellum. They act as a moderator for some of the analgesic, anti-inflammatory, anxiolytic, and antidepressant effects of opioids. They also affect cognition, exercise and dietary habits. There are no recognized subtypes of NOPs (Waldhoer et al. 2004), (Stein 2016), (Pasternak and Pan 2013).

Different kinds of ligands, including endogenous opioids (like endorphins), exogenous opioids (like morphine), and synthetic opioid ligands (like naloxone), can activate opioid receptors. Other substances, including allosteric ligands (like sodium ions), receptor heteromers (like MOR-DOR dimers), and receptor transport (like internalization), can further influence opioid receptors. Various G proteins are combined with opioid receptors to initiate distinct signaling pathways, including inhibition of cAMP, inhibition of $Ca++$ channels, and activation of $K+$ channels (Williams et al. 2013), (Corder et al. 2018).

Pains and opioids in pain management

There are three types of pain: nociplastic, neuropathic, and nociceptive. This type of pain is known as nociceptors; cuts, burns and sprains are examples of nociceptive pain. Nociceptive pain is physiological and results from tissue injury or inflammation. Injury or dysfunction of the somatosensory nervous system leads to abnormal sensory information processing and perception, which causes neurological symptoms. Symptoms of pathologic neuropathic pain include phantom limb pain and diabetic neuropathy. Nociceptive dysregulation, a pathogenic condition that can be caused by various diseases such as fibromyalgia and irritable bowel syndrome, also occurs without prominent nerve or tissue damage. Peripatetic and central neuropathic pain are two categories within neuropathic pain. Peripheral neuropathic

pain is caused by peripheral nerve injury or disease. Central neuropathic pain, which is characterized by a range of sensations such as burning and tingling, can be triggered by conditions such as trauma, infection and diabetes. In contrast, central neuropathic pain is caused by conditions that affect the central nervous system. Characteristic features include electrical shocks and burning sensations. Stroke and Parkinson's disease in particular are among the diseases associated with the occurrence of pain. Acute pain is a form of nociceptive pain that typically occurs shortly after a sudden accident or illness. Neuropathic pain and nociplastive pain are two types of chronic pain that have a longer natural healing time. Pain, inflammation, and extreme tenderness all have a helpful purpose in protecting tissues from additional damages. While the triggering of inflammation is well understood, the mechanisms that control its resolution are not as well understood (Ji et al. 2014), (Kuner and Kuner 2021), (Glare et al. 2019), (van der Vlist et al. 2022), (Mitsikostas et al. 2022), (Scholz et al. 2019).

Opioids have been a mainstay in pain therapy for a long time because of their analgesic properties (Jage 2013). They produce analgesia, sedation, euphoria, and other effects by interacting with opioid receptors in the central and peripheral nervous system, primarily mu-receptors (Wardhan and Chelly 2017). Opioids are commonly used in pain management for both acute and chronic ailments, including palliative care, neuropathic pain, cancer pain, and post-operative pain. Opioids derived from or mimicking natural substances from the opium poppy plant can be customized to meet individual patient requirements by choosing various formulations, dosages, routes of administration and dosage forms. To increase efficacy and mitigate potential side effects, opioids can be combined with other analgesics and non-pharmacological therapeutic approaches (Roth et al. 2020). However, opioids have serious side effects, which include decreased breathing, constipation, nausea, vomiting, itching, tolerance, dependence, and addiction (Antony et al. 2020), (Arango et al. 2006). In addition, opioids can inhibit the immune system and influence the course and recurrence of various malignancies. Consequently, the administration of opioids in pain therapy requires thorough consideration of the pros and cons, tailored dosing and titration, multimodal analgesia, monitoring and post-treatment care (Wardhan and Chelly 2017), (Beecham et al. 2006).

Opioid maintenance therapy (OMT) has been shown to have a positive impact on patient outcomes, including increased longevity, reduced risk of infections, and improved quality of life. However, it is important to note that OMT can also pose challenges for pain management due to differential patient responses to non-opioids and opioids. In the context of OMT, effective pain management requires a comprehensive approach that takes into account factors such as pain type, severity, duration, and etiology, as well as the patient's health status, psychosocial aspects, and the potential for substance abuse or cognitive distraction.

Adjusting OMT dosages is a crucial aspect of pain management. Other strategies for managing pain include collaborating with OMT doctors and pain experts, utilizing non-opioid or short-acting opioid analgesics, and exploring other pharmaceutical options. In the context of OMT, effective pain management requires a comprehensive approach that includes systematic patient education, vigilant monitoring, and comprehensive evaluation. Multimodal treatment of pain and opioid risk assessment are two recent examples of tactics being investigated to help ensure safer and more efficient opioid use (Sierżantowicz et al. 2020). Given the potential advantages and hazards of opioid therapy, it is essential to exercise sensible use and cautious patient selection.

(Fischer et al. 2014).

Opioid-induced tolerance

Long-term use of opioids for pain management is associated with negative consequences, including tolerance, addiction, and dependence. Opioid-induced tolerance is a condition that occurs when long-term exposure to opioids causes a decreased reaction to their analgesic effects, necessitating greater doses to produce the same amount of pain relief. This phenomenon reduces the effectiveness of opioids for treating pain and raises the possibility of overdosing and death (Mercadante et al. 2019). Changes in the brain, cells, and molecules at various stages of the pain pathway are just a few of the complex and multifaceted processes that lead to opioid-induced tolerance. Since opioid receptors are the principal targets of opioids, deactivation of these receptors is one of the fundamental processes behind opioid-induced tolerance. By preventing neurotransmitter release and adjusting ion channel activity, opioid receptors mediate the analgesic effects of opioids. When opioids activate opioid receptors over and over again, they become less available and responsive on the cell surface. This is because opioids phosphorylate, internalize and recycle them (Zhou et al. 2021).

Acute opioid tolerance (AOT) may be caused via serotonergic pathways, although the exact mechanism is unknown. For example, the 5-HT3 receptor is linked to tolerance and dependence on opioids. It has shown that this receptor affects the transcription of genes that regulate opioid tolerance. Furthermore, the 5-HT3 antagonist ondansetron can both prevent and reverse opioid-induced hyperalgesia (OIH) and tolerance in animal models (Colvin and Fallon 2010). Compared to longer-acting opioids, short-acting opioids like remifentanil appear to provoke OIH and acute tolerance more rapidly and frequently. This phenomenon may be associated with the relatively high dosage of remifentanil required for achieving analgesic effects. Consequently,

anesthesiologists need to be aware of the possible side effects of remifentanil infusion following surgery, including heightened pain thresholds and increased opioid usage (Kim et al. 2018).

