IBRO Neuroscience Reports 16 (2024) 43–50

Contents lists available at ScienceDirect

IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

The effect of cannabinoid type 2 receptor agonist on morphine tolerance

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ARTICLE INFO

Keywords:
Cannabinoid type 2 receptor
Morphine tolerance
Inflammatory cytokines
Microglia
Opioid receptor

ABSTRACT

Pain highly impacts the quality of life of patients. Morphine is used for pain treatment; however, its side effects, especially morphine tolerance, limit its use in the clinic. The problem of morphine tolerance has plagued health workers and patients for years. Unfortunately, the exact mechanism of morphine tolerance has not been fully clarified. The mechanisms of morphine tolerance that are currently being studied may include μ-opioid receptor (MOR) desensitization and internalization, mitogen-activated protein kinase (MAPK) pathway activation and crosstalk, the effects of microglia and the increase in inflammatory factors. Morphine tolerance can be alleviated by improving the pathophysiological changes that lead to morphine tolerance. Previous studies have shown that a cannabinoid type 2 (CB2) receptor agonist could attenuate morphine tolerance in a variety of animal models. Many studies have shown an interaction between the cannabinoid system and the opioid system. The CB2 receptor may modulate the effect of morphine through a pathway that is common to the MOR, since both receptors are G protein-coupled receptors (GPCRs). This study introduces the potential mechanism of morphine tolerance and the effect of CB2 receptor agonists on reducing morphine tolerance, which can provide new ideas for researchers studying morphine and provide beneficial effects for patients suffering from morphine tolerance.

Introduction

Pain, especially chronic pain, seriously affects the quality of life of patients, including those suffering from cancerous pain, inflammatory pain and neuropathic pain (Zhang et al., 2016; Zhang et al., 2018; Ma et al., 2021). Although morphine is ubiquitously used for pain treatment, the development of tolerance limits its clinical application (Eidson and Murphy, 2019). Although many studies have been performed on the mechanism of morphine tolerance, the exact mechanism is still not fully understood. To date, it has been suggested that the desensitization and internalization of the μ-opioid receptor (MOR), crosstalk signaling activated by the mitogen-activated protein kinase (MAPK) pathway, the role of microglia, and an increase in inflammatory cytokines could explain morphine tolerance.

The endocannabinoid system is a complex system involving numerous lipid agonists and multiple receptors and is involved in a broad range of physiopathological processes, such as energy metabolism, inflammation and pain transmission (Ozdemir, 2020). Cannabinoid type 2 (CB2) receptors are a family of G protein-coupled receptors (GPCRs) that are expressed by glia and neurons in the central and peripheral nervous systems (Romero-Sandoval et al., 2008). Moreover, many studies have suggested that CB2 receptor agonists could decrease morphine tolerance in models such as the Walker 256 tumor-bearing rat model (Zhang et al., 2016; Zhang et al., 2017; Kong et al., 2022), an inflammatory pain model in C57BL6/J mice (Yuill et al., 2017) and an anti-retroviral toxic neuropathy model (Carey et al., 2023). CB2 receptor agonists inhibit the development of morphine tolerance.

The molecular mechanisms and intercellular signaling pathways involved in morphine tolerance are complicated. There may be extensive interactions between CB2 and opioid receptors. Despite previous studies, the specific mechanism by which CB2 receptor agonists affect morphine tolerance has not been fully elucidated. To help patients suffering from chronic pain, it is imperative to conduct more in-depth research on alleviating pain. In this review, we attempt to summarize the recent findings on the current understanding of the role of CB2 receptor agonists in morphine analgesia and tolerance and then explore potential targets and seek new paths to provide new study directions for medical workers and guide clinical drug use.

Methods: literature search strategy

Relevant literature was identified by screening PubMed and Embase. To find the mechanism of morphine tolerance, we input keywords such as morphine or opioid tolerance, opioid receptor (only MOR was

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https://doi.org/10.1016/j.ibneur.2023.11.005
Received 5 September 2023; Received in revised form 24 October 2023; Accepted 14 November 2023
Available online 1 December 2023

included), microglia and inflammatory factors (such as interleukin, IL-1β, IL-6, and TNF-α), the MAPK pathway, transient receptor potential vanilloid 1 (TRPV1), Toll-like receptor 4 (TLR4) and NLRP3 inflammasome, and selected two, three or more keywords for pair-based combinations. A total of 615 literature were searched from January 1990 to July 2023, 132 relevant articles of which mentioned the mechanism of tolerance, and 74 met the inclusion criteria. On the reduction of morphine tolerance tolerance with CB2 receptor agonists, 47 papers were searched, and the last 18 met the inclusion criteria. The articles were filtered based on the search results. The submission deadline was July 10, 2023.

