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PHARMACOMETRICS AND QUANTITATIVE SYSTEM PHARMACOLOGY (S WOO, SECTION EDITOR)

Opioid Effects on the Central Nervous System and the Peripheral Immune System: Implications for Opioid Tolerance

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Abstract

Purpose of Review Opioids exert differential effects in the central nervous system (CNS) and the peripheral immune system. Both systems may play a role in the development of opioid tolerance. This review provides a brief overview of the opioid effects on the CNS and peripheral immune system and discusses the potential roles of the connections between the two systems in opioid tolerance.

Recent Findings Opioids induced pro-inflammatory response of the CNS immune cells through several mechanisms that involve mu-opioid receptor and Toll-like receptor 4. This neuroinflammation leads to enhanced neuron excitability and opioid tolerance and/or hyperalgesia. Opioid-exposed neuronal cells also contributed to CNS stress and inflammatory responses, further resulted in neuroinflammation. On the contrary, most studies have shown that opioids exert immunosuppressive effects in the peripheral immune system. There are, however, some evidence suggested that opioids may induce dose-, time-, and opioid agent-dependent pro-inflammatory responses. Though opioids have the opposite effects in the CNS and the peripheral immune system, newer evidence have suggested that the peripheral immune system plays a significant role in neuroinflammation and opioid tolerance.

Summary Opioid effects on the CNS and the peripheral immune system have been studied extensively; however, the integrated effects of opioids on tolerance development are yet to be explored. Further understanding of the integrated/interactive effects of opioids on peripheral immune cells and the CNS is required so that their interactions may be exploited for the identification of new therapeutics and biomarkers.

Keywords Opioids · Peripheral immune system · Central nervous system · Opioid tolerance

Introduction

Opioids have been used to treat pain for centuries. They are currently widely used as the first-line therapy for moderate to severe pain in patients with critical illness and cancer [1, 2]. They are also used as part of a multimodal approach to treat perioperative pain and may serve as adjuvant therapy for neuropathic pain, chronic pain, and postoperative pain when nonpharmacologic treatment or nonopioid analgesics are ineffective [3–5]. However, opioids are associated with several side effects that limit their use. These effects include respiratory suppression, constipation, central nervous system (CNS) depression, and the development of opioid tolerance, withdrawal, and addiction. Additionally, misuse and abuse of opioids lead to more than 46,000 overdose deaths in the USA in 2018 [6]. The number of opioid overdoses continues to rise since 2011 when the Center for Disease Control and Prevention declared that overdoses involving prescription opioids had reached epidemic levels. The early increase in overdoses had been attributed to an increase in opioid prescription for legitimate indications. Over time, however, this has led to an increase in heroin and fentanyl overdose deaths, as they are cheaper and more accessible alternatives.

Despite the misuse and abuse of opioids continuing to fuel the opioid epidemic, opioids are irreplaceable for many patients. Many clinical guidelines emphasize that prescribers must consider the risks (including misuse and abuse) versus

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benefits of initiating opioid treatment. Additionally, extensive research has been done to optimize opioid therapy and the treatment of opioid use disorder and to better understand the underlying mechanisms of opioid tolerance, withdrawal, and addiction. Opioid tolerance may be considered as the root cause of the challenges in opioid treatment and addiction. Opioid tolerance is defined as a reduction of opioid analgesic or euphoric effects after prolonged use. It often results in opioid dose escalation, which may subsequently lead to opioid physical dependence and opioid addiction [7].

The development of opioid tolerance involves two main processes: first, prolonged opioid use leads to reduced antinociceptive response through desensitization or internalization of opioid receptors and other compensatory processes; second, prolonged opioid use induces hypersensitivity of the nociceptors in the CNS through stimulations of the CNS immune cells (central immune signaling) [8]. Opioid-induced central immune signaling is a newer concept and is an emerging target to tackle problems with opioid tolerance and/or hyperalgesia [9••, 10]. Unlike their pro-inflammatory effects in the CNS, opioids mostly exert immunosuppressive effects in the peripheral immune cells [11••]. Yet newer evidence have suggested that the peripheral immune system may play an important role in opioid tolerance and neuroinflammation [12, 13]. Herein, this review provides a brief overview of the opioid effects on the CNS and peripheral immune system and discusses the potential roles of the connections between the two systems in opioid tolerance.

Pleiotropic Effects of Opioid Receptors

Opioids exert their major analgesic effects by reducing the excitability of the neurons in various regions of the brain, spinal cord, and peripheral nerve membrane [14, 15, 16••]. However, the opioid system is involved in a plethora of physiologic and pharmacologic effects in addition to analgesia [14]. Three major opioid receptor families have been identified: mu-opioid receptor (MOR), delta-opioid receptor (DOR), and kappa-opioid receptor (KOR) [14]. A nonclassical opioid receptor family, nociceptin receptor, was later added as the fourth member of the opioid receptor superfamily. These receptors are not only expressed in the nervous systems, but also distributed in other organs, such as the heart, lungs, liver, and gastrointestinal and reproductive tracts. The endogenous opioid peptides for these receptors are endorphin (MOR), enkephalin (DOR), dynorphin (KOR), and nociceptin/orphanin FQ (nociceptin receptor). These endogenous opioid peptides are generally not highly specific to their receptors, whereas exogenous opioid agonists are generally more specific for their opioid receptor targets [14]. These opioid receptors have been shown to involve in various functions including feeding/obesity, emotional response, central respiratory control, cardiovascular function, muscular function associated with Parkinson's disease, and immune modulation [14].

Opioid receptors are transmembrane G protein-coupled receptors (GPCR). The activation of these opioid receptors can lead to the dissociation of the heterotrimeric Gi/o proteins into $G\alpha i/o$ and $G\beta\gamma$ subunits, which then interact with ion channels and various intracellular proteins to exert their effects [15]. MOR is the most extensively studied opioid receptor due to its role in analgesia. Commonly used opioids for pain management including morphine, fentanyl, hydromorphone, oxycodone, and hydrocodone are substrates of MOR with varying potency. Activation of the MOR by an opioid in neurons leads to the dissociation of the $G\alpha i/o$ and $G\beta\gamma$ subunits, resulting in decreased Ca^{2+} influx, increased K^+ efflux, and the inhibition of adenylate cyclase. These events lead to the reduction of neuron excitability and analgesia [16••]. Additionally, the interactions between MOR and DOR have been shown to enhance the analgesic effect of MOR activation [14].