The activation of the innate immune system and the consequent synthesis of pro-inflammatory mediators is another way opioids induce tolerance. Long-term opioid exposure can cause inflammatory reactions in several cell types, including monocytes and microglia, by connecting to their receptors, or Toll-like receptor 4 (TLR4), which is expressed in different immune and brain cells. This process leads to the activation of the innate immune system and the synthesis of pro-inflammatory mediators, which have the potential to increase nociceptive transmission and activate peripheral and central pain pathways. These effects may result in decreased analgesia and elevated hyperalgesia (Carranza-Aguilar et al. 2022), (Zare et al. 2022).

The role of NLRs and inflammasome in opioid-induced hyperalgesia and tolerance

The activation of NLRs and the inflammasome serves a critical role in the pathophysiological mechanisms of OIH and tolerance. Opioid substances have the potential to elicit the secretion of crucial pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-18 (IL-18), and tumor necrosis factor-alpha (TNF-a). The production of these cytokines is initiated by immune cells, such as microglia and astrocytes, as a reaction to cellular stress and damage induced by opioids. Numerous studies have provided evidence indicating that opioid substances can stimulate the NLRP3 inflammasome, hence initiating the synthesis and subsequent release of IL-1β and IL-18. The involvement of the NLRP3 inflammasome in the pathogenesis of OIH and tolerance is demonstrated through its facilitation of neuroinflammation and oxidative stress. Furthermore, opioids can regulate the activity and expression of other NLRs, including NLRP1 and NLRC4, which have been related to the modulation of pain and inflammation (Zhang et al. 2015), (Hutchinson et al. 2008), (Liu et al. 2017).

The modulation of opioid analgesia is influenced by the central immune signaling pathway. Opioids interact with several receptors, including opioid receptors, Toll-like receptor 4 (TLR4), and purinergic receptors, which are present in immune cells such as microglia and astrocytes. This results in the release of cytokines and chemokines, including C–X–C motif chemokine ligand 1 (CXCL1) and IL-1β, as well as the disturbance of glutamate homeostasis within the central nervous system (Grace et al. 2016), (Dinarello 2011), (Hutchinson et al. 2010), (Hutchinson et al. 2007). Grace et al. reported that a concise regimen of morphine intervention, delivered upon the manifestation of neuropathic pain, induces enduring sensitization that persists for several weeks after termination of morphine treatment. The ipsilateral spinal lumbar dorsal inflammasome is expressed more frequently in response to this chronic sensitization, which is limited to microglia and does not depend on the activation of opioid receptors. The spinal NLRP3 inflammasome, a protein structure that had not previously been found in the spinal cord or associated with pain, is responsible for the onset of morphine-induced persistent sensitization. Spinal inflammasome activation is also crucial for perpetuating chronic sensitization (Grace et al. 2016).

Chang et al. observed that lipopolysaccharide (LPS) induces cerebral inflammation in rats by inhibiting the NLRP12 inflammasome, which possesses anti-inflammatory properties. As well, downstream elements such as Birc3 are activated, leading to increased production of chemokines (CCL2, CCL7, CXCL1, and CXCL3) and cytokines (IL-1β and IL-6), all associated with inflammation. Intriguingly, in the context of morphine tolerance, the expression of genes linked to the inflammasome diminishes upon exposure to LPS, implying a reduction in inflammation. Notably, LINCS analysis has corroborated that morphine tolerance modulates the LPS response, with VPS28 emerging as one of the genes influencing these alterations (Chang et al. 2017). Mao et al. uncovered that inhibition of the NLRP3 inflammasome attenuated the advancement of morphine tolerance and LPS-induced inflammation. These observations underscore the involvement of the NLRP3 inflammasome in regulating the inflammatory reaction and the development of opioid tolerance (Mao et al. 2013).

Qu et al. revealed that prolonged use of morphine led to the release of heat-shock protein 70 (HSP70) from neurons, which activates microglia and initiates the TLR4/MAPK/NF-κB/NLRP3 pathway. This results in an increase in the production of pro-inflammatory cytokines, leading to a reduction in the analgesic effects of morphine. Furthermore, the modulation of HSP70 secretion is directed by the mu-opioid receptor (MOR)/AKT/KATP/ERK signaling cascade (Qu et al. 2017). Similar signaling pathways are found in both chronic pain and morphine tolerance. This suggests that microRNAs (miRNAs) may affect how morphine-induced analgesic tolerance develops (McAdams et al. 2015). The occurrence of morphine tolerance is attributed to alterations in the transcription levels of certain messengers and neurotransmitters as a result of extended drug usage (Enquist et al. 2011). The study by Xie et al. looked into how microRNA-223 (miR-223) affected the development of morphine tolerance and the activation of the NLRP3 inflammasome in a rat model of neuropathic pain. They observed that prolonged administration of morphine resulted in a reduction in the expression of miR-223 and an increase in the expression of the NLRP3 inflammasome and its downstream

components, including caspase-1 and IL-1β, in the spinal cord of rats subjected to chronic constriction injury (CCI). Therefore, miR-223 may exert an influence on the development of morphine analgesic tolerance in the context of neuropathic pain through its targeting of the NLRP3 inflammasome (Xie et al. 2017).

Previous studies have demonstrated that opioids can activate of the NLRP3 inflammasome by stimulating TLR4 and P2X7R. Babelova et al. investigated the functional significance of biglycan as a danger signal in the activation of the NLRP3 inflammasome via toll-like and P2X receptors. The soluble form of biglycan can stimulate the synthesis and secretion of IL-1β by activating the NLRP3 inflammasome in macrophages. The biglycan interacts with TLR2/4 and purinergic P2X4/7 receptors on the outside of cells. These interactions result in cooperative receptor activity, the generation of reactive oxygen species, and the induction of NLRP3 expression and pro-IL-1β stimulation through TLR2/4 signaling, as reported in references (Yang et al. 2020), (Pelegrin 2021), (Babelova et al. 2009).

Grace et al. revealed that the injection of morphine after CCI can intensify cellular stress by stimulating NLRP3 inflammasomes, triggering a higher level of damage-associated molecular patterns (DAMPs). Elevated levels of DAMPs have the potential to initiate the activation of the NLRP3 inflammasome through TLR4 and P2X7 receptor (P2X7R) signaling pathways. This activation process establishes a self-reinforcing cycle that sustains the presence of persistent allodynia. This statement underscores the significance of comprehending the underlying mechanisms that contribute to the intensification of cellular stress and prolonged pain resulting from morphine administration. Such understanding may pave the way for identifying novel therapeutic targets to manage neuropathic pain (Grace et al. 2018).