Mechanisms of opioid/morphine tolerance

Morphine tolerance is defined as a decrease in the effects of a drug following prolonged management, resulting in the loss of drug potency and an increase in dose to maintain its analgesic effects (Zhang et al., 2016; Zhang et al., 2017). From known studies, morphine tolerance involves multiple mechanisms.

MOR expression, desensitization and internalization

Many types of opioid receptors (e.g., μ, κ, δ) are present in the nervous system, and they are all typical inhibitory GPCRs (Zhou et al., 2021). MOR is the main receptor associated with the effects of morphine and is widely expressed in the peripheral and central nervous systems, including the cerebral cortex, striatum, limbic system, hippocampus, thalamus, locus coeruleus, superficial laminae of the spinal cord (SC) dorsal horn, dorsal root ganglion (DRG) and peripheral nerves (Liu et al., 2019). MOR is the most well-studied opioid receptor in pain management and morphine tolerance.

Many mechanisms have been proposed to explain opioid tolerance, including the desensitization, internalization, and downregulation of MOR (Meuser et al., 2003; Lin-Xin et al., 2021). Chronic morphine treatment upregulates the expression of certain miRNAs (miR-16), which are partially complementary and bind to the 3′-UTR of MOR mRNA to halt MOR translation (Dai et al., 2018; Zhang et al., 2019). However, several studies have shown that, in comparison to other opioids, morphine does not result in MOR downregulation (Arttamangkul et al., 2008; Mcpherson et al., 2010). Therefore, the role of MOR downregulation in morphine tolerance may remain controversial.

MOR phosphorylation is one of the most important methods of receptor internalization and desensitization (Williams et al., 2013). MOR internalization and desensitization occur via G protein-coupled receptor kinase (GRK) phosphorylation and adenylate cyclase (AC) sensitization after morphine and MOR binding (Sanna et al., 2020; Ram et al., 2021). In addition, multi-phosphorylation in a specific region of the carboxy-terminal tail of MOR has been demonstrated to be involved in MOR internalization (Bohn et al., 2000). However, another study indicated that phosphorylation deficiency in the MOR C-terminus did not affect the development of tolerance (Kibaly et al., 2017). Moreover, β-arrestin is a fundamental molecule that suppresses G protein-associated signal transduction, and β-arrestin participates in the development of opioid tolerance by recruiting and reducing MOR (Kliewer et al., 2019; Singleton et al., 2021).

MAPK pathway crosstalk and microglial activation

Microglial cells are the primary immunocompetent cell type within the central nervous system (CNS). Emerging evidence indicates that glia and glia-derived proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, play a fatal role in morphine tolerance (Mayer et al., 1999; Watkins et al., 2005; Romero-Sandoval et al., 2008). According to existing studies, the expression of the CB2 receptor in microglial cells has received much attention. We only examined the expression of the CB2 receptor in microglia in this paper. Due to the wide expression of the CB2 receptor in immune cells, its anti-inflammatory effects have attracted increasing attention (Zhang et al., 2007; Adhikary et al., 2011; Elliott et al., 2011; Amenta et al., 2012; Ramirez et al., 2012; Ronca et al., 2015). In a model of adult male Sprague–Dawley rats (Tumati et al., 2012) and in a Walker 256 tumor-bearing rat model (Kong et al., 2022), a CB2 receptor agonist inhibited microglial activation and the inflammatory cytokines IL-1β, IL-6 and TNF-α to attenuate morphine tolerance (Hutchinson et al., 2007; H Hutchinson et al., 2011). Intracellular signaling cascades are the prime methods of communication between the plasma membrane and regulatory targets in various intracellular compartments. Sequential activation of kinases is a common mechanism of signal transduction in many cellular processes. MAPKs, including p38 MAPK, ERK and c-Jun N-terminal kinase (JNK), are downstream of many kinases that regulate signal transmission. MAPK has a significant role in regulating pain hypersensitivity (Widmann et al., 1999).