Opioid analgesic effects are known to diminish over time due to opioid tolerance. After the activation by opioids, MOR becomes substrates for G protein-coupled receptor kinase (GRK). The MOR/GRK complex can then recruit and bind to β-arrestin protein and result in MOR desensitization. β-arrestin can further trigger MOR internalization. Collectively, these events contribute to short-term opioid tolerance and may recover within minutes to hours if the opioid exposure is transient. In persistent opioid exposure, β-arrestin bound MOR leads to opioid receptor degradation. Interestingly, the degree of β-arrestin signaling may vary in different opioid agents due to their chemical structures. This biased signaling of GPCR has been described as "ligand bias" and may explain the various tendencies of opioid desensitization/tolerance observed in different opioid agents [17, 18]. Additionally, prolonged MOR activation also results in increased activities of adenylate cyclase, protein kinases C and A, and *N*-methyl-D-aspartate (NMDA) receptor, decreased glutamate transporters, and elevated glutamate levels. Collectively, these events further result in reduced opioid analgesic effects and increased neuron sensitivity [8, 16••].

Pro-Inflammatory Effects of Opioids in Central Immune Signaling

Other than targeting neurons, opioids have been shown to activate immune cells in the CNS (Table 1, Fig. 1). The innate immunity in the CNS mostly relies on the glial cells, namely, microglia and astrocytes. These cells can recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), express and respond to cytokines and chemokines, and disrupt the blood–brain barrier (BBB) in order to recruit peripheral immune cells [19]. Microglia also function like macrophages; they can kill pathogens by

Table 1 Opioid effects on immune cells in the central nervous system and the peripheral immune system

Study	Cell, system	Molecular target (antagonist)	Drug	Opioid dosing	Stimulation	Immune response
Central immune signaling						
[21]	Microglia, mouse & rat	MOR (naloxone), involved non-MOR	Morphine	10 mg/kg SC twice daily × 7 days	--	↑P2X4 receptor ↑BDNF ↓Neuronal cotransporter KCC2
[22]	Microglia, in vitro	MOR (naloxone)	Morphine	1 μM × 0.5–12 h	--	↑Chemotaxis ↑BDNF ↑ERK1/2 ↑PI3K/Rac
[23]	Microglia, mouse	MOR (naloxone)	Morphine	10 mg/kg IP twice daily × 5 days	--	↑Arachidonic acid ↑Microglial BK channel ↑P2X4 receptor
[24]	Microglia, in vitro	MOR (naloxone)	Morphine	1 nM × 5–60 min	LPS	↑TNF-α, IL-1β, IL-6, NO ↑PKCε/Akt, ERK1/2 ↑iNOS
[25]	Microglia, in vitro	MOR (β-FNA)	Morphine, DAMGO	Morphine: 10^{-18}–10^{-6}M × 30 min DAMGO: 10^{-12}–10^{-6}M × 30 min	--	↓Chemotaxis, C5a attraction
[26]	Microglia, in vitro	MOR (naloxone)	Morphine	10^{-8}–10^{-4}M × 5 days	--	↑Apoptosis
[27]	Astrocyte, in vitro	MOR	Oxycodone	1–20 μg/mL × 24 h	LPS	↑IκB-α ↓TNF-α, IL-1β, IL-6
[9••]	Glia, mouse & rat	TLR4 (TLR4 antagonist, knockout, etc.)	Morphine	Acute: 1–50 mg/kg IP; ~40 μg/kg IT Chronic: 0.5–1 mg/kg/h SC	--	↑Acid sphingomyelinase ↑PI3K/Akt ↑MAPK ↑NF-κB See the review article for details
Peripheral immune response						
[38]	Macrophage, in vitro & mouse	MOR (naltrexone)	Morphine, DAMGO	In vitro: 10^{-5}M In vivo: 20 mg/kg SC × 2 doses	--	↓TLR4 mRNA, expression
[39]	Macrophage	MOR	Morphine	See the review article for details	--	↓NF-κB ↓p38 MAPK ↓Chemokine receptor activity ↓Phagocytosis ↓miRNA-873
[40]	Macrophage, mouse	MOR	Morphine	20 mg/kg SC × 1 dose	LPS, IFN-γ (cytokine, NO production)	↓Phagocytosis ↓IL-1β, TNF-α, and IL-12 ↓NO, superoxide intermediates
[41]	Macrophage	MOR	Buprenorphine, morphine, oxycodone	Morphine, oxycodone: 20 mg/kg IP twice daily × 7 d Buprenorphine: 2 mg/kg IP twice daily × 7 days	SRBC Zymosan LPS	↑Humoral response (buprenorphine only) ↑NO ↑IL-6 and TNF-α
[42]	Macrophage, mouse	MOR (naltrexone)	Morphine	SC slow-release pellet 75 mg × 48 h	LPS, IFN-γ	↑IL-12, TNF-α
[43]	Macrophage, in vitro	MOR (naloxone)	Morphine	50 μM, 50 nM × 2 h	LPS	↓NF-κB, IL-6, TNF-α (μM) ↑NF-κB, IL-6, TNF-α (nM)
[44]	Dendritic cell, mouse & in vitro	MOR (naltrexone)	Morphine	Mouse: SC slow-release pellet 75 mg × 48 h In vitro: 10 nM to 1 μM × 24 h	Respiratory *Streptococcus pneumoniae* infection	↓IL-23/IL-17 ↓MyD88, IRAK1/4 ↓IRF3, ATF2

Table 1 (continued)