Neuroinflammation within the spinal cord has been implicated in the pathogenesis of opioid-induced hyperalgesia (OIH), as well as the diminution of morphine's analgesic efficacy over time (Roeckel et al. 2016), (Grace, Maier and Watkins, no date). Notably, morphine's impact on the IL-1β signaling pathway may contribute to the attenuation of its pain-relieving effects, potentially precipitating OIH, tolerance, and withdrawal in the spinal cord. Conversely, suppression of IL-1β may prolong the beneficial outcomes associated with morphine administration (Hutchinson et al. 2011), (Shavit et al. 2005). During neuroinflammation, there is a disruption in the balance between anti-inflammatory adenosine signaling at A1AR/A3AR and pro-inflammatory purinergic signaling at the purinergic G protein-coupled receptor (P2XR). This disruption is caused by an increase in ADK expression and activity within the cells, as well as the release of ATP (Aronica et al. 2013), (Fiebich et al. 2014), (Rodrigues et al. 2015). The activation of P2X7R by ATP initiates the assembly of NLRP3 and the activation of caspase 1 (Tsuchiya and Hara 2014); the activation of P2X4R regulates the function of microglia, while the activation of purinergic G protein-coupled receptor 1 enhances glutamatergic signaling in neurons and leads to increased reactivity of astrocytes and calcium flux between cells (Rodrigues et al. 2015). Consequently, neuroinflammatory cytokines, such as IL-1β, elicit an upregulation of adenosine kinase (ADK) expression to maintain this state of imbalance (Aronica et al. 2011). The relationship between oxidative stress-induced hippocampal damage (OIH) and tolerance is linked to heightened excitatory glutamate neurotransmission (Garzón et al. 2012). Additionally, IL-1β enhances glutamatergic signaling at the synaptic level by augmenting presynaptic glutamate release (Yan and Weng 2013) and reducing glial glutamate uptake (Sama et al. 2008).

Wang et al. demonstrated that long-term morphine therapy leads to leads to an upregulation of NLRP3 expression and its subsequent downstream products, including IL-1β and caspase-1, in the spinal cord of mice. They found that when NLRP3 was deleted, tolerance to morphine decreased and microglia stopped activating when morphine was present. The increase in spinal NLRP3 brought on by long-term morphine therapy was stopped by TLR4 knockdown or selective antagonist suppression of the P2X7 receptor. The activation of the NLRP3 inflammasome in microglia, mediated by the spinal cord TLR4/P2X7 receptor pathway, has been found to play a significant role in the development of morphine tolerance (Wang et al. 2020).

Doyle et al. demonstrated that prolonged morphine administration increased the expression of ADK and decreased the amount of naturally occurring adenosine available at the A3AR receptor site in the spinal cord. They also revealed that blocking ADK activity or activating A3AR with specific agonists stopped rats and mice from developing tolerance and hyperalgesia to morphine. The stimulation of the NLRP3 inflammasome and the ensuing inflammatory response induced by chronic morphine therapy were attenuated by adenosine A3 receptor (A3AR) signaling. Consequently, A3AR signaling becomes dysregulated during prolonged morphine treatment, contributing to the perturbation of NLRP3 inflammasome activity within the spinal cord, thereby manifesting as morphine-induced adverse effects (Doyle et al. 2020).

The intrathecal morphine administration can stimulate astrocytes and microglia within the spinal cord, resulting in enhanced release of inflammatory cytokines, including TNF-α and IL-1β. This mechanism has been associated with the development of morphine tolerance (Avci and Taşkiran 2020). Chen et al. found that prolonged administration of morphine leads to an elevation in TCF7L2 expression in the spinal cord and microglial cells. As part of the TLR4/NF-κB/NLRP3 pathway, the TCF7L2 gene controls how it works.

This pathway has been linked to both inflammatory and neuropathic pain. It has also been seen that TCF7L2 plays a part in the transcriptional activation of TLR4, which is an essential receptor involved in the neuroinflammation that morphine causes. To stop or reverse morphine tolerance, TCF7L2 may be a good target because it can change TLR4/NF-κB/NLRP3 to cause antinociception and hyperalgesia in microglia cells (Chen et al. 2021).

Liu et al. showed that prolonged administration of morphine increased the expression of caveolin-1 and activated the NLRP3 inflammasome. Blocking caveolin-1 with a specific inhibitor or siRNA improved the analgesic effect of morphine and prevented the activation of the NLRP3 inflammasome and the production of cytokines that cause inflammation. Additionally, the inhibition of caveolin-1 resulted in the suppression of the ERK/c-JUN pathway, which is known to be involved in the control of the NLRP3 inflammasome. This suppression was observed through the reduction of ERK and c-JUN phosphorylation. Hence, caveolin-1 may serve as a promising candidate for mitigating the morphine-induced inflammation and analgesic tolerance through the regulation of the NLRP3 inflammasome and ERK/c-JUN pathway (Liu et al. 2022).

Yuan et al. investigated the effect of activating NLRP3 inflammasomes in the spinal cord on the progression of remifentanil-induced postoperative hyperalgesia (RIH). NLRP3 inflammasome activation influences the activity of spinal cord glutamate transporters and N-methyl-D-aspartate (NMDA) receptors. An infusion of remifentanil also caused RIH in rats, increased IL-1β and phosphorylated NR1 (a subunit of the NMDA receptor), decreased the expression of GLT-1, and increased the activation of the NLRP3 inflammasome in the spinal cord. Furthermore, the prevention or reversal of radiation-induced headache and its accompanying molecular alterations can be achieved with the intrathecal infusion of IL-1β or NLRP3 inflammasome inhibitors (Yuan et al. 2022) (as shown in Fig. 1).

Ruyak et al. conducted a study to investigate the effects of prenatal exposure to opioids and alcohol on immunological and serotonin components in the human placenta. Both opioids and alcohol have an impact on the expression of cytokines, specifically IL-1β and TNF-α, within the human placenta. It appears that alcohol and opioids may disrupt the dynamic, bidirectional relationship between the placental immune system and the serotonin system, leading to elevated levels of 5-HT in the fetal circulation, which are linked to neurodevelopmental effects (Ruyak et al. 2022). The characteristics of selected studies have been shown in Table 1.

The potential therapeutic implications of targeting NLRs and inflammasome in opioid-induced hyperalgesia and tolerance

Activation of NLRs and inflammation is thought to be one of the fundamental mechanisms responsible for opioid-induced hyperalgesia and tolerance. The NLRP3 inflammasome has been shown to play a role in the processing and secretion of pro-inflammatory cytokines that influence pain sensitivity and responsiveness to opioids (Chen et al. 2021) (see Fig. 1).

Kido et al. indicated that a low-dose ketamine infusion in patients undergoing orthognathic surgery who received a remifentanil infusion resulted in a reduction in post-operative morphine and an improvement in pain scores. They also showed that in patients undergoing orthognathic surgery and receiving a remifentanil infusion, a low-dose ketamine infusion reduced the neutrophil-to-lymphocyte ratio (NLR). In patients undergoing orthognathic surgery, a low-dose ketamine infusion has been suggested to attenuate the inflammatory response and avoid remifentanil-induced acute opioid tolerance (Kido et al. 2019).