The phosphorylation of MAPK is a crucial step in morphine tolerance. The activated form of MAPK involves phosphorylation, and phosphorylated MAPK is regulated by enzymes. With long-term morphine treatment, morphine could inhibit the dephosphorylation of MAPK and MKPs (MKP-1, MKP-3) reduction, promote the phosphorylation of MAPK and p-p38, p-Akt, p-ERK1/2 and p-JNK increase. (Horvath et al., 2010; Kong et al., 2022). Although morphine has different effects on MAPK-related enzymes (phosphatases and protein kinases), it increases phosphorylated MAPK (p-p38, p-Akt, p-ERK1/2 and p-JNK), ultimately leading to microglial activation and the release of the downstream factors IL-1β, IL-6 and TNF-α (Chen et al., 2008; Kong et al., 2022). Since activated MAPK and inflammatory cytokines released by microglia are involved in morphine tolerance, reducing the activation of MAPK could ease tolerance. Dephosphorylation of MAPK reduced the production of proinflammatory factors and improved the outcomes of inflammation (Chen and Sommer, 2009; Kong et al., 2022). When JNK and ERK inhibitors were injected, morphine tolerance was attenuated by suppressing p38 activation and decreasing the release of IL-1β and TNF-α (Chen et al., 2008). However, morphine treatment increased p-ERK1/2 and p-Akt expression levels but did not modulate p-p38 or p-JNK1/2 in a murine microglial cell study (Merighi et al., 2012). This difference might involve differences such as in vitro and in vivo experiments, doses, species and experimental conditions, but the exact reason is still unknown. In addition, a previous study showed that electroacupuncture (EA) could inhibit morphine tolerance. Specifically, EA inhibited activation of the PI3K/Akt/JNK1/2 signaling pathway and then inhibited the release of inflammatory cytokines to alleviate morphine tolerance (Jiang et al., 2021).

TLR4, which is a member of the Toll-like receptor family, recognizes specific danger-associated molecular patterns and initiates an immune response. TLR4 functions as a prime signal that triggers the downstream signaling pathway, enhancing the transcription of NLRP3 and pro IL-1β. Subsequently, a second signal triggers several NLRP3 submits to form a protein complex known as the inflammasome, which then recruits caspase-1 and eventually leads to the maturation and secretion of IL-1β and TNF-α (Qu et al., 2017; Mangan et al., 2018; Wang et al., 2020; Chen et al., 2021; Wang et al., 2021; Carranza-Aguilar et al., 2022). The innate immune receptor TLR4 mediates morphine-induced cytokine release (Hutchinson et al., 2010). Repeated treatment with morphine increased the total expression of spinal TLR4 (Eidson et al., 2017), transforming growth factor β activated kinase 1 (TAK1) (Wang et al., 2021), NLRP3 and phosphorylated TAK, suggesting that TLR4-TAK1-NLRP3 signaling during neuroinflammation was related to tolerance. Moreover, heat shock protein 70 (HSP70) participates in activating microglia and triggering TLR-mediated neuroinflammation during morphine tolerance by activating the HSP70-TLR4-NLRP3 signaling pathway (Qu et al., 2017). When TLR4 was inhibited and knocked out or the NLRP3 inflammasome was inhibited, morphine tolerance could be attenuated (Eidson and Murphy, 2013; Wang et al., 2021). Repeated morphine administration in glial and neuronal cells in the dorsal raphe nucleus (DRN) in rats and

NLRP3-dependent pyroptosis played a role in morphine tolerance (Carranza-Aguilar et al., 2020). TLR4 and NLRP3 signaling, including pyroptosis, is critical for opioid tolerance and should be given more attention.

Other mechanisms

Studies have also shown that miRNAs play a critical role in the development and pathophysiology of the nervous system (Follert et al., 2014; Sun and Shi, 2015; Qu et al., 2020), and miR-128 was suggested to be downregulated in murine microglial cells in a spinal cord injury (SCI) mouse model. Conversely, overexpression of miR-128 significantly promoted the conversion between the M1 phenotype and M2 phenotype and decreased the concentrations of IL-1β, IL-6 and TNF-α, which suggested that miR-128 was involved in morphine tolerance via different microglial activation states (Yang et al., 2017), although the target of miR-128 and the exact mechanism are unknown. In addition, miRNA-30a-5p promoted morphine tolerance, and a miRNA-30a-5p inhibitor could decrease the levels of TNF-α or IL-1β in microglia and suppress the phosphorylation of NF-κB p65 via AMPK-autophagy activation to reduce tolerance in the SC in mice (Li et al., 2022). This is a new target for alleviating morphine-induced tolerance.