Study	Cell, system	Molecular target (antagonist)	Drug	Opioid dosing	Stimulation	Immune response
[45]	Dendritic cell, in vitro	MOR	Morphine	100 nM to 1 μM × 24 h	*S. pneumoniae* infection	↓IL-23 ↓TLR2, Nod2 signaling
[46]	Mast cell, in vitro	MOR (naloxone)	Morphine	0.1–1000 μM × 0.5–2 h	LPS	↓TLR signaling, TNF ↑β-arrestin-2/TRAF6 ↑IκB kinase ↓NF-κB
[47]	Mast cell, mouse	MOR	Morphine, fentanyl	Acute: Morphine: 0.1–10 mg/kg IP × 1 dose Fentanyl: 0.0001–0.1 mg/kg IP × 1 dose Chronic: Morphine: 10 mg/kg IP three times daily × 2–3 days Fentanyl: 0.1 mg/kg IP three times daily × 2–3 days	LPS	↓TNF-α (acute morphine and fentanyl) ↑TNF-α (chronic fentanyl)
[49]	Neutrophil, in vitro	MOR (naloxone)	Morphine	1 μM × 1 h	--	↓Chemotaxis toward IL8
[50]	Neutrophil, mouse	MOR	Morphine	Slow-release pellet 75 mg × 24–72 h	*S. pneumoniae* lung infection	↓Infection site neutrophil recruitment ↓TNF-α, IL-1, IL-6, MIP-2, KC, NF-κB at the infection site
[44]	Neutrophil, mouse	MOR	Morphine	SC slow-release pellet 75 mg × 48 h	Respiratory *S. pneumoniae* infection	↓IL-17/IL23 ↓Infection site neutrophil recruitment
[51]	Neutrophil, in vitro	MOR (naloxone)	Morphine	50 nM to 1 mM × 150 min	LPS	↓NO ↓NF-κB
[53]	Monocyte, human & in vitro	MOR	Heroin (abusers), morphine	Morphine: 10^{-6}–10^{-2} M × 0–24 h	--	↓miR-528-5p and miR-590-5p ↓CREB1/5, NF-κB ↓TNF-α ↑IL-10
[54]	Monocyte, human, retrospective cohort	MOR	Opioid use disorder patients	--	--	↓Monocyte proportion in WBCs
[57]	Monocyte, in vitro	MOR (CTAP)	DAMGO, morphine	DAMGO: 10^{-8}–10^{-10} M × 24–72 h Morphine: 10^{-6}–10^{-10} M × 24–72 h	--	↑CCR5, CXCR4 expression
[58]	Monocyte, in vitro	MOR (CTAP)	DAMGO	10^{-6}–10^{-12} M × 6–72 h	--	↑TGF-β1 ↑CCL5, CXCR4 expression
[56]	Monocyte, in vitro	MOR (naloxone)	Morphine, DAMGO	Morphine: 1 μM ×1 h DAMGO: 1 nM × 1 h	--	↓MIP-1α-induced chemotaxis
[49]	Monocyte, in vitro	MOR	Morphine	1 μM × 1 h	--	↓Chemotaxis toward RANTES
[59]	Monocyte, in vitro	MOR	Buprenorphine	40 nM × 1 h	CCL2	↓CCL2-mediated BBB monocyte transmigration
[60]	Monocyte, in vitro	MOR	Morphine	0.001–0.1 μM × 72 h	--	↑BBB endothelial CAMs ↑Monocyte adhesion to BMEC
[62]	NK cell, in vitro	MOR (naloxone)	Morphine, methadone, buprenorphine, loperamide, fentanyl	Morphine: 0.0867–8.67 μM Methadone: 0.162–16.20 μM Buprenorphine: 0.00213–0.21 μM Loperamide: 0.002–0.2 μM Fentanyl: 0.00297–0.29 μM	K562 leukemia-derived cells	↓NK cell cytotoxicity (except for fentanyl)

Table 1 (continued)

Study	Cell, system	Molecular target (antagonist)	Drug	Opioid dosing	Stimulation	Immune response
				All treated for 2 h		
[62]	NK cell, in vitro	MOR (naloxone), TLR4 (TAK-242)	Morphine	0.089–0.89 µM × 2 h	K562 leukemia-derived cells	↓NK cell cytotoxicity
[66]	NK cell, pig	MOR (naloxone)	Morphine	0.5–5 mg/kg IV × 1 dose	YAC-1 lymphoma cells	↑NK cell cytotoxicity (0.5 mg/kg) ↓NK cell cytotoxicity (1, 5 mg/kg)
[65]	NK cell, chronic noncancer pain patient	MOR	Opioids	--	--	↓Proportion of NK cells among lymphocytes, CD56^{bright} NK cells, IL-2-activated NK cells
[64]	NK cell, surgical patient	MOR	Morphine, oxycodone	Both: 0.1 mg/kg IV × 1 dose, then 1 mg bolus as needed	--	↓NK cell cytotoxicity-related gene expression (morphine only)
[69]	CD8 T cell, in vitro	MOR	Morphine	10 µM × 24 h	ImmunoCult™ Human CD3/CD28 T Cell Activator (T cell activation)	↑mTORC1, TNF-α/NF-κB, IL-2/IL-15 (morphine alone) ↓T cell receptor activity
[70]	CD8 T cell, chronic opioid user	MOR	Methadone	--	DAMGO, morphine (MOR activation); ImmunoCult™ Human CD3/CD28 T Cell Activator (T cell activation)	↓T effector memory RA+ cells ↓T cell receptor response ↑Methadone-exposed T cell receptor response
[71]	T cell	MOR	Morphine	See the review article for details	--	↓IL-2 ↓c-fos mRNA ↓NF-κB ↓GATA-3 activity ↓IFN-γ ↓T cell receptor activity ↑cAMP ↑Helper T cell type 2 to type 1 ratio ↑CREB/CREM/ICER
[72]	T cell, in vitro	MOR (CTAP)	Morphine	1 µM × 4 days	CD3/CD28	↓IL-2 mRNA ↓AP-1, NF-κB, and NFAT ↓TCR signaling
[73]	T cell, in vitro	MOR (CTAP)	Morphine	1 µM × 3-24 h	TNF	↓I-kB ubiquitination and degradation ↓NF-κB ↑Ubiquitin-specific protease 15
[57]	T cell, in vitro	MOR (CTAP)	DAMGO, morphine	DAMGO: 10^{-8}–10^{-10} M × 24–72 h Morphine: 10^{-6}–10^{-10} M × 24–72 h	--	↑CXCR4, CCR5 expression
[58]	T cell, in vitro	MOR (CTAP)	DAMGO	10^{-6}–10^{-12} M × 6–72 h	--	↑CXCR4 ↑TGF-β1
[75]	T cell, surgical patient	MOR	Fentanyl versus remifentanil	IV infusions during surgery	--	↓CD8 T cell (fentanyl) ↑Reduction of post-surgery plasma inflammatory cytokines (fentanyl > remifentanil)
[64]	T cell, surgical patient	MOR	Morphine, oxycodone	Both: 0.1 mg/kg IV × 1 dose, then 1 mg bolus as needed	--	↓T cell immune response-related genes (morphine only, maybe transient)
[74]		MOR	Morphine	IV, epidural, versus IT	Unspecified mitogen	↓IL-2 in CD4 T cell (all routes)