Moreover, Novac et al. observed a significant increase in the level of NLRP3 inflammasomes in both patient groups (midazolam + fentanyl and propofol + fentanyl) after the completion of minimally invasive surgery (MIS) compared to preoperative values. The observed increase in NLRP3 inflammasome levels in both cohorts of administered anesthetics indicates a pronounced inflammatory response during minimally invasive surgery (MIS). Total intravenous anesthesia (TIVA) with propofol and remifentanil has been shown to improve immunologic function and decrease inflammatory responses in patients undergoing minimally invasive gynecologic surgery. TIVA not only improves patient recovery, but can also reduce the incidence of post-operative problems, including infections (Novac et al. 2021).

A lipid mediator called aspirin-triggered lipoxin (ATL) is produced from aspirin and omega-3 fatty acids. It can prevent the development of morphine antinociception tolerance (MAT). Tian et al. demonstrated that ATL prevents the activation of the NALP1 inflammasome in the spinal cord. The administration of morphine to rats caused the induction of morphine-associated tolerance (MAT), an elevation in Akt phosphorylation, a protein kinase implicated in cellular survival and proliferation, an augmentation in caspase-1 activation, and an upregulation in the expression of NALP1 inflammasome constituents.

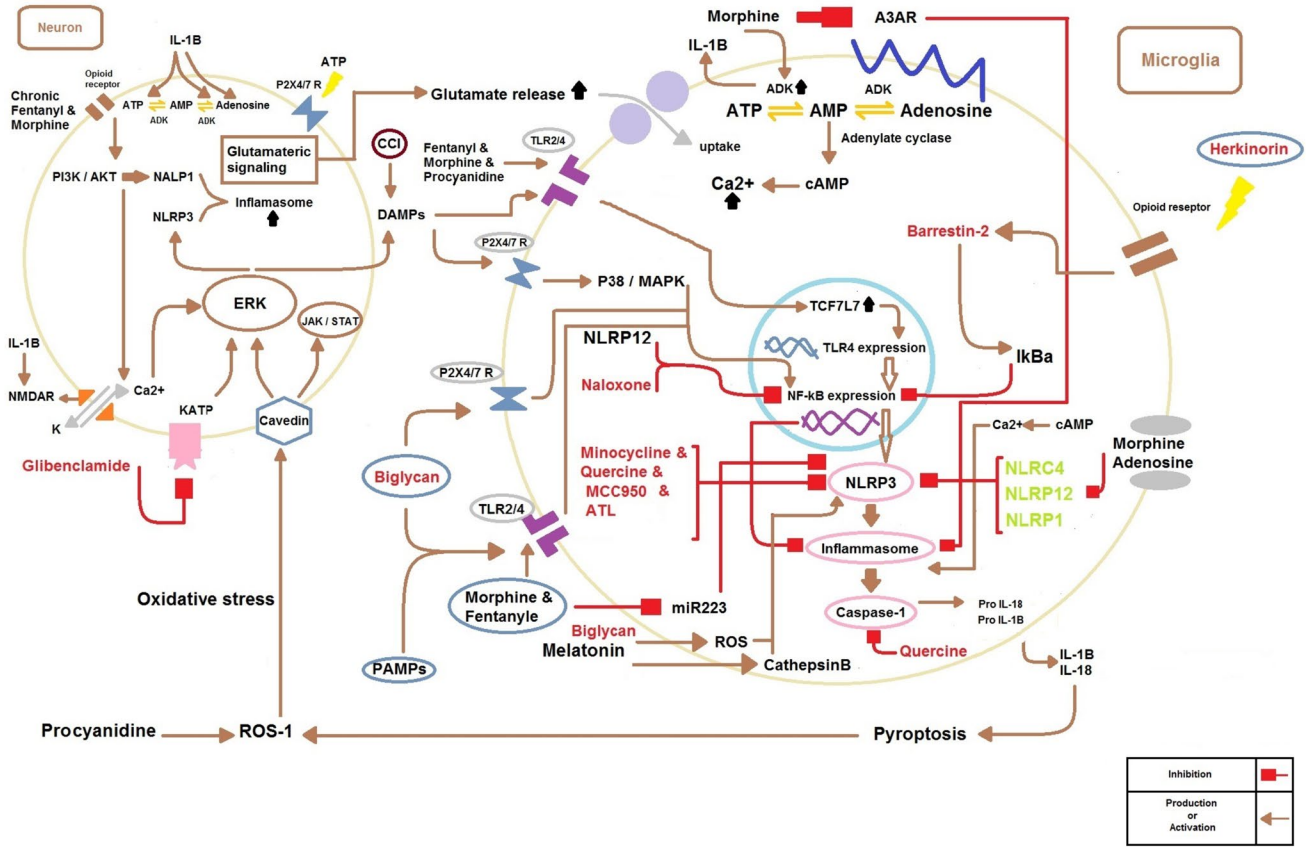

Fig. 1 The figure illustrates the role of NLRs (nucleotide-binding oligomerization domain-like receptors) and inflammasome signaling in developing opioid-induced hyperalgesia and tolerance. Opioids have an affinity for opioid receptors (ORs) located on neurons and immune cells, as well as Toll-like receptors (TLRs) and purinergic signaling at purinergic G protein-coupled receptor (P2XR). This binding interaction initiates many pathways that regulate the experience of pain and the inflammatory response. Certain signaling pathways are responsible for the activation of the NLRP3 inflammasome, which is a complex that facilitates the cleavage of pro-inflammatory cytokines IL-1β and IL-18, resulting in the production of their active versions. Hyperalgesia can result from these cytokines' propensity to boost neuronal excitability and sensitize nociceptors. Moreover, they may lessen the analgesic impact of opioids, which could result in tolerance and less pain relief. Additional NOD-like receptors (NLRs) can modulate the signaling of NF-κB and the production of major histocompatibility complex II (MHC II), both of which play crucial roles in the regulation of inflammatory processes and immunological responses. The diagram depicts the possible areas of focus for therapeutic intervention to mitigate or reverse the effects of opioid-induced hyperalgesia and tolerance through the modulation of NLRs and inflammasome signaling

Administration of ATL via intrathecal injection prior to morphine administration effectively prevented the onset of morphine-induced antinociceptive tolerance (MAT) and associated molecular changes by suppressing phosphorylation of Akt. The study suggests that ATL may serve as a therapeutic agent to prevent MAT by explicitly targeting the μ-receptor/PI3k-Akt signaling/NALP1 inflammasome pathway (Tian et al. 2015).

Cai et al. reported that the concurrent administration of procyanidins and morphine resulted in an enhanced antinociceptive effect of morphine while also mitigating the occurrence of acute and chronic morphine tolerance. Procyanidins were found to impede the augmentation of IL-1β and the activation of NLRP3 inflammasome generated by morphine. Furthermore, procyanidins repressed the amount of reactive oxygen species in microglia and downregulated the phosphorylation of p38 MAPK and NF-κB translocation (Cai et al. 2016).