TRPV channels are a subgroup of conserved integral membrane proteins that can regulate noxious stimuli and thermal pain (Samanta et al., 2018). Morphine tolerance was related to an increase in the protein expression of TPRV1 in a model of cancer pain (Chen et al., 2008). In the morphine tolerance model, TRPV1 increased, and when phosphorylated MAPK was inhibited, TRPV1 decreased correspondingly, suggesting that MAPK played a certein regulatory role in morphine induced by TRPV1 (Chen et al., 2008). Studies have also shown that chronic morphine administration can activate platelet-derived growth factor receptor-β (PDGFRβ) signaling, which is a specific mediator that regulates opioid tolerance (Li[a] et al., 2020; Jia et al., 2021). Morphine treatment activates PDGFRβ, and PDGFRβ induces the activation and expression of HSP27 via the p38/MAPK and PI3K/Akt signaling pathways. PGDFRβ-mediated HSP27 activation participates in morphine tolerance (Li et al., 2020). In a model of morphine tolerance in rats, activating PDGFR in spinal microglia induced autophagy in GABAergic neurons via the p38/MAPK pathway, and autophagy inhibition attenuated the development of morphine tolerance (Jia et al., 2021). The detailed mechanisms of PDGFR and autophagy deserve further exploration.

Although inflammatory immune responses are critical contributors to the regulation of the opioid receptor, how inflammatory factors act on the opioid receptor and how they affect opioid analgesic tolerance are still not entirely clear. Because of the complexity of the pathway of opioid tolerance, it is difficult to develop a single drug to inhibit all associated signaling.

Introduction to the CB2 receptor

Neurochemical, behavioral, and electrophysiological studies have demonstrated that CB2 receptor activation can modulate inflammatory nociception (Guindon and Hohmann, 2008). Inflammation and nerve injury dramatically increase the expression of CB2 receptors in microglia and astrocytes. In glia, CB2 receptor activation serves as a negative feedback mechanism to regulate glial activity.

CB2 plays a critical role in the neuroinflammatory response by mediating central immune signaling. Proinflammatory and anti-inflammatory signals are related to microglial phenotypes. The activation of CB2 receptor regulated M1/M2 polarization by switching microglia to the M2 phenotype, which downregulated proinflammatory cytokines and upregulated anti-inflammatory cytokines (Mecha et al., 2015). Studies have shown that during the neuroinflammatory response, The activation of CB2 receptor does not simply inhibit microglial activation or switch microglia to the M2 phenotype but also inhibits the neuroinflammatory response by decreasing the M1/M2 microglial ratio (Honig et al., 2019; Guley et al., 2019; Tanaka et al., 2020). In addition, the activation of CB2 receptors has been shown to exert antinociceptive effects on animal models of pain (Reichenbach et al., 2022).

The effect of CB2 receptor agonists on morphine tolerance

The level of CB2 receptor increases after sustained morphine treatment in the SC, and CB2 receptor agonists AM1241 reduce chronic morphine-induced CB2 receptor expression (Zhang et al., 2017; Zhang et al., 2018). In paclitaxel-treated mice, a prior history of CB2 receptor agonist M1710 treatment delayed the development of antinociceptive tolerance to morphine and attenuated morphine-induced physical dependence (Li et al., 2019), which suggested that the CB2 receptor was involved in morphine tolerance (Table 1).

Increases in MOR protein and mRNA expression

CB2 receptor agonists are commonly used by researchers to attenuate morphine tolerance. Coadministration of a nonanalogetic dose of AM1241 (CB2 receptor agonist) with morphine increased MOR protein expression in the SC and DRG and MOR mRNA expression in the SC in a Walker 256 tumor-bearing rat model (Zhang et al., 2016). CB2 receptor agonists attenuated morphine tolerance by regulating the expression of MOR. However, the exact pathway linking the CB2 receptor and MOR is still unclear, and the drug metabolism that occurs in rats after the binding of CB2 receptor agonists with CB2 receptor is unknown. How CB2 receptor agonists manage the related biological transformation process and expression in the body requires subsequent drug studies. Perhaps this can be used as a starting point to identify a new therapeutic target for reducing morphine tolerance in patients. Previous studies have shown that the expression and activation of MOR in the brainstem were attenuated by SR144528 (CB2 receptor antagonist) via the CB2 receptor (Páldy et al., 2008). AM630 (CB2 receptor antagonist) inhibited MOR expression, but JWH015 (CB2 receptor agonist) markedly induced MOR expression in Jurkat T cells. These regulatory events were mediated by the signal transducer and activator of transcription 5 (STAT 5) -IL-4-STAT6 signaling pathway (Börner et al., 2006). IL-4 expression has been detected in astrocytes in multiple sclerosis lesions (Hulshof et al., 2002) and in lipopolysaccharide (LPS)-activated microglia (Park et al., 2005). IL-4 induced MOR transcription in primary neurons (Kraus et al., 2001). Based on these studies, we hypothesize that CB2 receptor agonists induce MOR expression via an IL-4-dependent pathway in morphine tolerance models. Next, IL-4 and its upstream and downstream signaling pathways were explored, which may identify the role of IL-4 in morphine tolerance in different models of pain.