Table 1 (continued)

Study	Cell, system	Molecular target (antagonist)	Drug	Opioid dosing	Stimulation	Immune response
	T cell, postpartum women					↓IFN-γ in CD8 T cell (IV, epidural) ↓plasma IL-10, GM-CSF (epidural) ↑plasma IL-6 (IV, IT)
[76]	B cell, in vitro	MOR	Morphine	0.0001–100 μM	Anti-IgM, IL-4	↓B cell proliferation
[77]	B cell, rat	MOR	Morphine	20 mg/kg	--	↓MCH class II (may lead to ↓T cell proliferation, clonal expansion)
[78]	B cell, rat	MOR	Morphine	Acute: 10 mg/kg SC × 1 dose Chronic: 10–40 mg/kg SC twice daily × 9 days	--	↓MCH class II via HPA
[79]	Spleen, mouse	MOR	Tapentadol, morphine	Acute: Tapentadol: 20–30 mg/kg SC × 1 dose Morphine: 5–10 mg/kg SC × 1 dose Chronic: Tapentadol: 20 mg/kg SC daily × 4–7 days Morphine: 10 mg/kg SC daily × 4–7 days	Concanavalin A	↓IFN-γ, IL-2, IL-10, IL-4 (morphine only)
[80]	Spleen, rat	MOR	Heroin, heroin-conditioning	Acute: 1 mg/kg SC Conditioning: five 60-min sessions with 1 mg/kg SC heroin	LPS	↓iNOS, plasma NO (both acute and conditioned)
[81]	Spleen, mouse	MOR	Buprenorphine	Sustained-release SC injection	Ovalbumin	↑IL-10

MOR, mu-opioid receptor; *TLR*, Toll-like receptor; *SC*, subcutaneous; *β-FNA*, β-funaltrexamine; *DAMGO*, [D-Ala2, N-MePhe4, Gly-ol]-enkephalin; *IT*, intrathecal; *IV*, intravenous; *LPS*, lipopolysaccharide; *SRBC*, sheep red blood cell; *IFN*, interferon; *NK*, natural killer; *BDNF*, brain-derived neurotrophic factor; *KCC2*, potassium-chloride transporter member 5; *ERK*, extracellular signal-regulated kinase; *PI3K*, phosphoinositide 3-kinases; *TNF-α*, tumor necrosis factor; *IL*, interleukin; *NO*, nitric oxide; *PKC*, protein kinase C; *iNOS*, inducible nitric oxide synthase; *IκB-α*, inhibitory kappa B-α; *MAPK*, mitogen-activated protein kinase; *NF-κB*, nuclear factor kappa B; *miRNA*, micro-ribonucleic acid; *MyD88*, myeloid differentiation primary response 88; *IRAK*, interleukin-1 receptor-associated kinase; *IRF*, interferon regulatory transcription factor; *ATF*, activating transcription factor; *TRAF*, TNF receptor-associated factor; *MIP*, macrophage-inflammatory protein; *KC*, keratinocytes-derived chemokine; *cAMP*, cyclic adenosine monophosphate; *CREB*, cAMP-response element-binding protein; *TGF*, transforming growth factor; *RANTES*, regulated on activation, normal T cell expressed and secreted; *BBB*, blood–brain barrier; *CAM*, cell adhesion molecule; *BMEC*, brain microvessel endothelial cells; *mTORC*, mammalian target of rapamycin complex 1; *CREM*, cAMP responsive element modulator; *ICER*, inducible cAMP early repressor; *AP-1*, activating protein-1; *NFAT*, nuclear factor of activated T cells; *TCR*, T cell receptor; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *MHC*, major histocompatibility complex; *HPA*, hypothalamic–pituitary–adrenal

phagocytosis and are able to present antigens on their surface to activate adaptive immune response. Aside from glia, other CNS cells such as oligodendrocytes, endothelial cells of the BBB, and neurons can, to a lesser extent, contribute to immune signaling by the release of cytokines or chemokines and recruitment of peripheral immune cells [9••].

Like neurons, glial cells also express opioid receptors including MOR and KOR [14]. Although several animal studies have shown the correlation between opioid treatment and increased activity of microglia, the mechanism of such opioid effects is largely unknown [20]. Activation of MOR in spinal cord microglia appeared to increase the expression of purinergic P2X4 receptors, which increase the release of brain-derived neurotrophic factor (BDNF) from microglia and lead to the disinhibition of gamma-aminobutyric acid (GABA)-ergic neurons [21]. The induction of BDNF was found to be mediated by an extracellular regulated kinase (ERK) 1/2, a member of the mitogen-activated protein kinase (MAPK) superfamily [21, 22]. The disinhibition of GABAergic neurons prevents them from exerting their inhibitory effect and results in increased neuron activation (opioid-induced hyperalgesia). MOR activation in microglia can also increase arachidonic acid production, which may lead to microglial stimulation by activating their large-conductance calcium-activated potassium channels [23]. Additionally, morphine was found to induce chemotaxis of microglia through MOR, Gαi/o subunit, phosphoinositide 3-kinase (PI3K), and Rac pathways [22]. Increased activation and chemotaxis of microglia further contribute to neuroinflammation and opioid tolerance. Morphine, through MOR, has also been shown to enhance microglia responses to lipopolysaccharide (LPS), an endotoxin derived from Gram-negative bacteria [24]. LPS-induced production of inflammatory cytokines, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and nitric oxide (NO) was more pronounced in the presence of morphine. The mechanism of morphine-induced enhanced LPS response appeared to involve the activation of the PKCε and Akt pathways and inducible NO synthase. They reported that morphine alone did not enhance such pro-inflammatory responses in microglia. Though most studies have shown that MOR activation is stimulatory in glial cells, the opposite effects of morphine, including the inhibition of microglia response to a variety of stimuli and the induction of microglial apoptosis, have been reported by others [25, 26]. Additionally, oxycodone appeared to reduce the LPS-induced inflammatory response in rat hippocampal astrocytes. The mechanism was found to involve an increase in inhibitor kappa B-α (IκB-α), which inhibits the activation of nuclear factor kappa B (NF-κB) and reduces the production of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 [27].