Previous studies have provided evidence that NF-kB plays a crucial role in the regulation of NLRP3 transcription. In response to endotoxin stimulation, NF-kB can bind to the NLRP3 promoter and trigger NLRP3 transcription (Bauernfeind et al. 2009). Lin et al. presented empirical results demonstrating the inhibitory effect of naloxone on the activation of the NLRP3 inflammasome in already active THP-1 cells. Inhibition of NF-kB expression by naloxone is likely the mechanism by which this effect is mediated. This blockade slows the production of pro-IL-1 and NLRP3 transcription, both of which are increased by endotoxins. The results shed light on the potential

Table 1 The characteristics of selected studies

ID	DOI	Author, year	Country	Species (human, animal, cell culture)	Samples type (tissue, Serum…)	Biomarker	Type of opioid	Dose of opioids (mg/day)	Rout	Findings
1	10.1016/j.drugal-cdep.2012.12.022	Mao, 2013	USA	Fisher/NHsd 344 (F344, 4–5 weeks) rats	Spleen	TNF-α, IL-1β, IL-6, NLRP3, caspase 1, Gapdh, Casp12, Casp8, Card6, Naip2, Nlrp12, Nlrp5, Nlrc4, Nlrp1a, Nlrp3, Nlrp6, Nlrx1, Nod2, Pycard, Ccl12, Ccl2, Ccl5, Ccl7, Cd40lg, Bcl 2, Bcl 2l1, Bi rc2, Bi rc3, Cflar, Chuk, Ciita, Ctsb, Fadd, Hsp 90aa1, Hsp 90ab1, Ikb kb, Ikb kg, Ira k1, Ma p3k7, Ma p3k7 ip1, Ma p3k7 ip2, Ma pk1, Ma pk11, Ma pk1 2,Ma pk1 3, Ma pk1 4, Ma pk3, Ma pk8, Ma pk9, Me fv, Myd 88, Nfkb 1, Nfkb ia, Nfkb ib, P2 rx7, Pa nx1, Pe a15a, Pst pip1, Pt gs2, Rage, Rela, Ripk2, Su gt1, Tira p, Hsp 90b1, Tra f6, Txn ip, Xi ap, Ccl11, Cxcl1, Cxcl3, Ifnb1, Ifng, Il12a, Il12b, Il18, Il1b, Il33, Il6, Irf1, Irf2, Irf3, Irf4, Irf5, Irf6, Tnf, Tnfsf11,Tnfsf14, Tnfsf4	Morphine	Two pellets on day 1, four pellets on day 2 (pellets: 75 mg morphine sulfate per pellet)	S.C	In the morphine-tolerant state, LPS-induced expression of NLRP3 is suppressed and cytokine/chemokine expression is inhibited, which may be one of the mechanisms involved in morphine-induced immunosuppression
2	10.1016/j.bbi.2015.06.016	Tian, 2015	China	C57BL/6 mice	Spinal cord tissue & primary spinal neuron and astrocyte culture	Caspase-1, IL-1β, NALP1, ASC, ERK, p-JJN, p-p38, p-Akt, p-ERK	Morphine	Twice daily with 12-h interval at a dose of 10 mg/kg for 5 days, 10 μM/20h (cell culture)	S.C Treatment	The involvement of spinal NALP1 inflammasome activation in the development of morphine tolerance and the role of the l-receptor/ PI3k–Akt signaling/ NALP1 inflammasome cascade in this process. By inhibiting this signaling cascade, ATL blocked the development of morphine tolerance

Table 1 (continued)

ID	DOI	Author, year	Country	Species (human, animal, cell culture)	Samples type (tissue, Serum…)	Biomarker	Type of opioid	Dose of opioids (mg/day)	Rout	Findings
3	10.1186/s12974-016–0520-z	Cai, 2016	China	Adult CD-1 mice & cell culture	Spinal cord tissue, BV-2 cells	NLRP3, caspase-1, IL-1, TNF-α, p-p38, p38, p-ERK, ERK, p-JNK, JNK, p-NR1, NR1, p-PKC, PKC, ROS, NMDA-NR1, IBA-1, calcitonin gene related peptide (CGRP)	Morphine	10 mg/kg every 12 h for 7 days	S.C	Procyanidins suppresses morphine-induced activation of NLRP3 inflammasome and inflammatory responses in microglia, and thus resulting in significant attenuation of morphine antinociceptive tolerance
4	10.1073/pnas.1602070113	Grace, 2016	Australia	F344 and SD rats & cell culture	Spinal dorsal horn & microglia	IL-1β, TNFα, IL-6, GLT-1, GRK2, Iba1, GFAP, NeuN 1, P2X7R, p38, phospho-p38, p65/NFκB, NLRP3, caspase-1, phospho-NRI, mouse GRK2), GLT-1	Morphine	5 mg/kg, twice daily for 5 days	I.T and S.C	prolonged pain is an unrealized and clinically concerning consequence of the abundant use of opioids in chronic pain

Table 1 (continued)

ID	DOI	Author, year	Country	Species (human, animal, cell culture)	Samples type (tissue, Serum…)	Biomarker	Type of opioid	Dose of opioids (mg/day)	Rout	Findings
5	10.3390/brainsci7020014	Chang, 2017	USA	Fisher/NHsd 344 (F344) rats	Brain	VPS28, PROCR, CHMP2A, MB, ZNF768, RBPJ, WARS2, TBX2, MRPS2, MAP3K14, SMARCE1, AHRR, GPX7, ATP5F1, CALR, GPR110G, ELF4, FGFR1, F7, AHR, UBE2L6, PAFAH1B3, JUNB, RYK, ARG1, ZNF324, ATP5D, Card6, Casp1, Casp12, Casp8, Naip2, Nlrp12, Nlrp5, Nlrc4, Nlrp1a, Nlrp3, Nlrp6, Nlrx1, Nod2, Pycard, Bcl2, Bcl2l1, Birc2, Birc3, Cflar, Chuk, Ciita, Ctsb, Fadd, Hsp90aa1, Hsp90ab1, Ikbkb, Ikbkg, Irak1, Map3k7, Map3k7ip1, Map3k7ip2, Mapk1, Mapk11, Mapk12, Mapk13, Mapk14, Mapk3, Mapk8, Mapk9, Mefv, Myd88, Nfkb1, Nfkbia, Nfkbib, P2rx7, Panx1, Pea15a, Pstpip1, Ptgs2, Rage, Rela, Ripk2, Sugt1, Tirap, Hsp90b1, Traf6, Txnip, Xiap, Ccl11, Ccl12, Ccl2, Ccl7, Cxcl3, Cd40lg, Ifnb1, Ifng, Il12a, Il12b, Il18, Il1b, Il33, Il6, Irf1, Irf2, Irf3, Irf4, Irf5, Irf6, Tnfsf11, Tnfsf14, Tnfsf4	Morphine	Two 75 mg morphine sulfate pellets on day 1, four pellets on Day 2	S.C	in the morphine tolerant state, the expression of NLRP12 and its related genes is altered in response to LPS and that the Vacuolar protein-sorting-associated protein 28 (VPS28), which is involved in the transport and sorting of proteins into sub-cellular vesicles, may be the key regulator of these alterations
6	10.1177/1744806917706582	Xie 2017	China	Sprague–Dawley adult male rats	Lumbar spinal cord	NLRP3, apoptosis-associated speck-like protein, Caspase-1, IL-1β, and IL-18	Morphine	10 mg/kg	I.T	miR-223 could suppress the activities of NLRP3 inflammasomes (NLRP3, apoptosis-associated speck-like protein, and Caspase-1) to relieve morphine analgesic tolerance in rats by down-regulating NLRP3