However, in a C57BL6/J mouse tolerance model, the administration of O-1966 (CB2 receptor agonist) prior to each morphine injection led to significantly more pronounced tolerance than when morphine was administered prior to O-1966 during the chronic dosing regimen. O-1966 decreased morphine-induced acute antinociception and increased morphine-induced antinociceptive tolerance, which was related to O-1966 decreasing the functional activation of the MOR (Reichenbach et al., 2022).

CB2 receptor agonists inhibit the MAPK pathway and microglial activation

Microglial cells, which are a hub for information transmission, play a critical role in morphine tolerance because morphine promotes the release of inflammatory cytokines in microglia. Activation of the CB2 receptor reduced the inflammatory response in glial cells (Kong et al., 2022). Tolerance is related to a complex mechanism by which CB2 receptor regulates microglial phenotype during the neuroinflammatory response. Research has demonstrated that spinal CB2 receptor activation reduces glial activation (Romero-Sandoval et al., 2008). Coadministration of the selective CB2 receptor agonist AM1241 and morphine

Table 1
the Effect of CB 2 receptor agonist on morphine tolerance ("↑": increase, "↓": decrease).

CB2 receptor agonist	CB2 receptor antagonist	Model	Tissue or cell	Mechanism	Behavioral assay	Reference
AM1241	AM630	cancer pain-morphine tolerance rat	SC, DRG	the protein of TLR4 and p38 MAPK ↑	Thermal withdrawal latency	Ma et al., 2021
AM1241	AM630	Male Institute of Cancer Research (ICR) mice	SC	the protein of MKP-1 and MKP-3 ↓, microglial activation ↓	Hot plate test	Kong et al., 2022
AM1241	AM630	Walker 256 tumor-bearing rat	SC, DRG	MOR protein ↑	Mechanical hyperalgesia test and Thermal nociception test	Zhang et al., 2016
AM1241		Adult male Sprague–Dawley rat	microglia	microglial activation ↑	Thermal hyperlgesia, Mechanical allodynia	Tumati et al., 2012
AM1241	AM630	walker 256 tumor-bearing rat	DRG	TRPV1 protein ↓	Paw withdrawal latency	Zhang et al., 2017
AM1241	AM630	ICR	SC	IL-1β, TNF-α and IL-6 ↓	The von Frey filament test, Hot plate test	Zhang et al., 2018
O-1966	SR144528	C57BL6 mice	CHO cell	MOR internalization ↓	Hot plate withdrawal latency	Reichenbach et al., 2022
JWH133	SR144528	inflammatory pain in C57BL6/J mice		inflammatory cytokines ↓	AUC of pain behavior	Yuill et al., 2017
JWH133		Male Wistar rat		inflammatory cytokines ↓		Mlost et al., 2021
JWH 015			Jurkat T cell	the protein of MOR ↑		Börner et al., 2006
JWH 015	SR144528		human monocytic cell THP-1	inflammatory cytokines ↓		Klegeris et al., 2003
JWH 015	AM630	sciatic nerve injury-induced neuropathic pain in Male C57BL/6 J mice		cGMP–PKG–JNK signaling pathway ↓	the von Frey fifilaments and cold plate test	Hervera et al., 2012
AM1710			HEK 293 cell	p-ERK1/2 and JNK ↓	Mechanical allodynia Cold allodynia	Li et al., 2019
AM1710	AM630	in a chemotherapy-induced neuropathy model	DRG, SC	mRNA level of TNF-α ↓	Paw withdrawal threshold and Cold allodynia	Deng et al., 2015
AM1710		Adult male/female C57BI6/J mice	DRG	mRNAs of IL-1β and TNF-α ↓		Carey et al., 2023
LY2828360		Adult male/female C57BI6/J mice	DRG	mRNAs of IL-1β and TNF-α ↓	Paw withdrawal threshold and Cold allodynia	Carey et al., 2023
LY2828360		wildtype (WT) mice	Hek cell	p-ERK1/2 ↓	Paw withdrawal threshold and Cold allodynia	Lin et al., 2017