Interestingly, glial cells also recognize opioids through a different receptor, Toll-like receptor (TLR) 4. TLR4 is known for its ability to recognize LPS and trigger inflammatory responses. The downstream signaling pathways of TLR4 resemble the pathways activated by IL-1β, a potent pro-inflammatory cytokine. Opioid-bound TLR4/myeloid differentiation factor 2 (MD-2) complex initiates the signaling and activates MAPK and NF-κB pathways that result in inflammatory responses [9••]. Through TLR4, opioids can also activate PI3K/Akt pathway. This pathway activation has been linked to neuroinflammation and neurodegenerative diseases [28]. Additionally, the nucleotide-binding domain leucine-rich repeat-containing receptors (NLRs), especially the NLR family pyrin domain containing 3 (NLRP3), in the cytoplasm of the glial cells may be important for the opioid-induced immune signaling [29•]. In general, activation of NLRP3 initiates the formation of the NLRP3 inflammasome, which in turn convert immature pro-inflammatory cytokines, such as IL-1β and IL-18, to their mature forms [30]. Collectively, TLR4 activation by opioids causes the release of pro-inflammatory cytokines from the glial cells and results in increased sensitization of neurons and hyperalgesia.

Aside from CNS immune cells, spinal neurons may also contribute to morphine-induced central immune signaling [29•]. Morphine has been shown to increase the release of DAMPs, high mobility group box 1 (HGMB1), from the spinal neurons [31, 32]. The induction of HGMB1 appeared to be mediated by TLR4 and the purinergic receptor P2X7R, but not MOR. HGMB1 is typically released from damaged or dead cells or secreted by immune cells after they are stimulated with LPS, TNF-α, or IL-1β. HGMB1 is an endogenous agonist of several receptors, including TLR4. HGMB1–TLR4 signaling has been shown to activate NF-κB and increase the production of TNF-α, IL-1β, and IL-6 in macrophages, monocytes, and glial cells. As a result, it is believed that HGMB1 may contribute to the vicious cycle that causes long-lasting opioid-induced hyperalgesia. Additionally, activation of chemokine receptors in the CNS may be involved in opioid tolerance. Chemokine receptor activation was found to cross-desensitize MOR [9••, 33•]. In summary, most studies have shown that opioids induced signaling of the CNS immune cells through several mechanisms involving MOR and TLR4. Opioid-exposed neuronal cells could also contribute to CNS inflammatory responses and further worsen opioid tolerance and/or hyperalgesia by enhancing neuron excitability.

Immunomodulatory Effects of Opioids in Peripheral Immune Cells

Unlike most studies that showed opioid pro-inflammatory effects in the CNS, opioids appear to exert immunosuppressive effects in peripheral immune cells (Table 1, Fig. 1). The primary function of the immune system is to defend the body from the invasion of other organisms. It was a surprise when opioid receptors were first discovered on immune cells. The

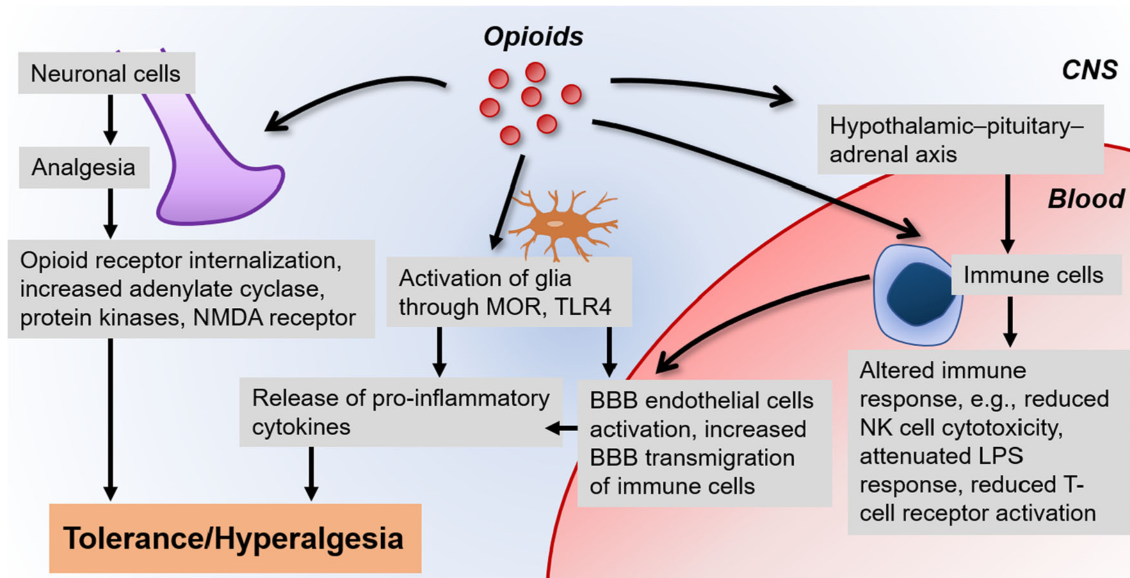

Fig. 1 An overview of various opioid effects on neurons, glial cells, and peripheral immune cells. CNS, central nervous system; MOR, mu-opioid receptor; TLR4, Toll-like receptor 4; NMDA, *N*-methyl-D-aspartate; BBB, blood–brain barrier; NK, natural killer; LPS, lipopolysaccharide

earliest report of immunomodulatory effects of opioids was in 1979 when Wybran and colleagues [34] observed that morphine inhibited the rosetting of human peripheral T cells with sheep red blood cells (SRBC). Rosetting of T cells with SRBC is the result of binding of a T cell surface protein to an SRBC surface adhesion molecule and is a method used to isolate T cells from other mononuclear cells. This phenomenon was reversed by pretreatment with MOR antagonist, naloxone [34]. This discovery unearthed the link between opioids and the immune system, followed by a large body of literature examining the effects of opioids on peripheral immune cells [11••]. The link between opioid use and the immune system becomes a hot topic in the 1980s during the acquired immunodeficiency syndrome (AIDS) epidemic. Because a portion of the AIDS patients were opioid users, it prompted investigations on the impact of opioids on the immune system [11••]. More recently, increasing investigations have focused on the impact of opioids on immune function post-surgery and in cancer patients [35, 36].