Table 1 (continued)

ID	DOI	Author, year	Country	Species (human, animal, cell culture)	Samples type (tissue, Serum…)	Biomarker	Type of opioid	Dose of opioids (mg/day)	Rout	Findings
7	10.1186/s12974-017–0997-0	QC 2017,	China	Adult male CD-1 mice & cell culture	microglial cell line BV-2 & neural cell line SH-SY5Y	p38, p-p38 (Tyr182), caspase-1, IL-1β, HSP70, p-p65, ERK, p-ERK (Thr202/Tyr204), AKT, p-AKT (Ser473), NLRP3 and caspase-1, and Kir6. (NF-κB) p65	Morphine	(10 µg/10 µL) once daily for seven consecutive days/ cell culture treated with morphine (100, 200, 400 µM) for 12 h	I.T	morphine-induced extracellular HSP70 was an alternative way for the activation of TLR4-NLRP3 in analgesic tolerance. The release of HSP70 was regulated by MOR/AKT/ K_{ATP}/ERK pathway. Our study suggested a promising target, K_{ATP} channel and a new leading compound, glibenclamide, for treating morphine tolerance
8	10.1016/j.bbi.2017.08.018	Grace 2018	USA	Adult male Fischer 344 (F344) rats	Lumbar dorsal quadrant of the spinal cord	NLRP3 inflammasome (Caspase-1, IL-1β)	Morphine	5 mg/kg	S.C	After peripheral nerve injury, morphine treatment results in persistent DAMP release via TLR4, P2X7R and caspase-1, which are involved in formation/activation of NLRP3 inflammasomes. These DAMPs are responsible for maintaining persistent allodynia, which may be due to engagement of a positive feedback loop, in which NLRP3 inflammasomes are persistently activated by DAMPs signaling at TLR4 and P2X7R

Table 1 (continued)

ID	DOI	Author, year	Country	Species (human, animal, cell culture)	Samples type (tissue, Serum…)	Biomarker	Type of opioid	Dose of opioids (mg/day)	Rout	Findings
9	10.1124/jpet.120.000004	Doyle 2020	USA	Sprague Dawley rats & male CD-1 mice & male C57BL\6 wild-type mice& male Balb/c mice	interscapular region & chronic intrathecal cannulas & intrathecal catheter	Caspase 1, NLRP3, IL-1β, TNF-α, IL-10	Morphine	6 mg/kg on days 1, 3, and 6 twice daily for 3 days: day 1, 7.5 and 15 mg/kg; day 2, 30 and 30 mg/kg; and day 3, a single dose of 30 mg/kg 75 µg/µl/h (~8.2–9 mg/kg per day) over 6 days (3 mg/kg) (day 7 post-CCI	I.P S.C	These adverse effects are due to reduced adenosine signaling at the A_3AR, resulting in NOD-like receptor pyrin domain-containing 3-interleukin-1β neuroinflammation in rat spinal cord. These effects are attenuated by A_3AR agonists, suggesting that A_3AR may be a target for therapeutic intervention with selective A_3AR agonist as opioid adjuncts
10	10.2147/JIR.S266995	Wang 2020	China	Male C57BL/6 mice (8–10-weeks-old; 20–25 g)	The lumber section of the spinal cord	NLRP3, P2X7	Morphine	15 µg once daily for 7 days	I.T	NLRP3 inflammasome in microglia plays a crucial role in morphine tolerance and that both TLR4- and P2X7R-dependent pathways are required for NLRP3 inflammasome activation over the course of the development of morphine-induced tolerance. It suggests a new perspective for the targeted treatment of morphine-induced tolerance

Table 1 (continued)

ID	DOI	Author, year	Country	Species (human, animal, cell culture)	Samples type (tissue, Serum…)	Biomarker	Type of opioid	Dose of opioids (mg/day)	Rout	Findings
11	10.1007/s10571-020–00957-5	Carranza-Aguilar 2022	Mexico	Male Wistar rats (250–300 g)	Brain	NLRP3, CD11b, GFAP, Caspase 1, GSDMD-N, TLR4,	Morphine	morphine (10 mg/kg) or fentanyl (0.1 mg/kg) 3×daily for 7 days	I.P	morphine and fentanyl differentially induce cell-specific activation of NLRP3 inflammasome and pyroptosis in the DRN through TLR4 receptors in astrocytes and through opioid receptors in neurons, indicating that neuroinflammation is involved in opioid-induced analgesia and fentanyl-induced hyperalgesia after repeated administrations
12	10.1016/j.redox.2020.101560	Liu 2020	China	mice (25–30 g) at an age of 8	Tissue (Brain, blood) and BV2 cells	NLRP3, IL-1β, ASC IRF7, GSDM, CTSB, ROS	Morphine	10 mg/kg daily for 7, 14 and 21 days	S.C	There is a significantly elevated level of serum IL-1β, which indicates an increase of NLRP3 inflammasome activity associated with the reduced level of serum melatonin, in heroin-addicted patients relative to healthy individuals. results provide a solid basis for conducting a clinical trial with the co-administration of melatonin and morphine for the relief of severe pain

Table 1 (continued)