reduced morphine-mediated glial activation (Tumati et al., 2012; Zhang et al., 2018). In a chemotherapy-induced neuropathy model, AM1710 (CB2 receptor agonist) inhibited morphine tolerance by decreasing TNF-a mRNA level (Deng et al., 2015; Carey et al., 2023). In male Wistar rats, JWH133 and JWH015 (CB2 receptor agonist) inhibited inflammatory cytokines to ease morphine tolerance (Klegeris et al., 2003; Mlost et al., 2021).

MAPK activation and glial proinflammatory mediator release have been linked to morphine tolerance (Raghavendra et al., 2002; Yu et al., 2006; Mika et al., 2007). Administration of theCB2 receptor agonist JWH015 reduced phosphorylation of the p38 MAPK pathway in neuropathic pain (Paszcuk et al., 2011) and morphine-induced inflammatory responses in activated microglial cells (Merighi et al., 2012). MAPK mainly involves ERK, p38 and JNK expression. A previous study showed that AM1710 inhibited forskolin-induced cAMP production and induced enduring activation of ERK1/2 phosphorylation in HEK cells that were stably expressing mCB2 (Li et al., 2019). Another study suggested that CB2 receptor agonist JWH133 induced ERK dephosphorylation to reduce microglial accumulation in inflammation-induced secondary brain injury after germinal matrix hemorrhage (GMH) in rats (Tang et al., 2015). JWH015 (CB2 receptor agonist) could inhibit ERK1/2 phosphorylation and decrease the subsequent production of downstream factors to alleviate tolerance (Merighi et al., 2012). In addition, coadministration with JWH-133 (CB2 receptor agonist) protected against the development of morphine tolerance might by inhibiting the JNK pathway (Yuill et al., 2017).

Mitogen-activated protein kinase phosphatases 1 and 3 (MKP-1 and MKP-3) are major regulators of MKPs. MKP-3 is a selective ERK pathway inhibitor, and MKP-1 mainly downregulates p38 or JNK but can regulate ERK (Kawakami et al., 2003; Eljaschewitsch et al., 2006; Zhou et al., 2007). In morphine-tolerant mice, intrathecal injection of AM1241 increased MKP-1 and MKP-3 in the SC and reduced p-p38, p-ERK1/2 and the downstream cytokines IL-1β, IL-6 and TNF-a in microglia. In addition, the effect of AM1241 on morphine tolerance was blocked by MKP-1 and MKP-3 antagonists (Kong et al., 2022). CB2 receptor agonists can regulate the state of MAPK through enzymes, affect microglia and reduce the release of inflammatory factors to reduce morphine tolerance. CB2 receptor agonists bind to MAPK, and how to regulate the biological effects of enzymes is worthy of further study. In sciatic nerve injury-induced neuropathic pain in male C57BL/6 J mice, JWH015 inhibited the nitric oxide-cGMP-PKG-JNK signaling pathway to ease tolerance (Hervera et al., 2012). LY2828360 (CB2 receptor agonist) inhibited morphine tolerance through arrestin recruitment, CB2 receptor internalization and the inhibition of forskolin-stimulated cAMP accumulation and ERK1/2 phosphorylation (Lin et al., 2017).

TLR4 activation has been shown to enhance the production of proinflammatory cytokines, including IL-1β, IL-6 and TNF-a. In a morphine tolerance model, microglial activation is caused by a TLR4-independent mechanism (Fukagawa et al., 2013). In addition, compelling evidence has suggested that morphine induces spinal microglial activation by binding with TLR4, which activates the downstream intracellular signaling pathway and leads to the release of cytokines via the inflammatory response (Pan et al., 2016; Ma et al., 2021). Animals treated with the selectiveCB2 receptor agonist O-1966 has a significant reduction in TLR4 (Adhikary et al., 2011). A study also suggested that the CB2 receptor had a protein—protein interaction with TLR4 and inhibited TLR4 expression by directly binding with it (Wei et al., 2018). AM630 inhibited the interaction between the CB2 receptor and TLR4 in primary macrophages and attenuated the inhibition of TLR4 by CB2 in the tumor microenvironment (Wei et al., 2018). CB2 receptor agonists

might inhibit TLR4 signal activation and reduce the expression of proinflammatory cytokines to suppress morphine tolerance.