Innate Immunity

Innate immune responses involve proteins and immune cells that recognize certain features of pathogens that are not specific to a particular pathogen [37]. The activation of innate immune system results in inflammatory responses and phagocytosis. These responses typically eliminate pathogens before they cause disease symptoms. The members of innate immunity include localized immune cells such as macrophages, dendritic cells, and mast cells, and circulating immune cells such as neutrophils, monocytes, and natural killer (NK) cells. The level of understanding of the opioid effects on different immune cells is vastly different. In macrophages, the immunosuppressive effects of morphine appeared to involve MOR activation, which results in reduced TLR4 mRNA and protein expression [38]. This cross-desensitization of TLR4 further suppresses the NF-κB and p38 MAPK pathways [39]. Phenotypically, opioid-exposed macrophages have reduced ability to eliminate bacteria, including weakened phagocytosis, decreased production of inflammatory cytokines, such as IL-1β, TNF-α, and IL-12, and reduced releasing of NO and superoxide intermediates that promote killing of bacteria [39, 40].

On the contrary, Filipczak-Bryniarska and colleagues [41] found that opioids have pro-inflammatory effects on macrophages. Buprenorphine but not morphine appeared to increase the macrophage-induced humoral immune response, which was measured by the number of antibody-producing B cells after exposure to SRBC. Both morphine and buprenorphine increased the production of NO from zymosan-activated macrophages and induced the release of proinflammatory cytokines, IL-6 and TNF-α, in the LPS-stimulated macrophages. Similarly, Peng and colleagues [42] also reported an increase in pro-inflammatory cytokines IL-12 and TNF-α after the treatment of morphine in LPS-stimulated macrophages. Both studies utilized prolonged treatment of opioids (daily opioid for 7 days in the former study [41] and morphine pellet implantation for continuous release for 48 h for the latter [42]), while other previous studies examined the acute effect of opioids. Interestingly, Roy and colleagues [43] reported that morphine exerts a dose-dependent impact on LPS-stimulated macrophages, where higher concentrations (micromolar) inhibit IL-6 and TNF-α and lower concentrations (nanomolar) upregulate their expression. The exact mechanism of such opposite effects is not known, but the effects are correlated with the

level of NF-κB activation. Both time- and dose-dependent effects of the opioid on macrophages warrant further investigations.

There is a paucity of studies on opioid effects on dendritic and mast cells. Dendritic cells reside in body tissues. They have the properties of macrophages but also distinctively served as antigen-presenting cells that activate adaptive immune responses after traveling into the lymphatic system. Morphine appeared to inhibit the dendritic cell production of IL-23, an initiator of the adaptive immunity, through myeloid differentiation primary response 88 (MyD88) and IL-1 receptor-associated kinase 1 and 4 (IRAK1/4)-dependent TLR2 and Nod2 signaling pathways. These pathways are involved in the regulation of interferon regulatory transcription factor 3 (IRF3) and the activation of transcription factor 2 (ATF2) and NF-κB [44, 45]. Like NF-κB, IRF3 and ATF2 regulate the expression of cytokines.

Mast cells reside in connective tissues. Degranulation of the activated mast cells releases histamine and other inflammatory mediators to exert their immune response. The acute activation of MOR by morphine inhibits the LPS-induced TLR signaling and reduces the release of TNF secretion of mast cells [46, 47]. The underlying mechanism of the opioid immunosuppressive effect may involve the negative crosstalk between MOR and TLR4 pathways that induces the formation of β-arrestin-2/TNF receptor-associated factor 6 (TRAF6) complex [46]. This complex in turn reduced the NF-κB activity. Interestingly, repeated administration of fentanyl for 3 days showed an increase in TNF-α in LPS-stimulated mast cells [47]. Additionally, morphine has also been shown to exert positive crosstalk between MOR and TLR2/4 in gut epithelial cells, resulting in a disruption in gut epithelial tight junction and an increase in gut permeability [48]. This crosstalk appeared to require functional mast cells. As they appeared, opioid effects on mast cells depend on the opioid type, exposure time, and cell functions.

Like macrophages, neutrophils are also phagocytic cells. However, neutrophils circulate in the blood and are recruited to the local sites when summoned. Localization and penetration of neutrophils typically require the interaction between the surface adhesion molecules on neutrophils and the complementing adhesion molecules on infection site vascular endothelial cells. The migration process is facilitated by chemokines and cytokines, which increase cell–cell interaction and promote extravasation. Morphine was found to inhibit neutrophil migration to the infection sites and reduce the neutrophil bactericidal function by decreasing the production of superoxide [43]. The migration impairment appeared to involve the reduced response of the neutrophils to chemokine IL-8, reduced infection site production of chemokines (CXCL1/IL-8/KC and CXCL2/MIP-2) and cytokines (TNF-α, IL-1, IL-6, and IL-17/IL23), and LPS-induced NO production [44, 49–51].

Monocytes circulate in the blood and have the potential to penetrate tissues and differentiate into dendritic cells and macrophages [52]. The functions of monocytes in immune response include phagocytosis, antigen presentation, T cell stimulation, production of reactive oxygen species, and cytokines secretion. Long and colleagues [53] found that morphine and heroin suppressed two microRNAs (miRNA), miR-528-5p and miR-590-5p, in human monocytes. miRNAs are noncoding RNA molecules that regulate post-transcriptional gene expression. They reported that the suppression of miR-528-5p and miR-590-5p correlated with increased cAMP-response element-binding protein 1 and 5 (CREB1/CREB5), which in turn reduced the activity of NF-κB. Additionally, a lower percentage of monocytes in white blood cells (WBCs) was found in patients with opioid use disorder compared with healthy individuals [54].

Like neutrophils, the migration of monocytes also requires adhesive interactions with the endothelial cells [55]. The process is also facilitated by chemokines. The impact of opioids on chemokines was summarized in a recent publication [33•]. One-hour MOR agonist exposure has also been shown to reduce chemotaxis of monocytes through macrophage inflammatory protein-1α [56]. However, longer exposure of MOR agonists appeared to increase chemokine receptors CCR5 and CXCR4 on monocytes [57, 58]. Furthermore, some studies have investigated the interaction of monocytes and BBB endothelial cells. Using brain microvascular endothelial cell (BMEC), Jaureguiberry-Bravo and colleagues [59] found that buprenorphine inhibited the chemokine CCL2-mediated BBB monocyte transmigration. On the contrary, Strazza and colleagues found that morphine causes an increase in adhesion molecules on the BMEC surface. Additionally, prolonged exposure (72 h) of morphine increased monocyte transmigration across BBB [60]. The authors speculated that the enhanced migration of monocytes may involve TLR4, which has been shown to be present on brain endothelial cells and can be activated by morphine. Collectively, opioid effects on monocytes may be affected by the opioid type and exposure time.