ID	DOI	Author, year	Country	Species (human, animal, cell culture)	Samples type (tissue, Serum…)	Biomarker	Type of opioid	Dose of opioids (mg/day)	Rout	Findings
13	10.1016/j.taap.2021.115458	Chen 2021	China	Adult male CD-1 mice (18–22 g)	L5 & L6 spinous processes of the spinal cord	TCF7L2, TLR4, p-p65, NLRP3, Caspase-1, TNF-α, IL-1β	Morphine	10 mg/kg once daily for day	I.T	TCF7L2 regulates the activation of TLR4/ NF-κB/ NLRP3 pathway in microglia, and is involved in the formation of morphine tolerance
14	10.1007/s12031-022–01989-w	Liu 2022	China	male Sprague–Dawley rats (weighing 220 ± 20 g)	the spinal dorsal horn sections (spinal cord)	Caveolin, ERK, IL-6, IL-1β, CSD, TNF-α, p-ERK/ERK, p-cJUNk	Morphine	75 μg/μL/h	S.C	locking of Caveolin-1 can attenuate morphine-induced inflammation and analgesic tolerance through inhibiting NLRP3 inflammasome and ERK/c-JUN pathway
15	10.1002/jcb.29929	Cui 2021	China	Pregnant rats	Rat primary neurons culture	NLRP3, Caspase-1, IL-1β, IL-6, TNF, (NF-κB) p65, IκBα, β-arrestin2, ROS	Herkinorin	0.1 & 0.5 & 1 μM	Treatment	Herkinorin negatively regulated NLRP3 inflammasome to alleviate neuronal ischemic injury through inhibiting NF-κB pathway mediated primarily by MOR activation. Inhibition of the NF-κB pathway by Herkinorin may be achieved by decreasing the ubiquitination level of IκBα, in which β-arrestin2 may play an important role

Table 1 (continued)

ID	DOI	Author, year	Country	Species (human, animal, cell culture)	Samples type (tissue, Serum…)	Biomarker	Type of opioid	Dose of opioids (mg/day)	Rout	Findings
16	10.1007/s10787-017–0356-x	Ruiz-Miyazawa 2017	Brazil	male Swiss mice (C57BL/6 mice), cell culture	Femora and tibiae, bone marrow-derived macrophages (BMDMs)	NLRP3, ASC, Pro-caspase-1, Pro-IL-1β, TNF-α, anti-oxidant capacity (GSH, FRAP), gp91phox, NRF2, and HO-1 and superoxide anion production	Morphine	morphine (0.2; 2 or 20 μM)	Treatment	Quercetin inhibited MSU-induced mechanical hyperalgesia, leukocyte recruitment, TNFα and IL-1β production, superoxide anion production, inflammasome activation, decrease of antioxidants levels, NFκB activation, and inflammasome components mRNA expression. Naloxone pre-treatment prevented all the inhibitory effects of quercetin over MSU-induced gout arthritis. Quercetin exerts analgesic and anti-inflammatory effect in the MSU-induced arthritis in a naloxone-sensitive manner

Table 1 (continued)

ID	DOI	Author, year	Country	Species (human, animal, cell culture)	Samples type (tissue, Serum…)	Biomarker	Type of opioid	Dose of opioids (mg/day)	Rout	Findings
17	10.1007/s10571-020–00957-5	Carranza-Aguilar 2020	Mexico	male Wistar rats (250–300 g)	Brain	NLRP3, caspase-1, GSDMD-N, TPH-2	Morphine and Fentanyl	morphine (10 mg/kg) or fentanyl (0.1 mg/kg) 3×daily for 7 days	I.P	Morphine and fentanyl differentially induce cell-specific activation of NLRP3 inflammasome and pyroptosis in the DRN through TLR4 receptors in astrocytes and through opioid receptors in neurons, indicating that neuroinflammation is involved in opioid-induced analgesia and fentanyl-induced hyperalgesia after repeated administrations
18	10.47162/RJME.62.4.08	NOVAC, 2021	Romania	female patients with invasive gynecological surgery	Blood	IL-6, IL-10, TNF-α, NOD, NLRP3,	Fentanyl	Fentanyl 3 µg/kg	I.V	both groups of patients, NLRP3 and cytokines concentrations in the serum were higher after minimally invasive surgery (MIS) than those before MIS. It appears that both Midazolam and Fentanyl and Propofol and Fentanyl have an immunomodulatory action due to the anti-inflammatory effect of both anesthetics

Table 1 (continued)

ID	DOI	Author, year	Country	Species (human, animal, cell culture)	Samples type (tissue, Serum…)	Biomarker	Type of opioid	Dose of opioids (mg/day)	Rout	Findings
19	10.1177/17448069221093016	Yuan, 2022	China	Adult male Sprague–Dawley rats (weight, 240–260 g	L4-L6 segments of the spinal cord	caspase-1, NLRP3, P2X7R, TLR4, IL-1β, GLT-1, phospho-NR1	Remifentanil	1.2 μg/kg/min for 60 min	I.V	NLRP3 inflammasome activation mediates IL-1β release and contributes to RIH in rats by inducing NMDA receptor NR1 subunit phosphorylation and decreasing GLT-1 expression
20	10.1016/j.expneurol.2022.114057	Ruyak, 2022	USA	Pregnant women	Placenta	TLR4, NLRP3, IL-1β, TNF-α, SERT, TPH1, IDO1	Buprenorphine, Methadone, Other opioids			prenatal alcohol exposure may inhibit SERT expression while simultaneously promoting increased TPH1 protein expression in human placenta. This may result in increased 5-HT in fetal circulation known to affect neurodevelopment. opioids and alcohol may disturb the bidirectional, dynamic interaction between the placental immune and serotonin system

I.P. intraperitoneal, *S.C.* subcutaneous, *I.T:* intrathecal, *I.V.* intravenous, *I.O.* intraoral (drinking), (NOD)-like receptor protein 3 (NLRP3), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), serotonin transporter (SERT), tryptophan hydroxylase (TPH1), indoleamine 2,3-dioxygenase 1 (IDO)

therapeutic benefits of naloxone in regulating NLRP3 inflammasome activation and subsequent inflammatory responses (Lin et al. 2017).

Green-Fulgham et al. investigated the impact of morphine in conjunction with TLR4 and P2X7 antagonists on voluntary cycling behavior in male rats subjected to unilateral chronic constriction injury (CCI) of the sciatic nerve. Over seven weeks after CCI, the rats' running distance and speed were measured during the active phase of the circadian cycle. Administration of CCI led to a reduction in locomotor activity, indicating neuropathic pain and impaired motor function. Interestingly, the short-term administration of morphine did not affect the CCI rats, but increased the running activity of the sham rats, indicating the induction of hyperactivity by morphine. Nevertheless, the rats' CCI running behavior normalized more than five weeks after the last dose of morphine when combined with either a TLR4 antagonist ((+)-naloxone) or a P2X7 antagonist (A438079), suggesting that the painkillers and anti-inflammatory drugs acted over a longer period of time (Green-Fulgham et al. 2022). Consequently, the TLR4 and P2X7 receptors may be viable targets for reducing morphine tolerance and neuropathic pain as a result of their cross-talk with the NLRP3/inflammasome (Pelegrin 2021), (Yang et al. 2020).