Moreover, a study showed that activation of the MAPK signaling pathway promoted TLR4 activation, and inhibiting MAPK phosphorylation reduced TLR4 protein expression (Zhang[a] et al., 2019). TLR4 also participated in p38 phosphorylation induced by morphine (Pan et al., 2016). These results suggested that TLR4 and MAPK are involved in the reduction of morphine tolerance by CB2 receptor agonists. CB2 receptor agonists inhibited microglia from releasing IL-1β, IL-6 and TNF-a, which is the last process in the MAPK-TLR4 pathway, to alleviate morphine tolerance. There are complex trafficking mechanisms and conduction networks between them, which should be explored in future studies.

LY2828360 inhibited morphine tolerance and reversed established morphine tolerance, and it was more effective in male mice than female mice in a model of anti-retroviral toxic neuropathy, but these effects were eliminated when the CB2 receptor was removed (Carey et al., 2023). This difference in the results is novel, and the mechanism of the difference in the tolerance retention effect of LY2828360 in males and females needs to be further investigated. Furthermore, in a clinical setting, the ability of drugs to reverse established tolerance may be critical. Interestingly, in the absence of LY2828360, female and male mice developed tolerance to morphine to a similar extent (Carey et al., 2023). Further experiments are necessary to examine whether differences in CB2 receptor expression in male and female mice can be detected in regions of nociceptive circuitry (such as primary afferent neurons) that control the development of morphine tolerance (Corder et al., 2017). Moreover, further experiments are needed to determine whether CB2 receptor stimulation produces more upregulation of MOR mRNA in male mice or is more effective in inhibiting the opiate-induced increase in proinflammatory cytokines in male mice than in female mice.

TRPV1 phosphorylation

TRPV1 is critical in the development of thermal and mechanical hyperalgesia in inflammatory, neuropathic and cancer pain (Zhang et al., 2012) and is involved in morphine tolerance in normal animals (Nguyen et al., 2010). A study showed that the CB2 receptor and TRPV1 are colocalized in human and rat DRG sensory neurons (Anand et al., 2008). Coadministration of a nonanalgesic dose of AM1241 and morphine attenuated TRPV1 protein expression and inhibited tolerance in a cancer pain rat model that was evaluated by measuring paw withdrawal latency to radiant heat stimulation, and the effect of AM1241 was abolished by AM630 (Zhang et al., 2017). A selective TRPV1 antagonist decreased TRPV1 immunoreactivity and attenuated morphine tolerance and dependence in normal rats (Qian et al., 2020). CB2 receptor agonist L759656 could indirectly mediate TRPV1 phosphorylation by inhibiting AC and depleting cAMP (Spahn et al., 2013), but further elucidation of the association between CB2 receptor agonists and TRPV1 in morphine tolerance is needed. Moreover, inhibiting MAPK phosphorylation reduced the increase in TRPV1 protein expression, and the increase in TRPV1 immunoreactivity contributed to morphine tolerance in a MAPK-dependent manner (Chen et al., 2008). Although it is generally accepted that cannabinoid agonists can reduce morphine tolerance in most studies, it has been shown that cannabinoid inhibitors can reduce tolerance, and some effects of CB2 receptor agonists and antagonists on morphine-induced antinociceptive tolerance remain controversial. JTE907 (CB2 receptor antagonist) decreased morphine analgesia and attenuated morphine antinociceptive tolerance in rats, as shown by the tail-flick and hot-plate tests of antinociception (Ahmet et al., 2015). Differences in experimental paradigms, biased signaling of the CB2 receptor agonist used, or the presence/absence of a pathological pain state may explain these disparities.

Conclusion

The present review summarized the mechanisms of morphine tolerance and the possible effect of CB2 receptor agonists on tolerance, as shown by a literature search. Despite this conclusion, the exact mechanism of this intercellular regulation is still not fully understood. Since the combination of CB2 receptor agonist and morphine is beneficial to morphine-induced tolerance, it provides some inspiration for further research and development of drugs to inhibit morphine tolerance. The benefits of combination therapy include reduced doses, consequent reductions in side effects, precise regulation of analgesia, and synergies that may enhance the efficacy of combination therapy. Moreover, this strategy is beneficial to patients, as it can not only reduce pain but also reduce their economic burden.