NK cells are found in circulating blood and in the tissues. The circulating NK cells also respond to chemokines and migrate to inflamed peripheral tissues [61]. NK cells kill target cells by either releasing cytotoxic molecules that induce apoptosis or secreting cytokines (especially IFN-γ) that further enhance the immune response by other immune cells. Several studies suggest that morphine indirectly suppresses NK cell cytotoxicity through the sympathetic nervous system and hypothalamic–pituitary–adrenal axis [11••]. Recent studies by Maher and colleagues [62] showed that different opioids including morphine, methadone, buprenorphine, and loperamide (but not fentanyl) in clinically relevant concentrations reduced NK cell cytotoxicity, which was measured by an in vitro apoptosis assay against leukemic K562 cells. The morphine-induced reduction in NK cell cytotoxicity was

found to be mediated by both MOR and TLR4, where the observation was reversed by both MOR and TLR4 antagonists but not by either antagonist alone [63]. Additionally, Wodehouse and colleagues [64] reported that gene expressions related to NK cell function were downregulated by morphine at 6 h after surgery, but the impairment was not seen in patients who received oxycodone or did not receive any opioid. Others have reported a lower proportion of NK cells among lymphocytes, a lower number of a subset of NK cells (CD56^{bright}), and a lower proportion of IL-2-activated NK cells among patients who received long-term opioid therapy [65]. Interestingly, like previously reported, a pig study showed that higher doses (1 and 5 mg/kg) suppressed NK cell cytotoxicity; however, low dose morphine (0.5 mg/kg) increased NK cell cytotoxicity by 4-fold compared with normal saline treatment [66]. As discussed, opioids appear to suppress NK cell cytotoxicity; however, the immunosuppressive effect may be dose-dependent. Overall, opioids suppress innate immune responses. Some studies, however, observed time- and dose-dependent immunomodulatory effects.

Adaptive Immunity

Adaptive immune responses are usually initiated after the activation of the innate immune system [67]. In the innate immune response, immune cells contain an array of fixed surface receptors and soluble effectors that recognize and kill the pathogens. In adaptive immunity, only a very small portion of lymphocytes recognize the pathogens or antigen-presenting cells (APCs, e.g., dendritic cells) that carry peptide fragments of the pathogen. Subsequently, these lymphocytes can activate the adaptive immune response and result in their proliferation and differentiation [67]. The APCs such as dendritic cells may present the peptide antigen that is bound to either surface protein major histocompatibility complex (MHC) class I or class II. MHC class I is recognized by cytotoxic T cells (CD8 T cells), and their interaction leads to T cell activation. These cytotoxic T cells can kill infected host cells that present MHC class I/antigen complex, utilizing toxic substances such as cytotoxins and cytokines [68], whereas MHC class II activates helper T cells (CD4 T cells). Activated helper T cells defend against pathogens that are extracellular of the host cells by enhancing the phagocytotic ability of phagocytes and activating pathogen-exposed B cells to aid their differentiation into plasma cells. Plasma cells can further produce antibodies to aid phagocytosis of the phagocytes or to neutralize bacterial toxins [67]. Additionally, the initial selection and differentiation of T and B cells also produce memory cells that are long-lived. These memory cells are responsible for the secondary adaptive immune responses, in which they are activated quickly by the returning pathogens [67].

Mazahery and colleagues [69] conducted transcriptomic analysis on CD8 T cells to examine the impact of MOR agonists. MOR agonists appeared to increase CD8 T cell immune regulatory pathways including mammalian target of rapamycin complex 1 (mTORC1), TNF-α/NF-κB, and IL-2/IL-15 signaling pathways but downregulate IFN-α and IFN-γ. However, the cross-linking (activation) of T cell receptors among the opioid-exposed CD8 T cells resulted in the inhibition of several immune regulatory pathways. The authors suggested that the crosstalk of MOR and T cell receptors was regulated by lipid metabolism. It was found that opioid exposure upregulated lipid metabolism and cholesterol homeostasis in CD8 T cells. The regulation of cholesterol metabolism may then modulate signal transduction of lipid raft-associated receptors like T cell receptors. From the same laboratory, Mazahery and colleagues [70] found that chronic methadone users have a lower number of T effector memory RA+ cells, which is a subset of CD8 T cells that has higher cytotoxicity. They also showed that T cells from methadone users have reduced response to T cell receptor activation when compared with controls. These findings were consistent with their previous report, in which opioid-exposed CD8 T cells had reduced immune response. On the contrary, methadone users have increased T cell inflammatory response (upregulated CD45RA, CD69, and CD25) after being further exposed to opioids without T cell receptor stimulation [70].

Earlier opioid studies on T cells mostly showed immunosuppressive effects [39, 71]. IL-2 is a cytokine that binds to its receptor on activated T cells to cause T cell proliferation and expansion. IL-2 was found to be downregulated by morphine. The IL-2 suppression appeared to be mediated by inhibition of c-fos mRNA and modulation of several transcription factors including CREB and NF-κB. Börner and colleagues utilized primary human T cells from healthy volunteer peripheral blood mononuclear cells and human T cell line Jurkat to examine the immunosuppressive effect of morphine. They found that morphine inhibited the transcription of IL-2 and the activation of the transcription factors activating protein-1 (AP-1), nuclear factor of activated T cells (NFAT), and NF-κB. IL-2 and the transcription factors are important for the activation of T cells and the regulation of immune responses. They also found that the activation of MOR by morphine resulted in the activation of the cAMP/PKA pathway that led to increased activity of C-terminal Src kinase and enhanced the inhibitory effect of leukocyte-specific protein tyrosine kinase (Lck), resulting in the inhibition of TCR signaling [72]. Later, the same group examined the mechanism of inhibition of NF-κB by morphine in T cells. They found that morphine inhibited the TNF-stimulated ubiquitination and degradation of I-κB, which resulted in reduced NF-κB signaling. Additionally, the deubiquitinating enzyme ubiquitin-specific protease 15 was induced by morphine, resulting in the stabilization of I-κB and the inhibition of NF-κB [73]. Additionally, morphine could affect the balance of type 1 and type 2 helper T cells by shifting towards type 2 [71]. Increased type 2 helper T cells may result in impaired immune response. On the contrary, chemokine receptors CXCR4 and CCR5 on T cells may be

increased indirectly by opioid-induced cytokines TGF-β and TNF-α, respectively [33•, 57, 58].