Ruiz-Miyazawa et al. studied the effects of the flavonoid molecule quercetin on gout arthritis induced by monosodium urate (MSU) crystals in a mouse model. They investigated what happened when mice were administered quercetin and/or naloxone and how this affected mechanical hyperalgesia, paw edema, cytokine levels and activation of the NLRP3 inflammasome. They showed that quercetin could dose-dependently reduce the pain, inflammation and IL-1β production induced by MSU injection. They also indicated that quercetin exerts its effect by interacting with opioid receptors. It was found that quercetin could stop the expression and activation of NLRP3/inflammasome and its downstream parts, such as caspase-1 and ASC, in the paw tissue and peritoneal macrophages of mice injected with MSU. The results suggest that quercetin, through its modulation of the NLRP3 inflammasome and opioid system, has the potential of a natural therapeutic agent for the treatment of gout arthritis (Ruiz-Miyazawa et al. 2017).

Qu et al. showed that blocking the KATP channel with glibenclamide stopped the release of HSP70 and turned on the TLR4-NLRP3 inflammasome. This intervention also attenuated morphine tolerance and hyperalgesia. They suggested that the KATP channel and the HSP70-TLR4-NLRP3 axis could be potential targets for mitigating morphine tolerance and neuroinflammation (Qu et al. 2017).

Morphine and fentanyl can affect the activation of the NLRP3 inflammasome in glial and neuronal cells in the dorsal raphe nucleus (DRN), a region involved in pain modulation. Morphine and fentanyl both work by activating TLR4 receptors in astrocytes and opioid receptors in neurons. These receptors then activate the NLRP3 inflammasome and trigger pyroptosis in the DRN in different ways. This suggests that neuroinflammation plays a role in opioid-induced analgesia and fentanyl-induced hyperalgesia after repeated administration. Furthermore, blocking the NLRP3 inflammasome with MCC950 or the anti-inflammatory drug minocycline slowed down the development of pain tolerance and stopped the occurrence of fentanyl-induced hyperalgesia. Therefore, it is plausible that the NLRP3 inflammasome and pyroptosis mechanisms are involved in the neuroinflammatory response and pain modulation related to opioid effects (Carranza-Aguilar et al. 2022).

Reactive oxygen species (ROS) facilitate the stimulation of the inflammasome. The inflammasome is triggered by reactive oxygen species (ROS) through the MAPK (mitogen-activated protein kinase) and ERK1/2 pathways (Harijith et al. 2014). Moreover, oxidative stress has been shown to stimulate NLRP3 by upregulating the activity of cathepsin B (Bai et al. 2018). Liu et al. have indicated that melatonin has the potential to alleviate the development of analgesic tolerance and hyperalgesia due to prolonged morphine therapy. This activation could be stopped by melatonin because it lowers the levels of ROS and cathepsin B. Morphine also increased the activation of the NLRP3 inflammasome in the brain and blood of mice. In addition, Liu et al. found that, in comparison to healthy people, heroin addicts had lower blood levels of melatonin and higher serum levels of IL-1β. A possible treatment approach for managing chronic pain without causing tolerance or hyperalgesia is to co-administer melatonin with low-dose morphine (Liu et al. 2020).

Cui et al. studied the neuroprotective effects of herkinorin, a natural substance derived from salvinorin A and a mu-opioid agonist. They reported that herkinorin demonstrated the capacity to protect neurons from harm due to oxygen–glucose deprivation/reperfusion (OGD/R). This protective effect was attributed to the inhibition of NLRP3 inflammasome activation and the subsequent reduction in the production of pro-inflammatory cytokines. The herkinorin compound stopped the NF-κB pathway from working, which is a signaling pathway that helps control the NLRP3 inflammasome. The reduction of phosphorylation and ubiquitination events targeting IκBα, a well-known NF-B inhibitor, was responsible for this inhibition. Cui et al. also found that the effects of herkinorin on the IκBα and NF-κB pathway were mediated via β-arrestin2. Therefore, herkinorin could have potential as a pharmacological intervention for treating ischemic stroke through its modulation of the mu-opioid receptor (MOR) and NF-κB pathway (Cui et al. 2021).

Conclusion and future directions

There is convincing evidence for the possible involvement of NLRs and the inflammasome in the pathogenesis of opioid-induced hyperalgesia (OIH) and tolerance. The present work emphasizes the essential involvement of the innate immune system in these pathophysiological circumstances, which pose significant challenges to the adequate control of chronic pain by opioids. Numerous studies have elucidated the functional significance of NLRs (nucleotide-binding domain and leucine-rich repeat-containing receptors) and inflammasomes, revealing their involvement not only in immune responses but also in the regulation of neuronal activity. Our research provides valuable insights into the neuro-immune connections underlying opioid-induced hyperalgesia and tolerance. Consistent with previous research, our findings suggest that activation of NLRs and inflammasomes plays a critical role in the neuroinflammatory response associated with prolonged opioid exposure. This activation leads to sensitization of nociceptive neurons and a reduction in opioid efficacy. Therefore, inhibition of the NLR inflammasome signaling pathway could potentially serve as a therapeutic approach to prevent or reverse opioid-induced hyperalgesia (OIH) and opioid tolerance. Nevertheless, it is essential to further validate these findings in additional experimental models and clinical contexts. The unique molecular pathways by which the NLR inflammasome pathway contributes to OIH and opioid tolerance also require further investigation.

Although activation of the NLRP3 inflammasome is the main cause of OIH and tolerance, the exact mechanisms by which this occurs are still unclear. Therefore, the use of sophisticated methods such as single-cell RNA sequencing or proteomics may help to elucidate these processes. While the NLRP3 inflammasome has received much attention, other NLRs such as NLRC4 and NLRP1 have also been linked to the development of chronic pain. More research needs to be done to fully understand how these NLRs influence how opioids cause tolerance and increased pain.

Since the immune system plays an important role in the development of hyperalgesia and tolerance after opioid administration, future studies could focus on finding out the exact types of immune cells and cytokines involved in this process and how they interact with NLRs and inflammasomes. In addition, investigating how genetic and environmental factors influence the manifestation and activation of NLRs and inflammasomes could help us understand why different people develop different levels of tolerance and hyperalgesia when exposed to opioids. It is also essential to identify effective treatment targets to mitigate or reduce the incidence of opioid tolerance and hypersensitivity. Most discoveries in this field have come from animal models. Although these models provide valuable insights into basic systems, it is imperative to initiate the crucial next phase of adapting these discoveries to the human context. The use of clinical trials in humans receiving opioids for the treatment of chronic pain has the potential to provide important and insightful findings. By looking more closely at these areas, future research can build on the results of this study and help us learn more about how opioids cause tolerance and increased pain. This, in turn, may facilitate the development of more effective pain management strategies.

Author contributions Nasrin Zare conducted the design and coordination of the study, the literature searches, the quality rating, and drafted the manuscript. Fateme Sharafeddin, AmirMahdi Montazerolghaem, Nastaran Moradiannezhad, and Mohammaderfan Araghizadeh participated in the selection of reviews and the data extraction. The first draft of the manuscript was written by Nasrin Zare and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest No potential conflict of interest was reported by the author(s).

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