Morphine mainly exert biological effects with MOR, many previous studies have reported that MOR is located in the CNS, while CB2 receptor is widely present in the CNS, including the immune system. Both of CB2 receptor and MOR are GPCRS. The use of CB2 receptor agonist AM1241 increases the expression of MOR and reduces morphine tolerance (Zhang et al., 2016). Börner reported that CB2 receptor agonist JWH015 increased the mRNA expression of MOR dependent on the CB2 receptor (Börner et al., 2006). Morphine also induced upregulation of neuronal expressed CB2 receptor in the spinal cord (Grenier et al., 2021). CB2 receptor and MOR might coexpression in the nervous system through previous studies. The interplay between CB2 receptor agonist and morphine may be due to the colocalization of the CB2 receptor to the MOR receptor.

However, how the CB2 receptor and MOR interact remains to be studied. MAPK pathway, as a common signal pathway information exchange transfer station, transmits information upward and exerts biological effects on downward regulation. In the study of morphine tolerance, MAPK phosphorylation play an important role that promotes the release of downstream inflammatory factors, which induced morphine tolerance. CB2 receptor agonist reduced the release of proinflammatory by reducing MAPK phosphorylation, thereby reducing tolerance.In addition, a signal transducer and activator of transcription (STAT)-IL-4-STAT6 signal pathway was involved in MOR mRNA expression relulation by CB2 receptor agonist (Börner et al., 2006). Nevertheless, more experiments are needed to explore the regulation between CB2 receptor and MOR, whether there is a feedback system and whether there are other signaling pathways involved.

CB2 receptor agonists have been used in rat models of morphine tolerance, but drugs targeting MOR are still in preclinical or early clinical studies designed to evaluate their impact on opioid tolerance. We should further our understanding of the opioid lifecycle, as well as the underlying molecular mechanisms of morphine tolerance and CB2 receptor agonists, to address this matter. In addition, prior to planning clinical trials, it is critical to improve our understanding of how CB2 receptor agonists interact with opioid receptors and which CB2 receptor agonist-mediated pharmacological methods (including excitation, antagonism, and allosteric regulation), mode and route of administration, dose, and duration of treatment regulate morphine tolerance. Direct effects on one of the signaling molecules may be beneficial in reducing side effects. Moreover, multicenter randomized controlled clinical trials are needed in the future. With the development of biomarkers and genetic diagnostic tests, opioid treatment could be personalized, which may aid in addressing opioid tolerance and improving therapeutic outcomes for individual patients (Fig. 1).

Statement of all funding sources that supported the work

This research was supported by funds from the Haiyan Scientific Research Fund of Harbin Medical University Cancer Hospital (no. JJMS 2022–11).

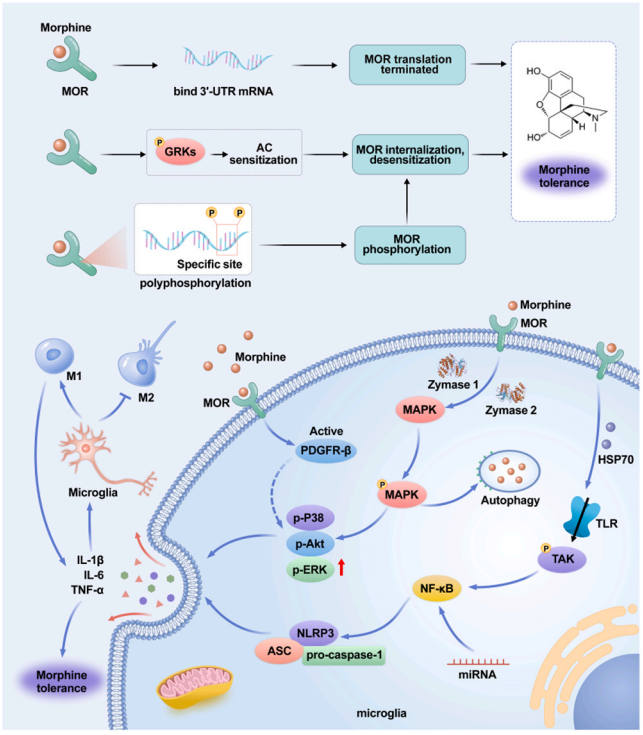

Fig. 1. The mechanisms of morphine tolerance.

Significance

In this review, we attempt to summarize the recent findings about the currently possible understanding of the role of CB2 receptor agonist on morphine analgesia and tolerance, so as to provide new targets and new treatment strategies for future research.

Conflict of interest

The authors have no conflicts of interest to declare.

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