Using gene expression profiling, Wodehouse and colleagues found that morphine downregulated multiple immune response-related genes in T cells 2 h after surgery, but the suppressive effects were not seen in oxycodone or nonopioid controls. Interestingly, the gene expression analysis at 6 h showed an increase in the proliferation of helper T cells, suggesting that the immunosuppressive effect of morphine may be transient or that the morphine affected cytotoxic and helper T cells differently [64]. Chen and colleagues [74] examined mitogen-activated cytokine production in peripheral blood and plasma before and after morphine administration by intravenous, epidural, or spinal route postpartum in women. They found a lower IL-2 expression in CD4 cells and lower IFN-γ in CD8 cells. Plasma IL-6 was increased, and IL-10 and GM-CSF were reduced. Lu and colleagues [75] examined the impact of fentanyl versus remifentanil on T cell subtypes and inflammatory cytokines in patients who underwent radical surgery for cervical cancer and found that remifentanil has a smaller impact on immune response compared with fentanyl.

There are fewer studies on opioid effects on B cells in recent years. B cell proliferation and antibody production were generally found to be suppressed by morphine [11••, 76, 77]. Additionally, MCH class II on B cells appeared to be suppressed by morphine through the hypothalamic–pituitary–adrenal (HPA) axis, resulting in reduced helper T cell proliferation [78]. B cell function may also be modulated through the depression of macrophages and other polymorphonuclear leukocytes [71].

WBCs in the spleen are mostly made up of lymphocytes with a small amount of other immune cells. Franchi and colleagues [79] compared the effects of tapentadol and morphine on concanavalin A-stimulated splenic cytokine production in mice that underwent sciatic nerve chronic constriction injury; they found that morphine, but not tapentadol, suppressed IFN-γ, IL-2, IL-10, and IL-4. Paniccia and colleagues [80] showed that heroin use reduced the expression of splenic inducible nitric oxidase and the production of plasma NO after the rats were challenged with LPS. Using sustained-release buprenorphine, Allen and colleagues [81] reported that it had no significant immunomodulatory effect (i.e., TNF-α, IFN-γ, and antibody production) on mouse ovalbumin-stimulated splenocytes. Like in innate immunity, opioids also generally suppress adaptive immunity with some exceptions.

The Connection Between Opioid-Related Central and Peripheral Immune Responses

As reported in most studies, opioids exert immunosuppressive effects in peripheral immune cells but pro-inflammatory effects in the CNS. In peripheral immune cells, a large proportion of the studies examine the opioid effects on TLR/NF-κB and MAPK pathways using LPS, a model TLR4 agonist, and found that MOR activation attenuates LPS-induced TLR4 signaling. The direct effect of opioids on TLR4 signaling of the peripheral immune cells in the absence of TLR4 stimulation is not as well studied. In contrast, opioids activate both MOR and TLR4 on glial cells and cause neuroinflammation in the CNS. MOR activation may also enhance the microglial LPS-induced TLR4 signaling and immune response. These opposite effects of the opioid on peripheral immune cells versus in the CNS are not well understood. It has been argued that the proinflammatory effects of opioids in the CNS may be a result of leaked LPS that activate the TLR4, as LPS is ubiquitous and difficult to remove [11••]. However, the contrasting opioid actions may also be the results of cell type-specific opioid responses.

As they appeared, the immunosuppressive effects of opioids in the peripheral immune cells are not congruent with the central immune signaling, which contributes to opioid tolerance and hyperalgesia. However, opioid-related central and peripheral immune responses may cause neuroinflammation in other ways. BBB endothelial cells may be activated by opioid-induced central immune signaling. This action may result in leaky tight junctions that expose the CNS to peripheral immune cells. As discussed earlier, morphine may increase monocyte BBB transmigration by upregulating the adhesion molecules on BBB endothelial cells. Infiltration of peripheral immune cells has been implicated in CNS diseases such as Alzheimer's disease (AD) [9••]. Like opioid tolerance, microglia-mediated neuroinflammation plays a crucial role in AD. Interestingly, systemic inflammation is associated with worse neurological outcomes in AD. As such, the interaction between microglia and peripheral immune cells has been extensively studied and presents promising lines of investigation [13].

Additionally, the communication between peripheral and central inflammatory responses through endogenous IL-1β-containing microparticles may play an essential role in opioid tolerance. In a recent study, Ruhela and colleagues [12] investigated the roles of endogenous microparticles in morphine tolerance in mice. A portion of IL-1β secreted from cells into the extracellular environment is protected in exosomes or microparticles and released from the vesicles when they are in contact with IL-1 receptor-expressing cells [82]. The investigators found a significant increase in blood-borne microparticles that carry IL-1β released by both peripheral cells (i.e., neutrophils, all leukocytes, platelets, and endothelium) and CNS cells (i.e., microglia, astrocytes, and neurons) among morphine tolerant mice. Furthermore, the administration of anakinra (an IL-1β antagonist), polyethylene glycol Telomer B (a peripherally restricted surfactant that lyses microparticles), or methylnaltrexone (a peripherally restricted MOR and TLR4 antagonist) prevented morphine tolerance, supporting the important roles of IL-1β and blood-borne microparticles in tolerance development. Surprisingly, these

peripherally restricted agents, polyethylene glycol Telomer B and methylnaltrexone, also inhibited the microparticles originated from microglia in cervical lymph nodes, to which the cerebrospinal and CNS interstitial fluid drain. These findings suggest that opioid tolerance through central immune signaling may be initiated in the peripheral immune system.

Additionally, it was found that neutropenia prevented morphine tolerance in mice [12]. Neutropenic mice also failed to increase the microparticles originated from the endothelium, suggesting that neutrophils may be responsible for the endothelial activation in tolerant mice. This may provide further evidence of the association between opioid-induced transmigration of peripheral immune cells into the CNS and opioid tolerance. These investigators also observed the elevation of microparticles in patients with opioid use disorder [12]. On the other hand, IL-1β in the basolateral amygdala and dorsal hippocampus was found to be responsible for heroin-conditioned immunosuppression, which is measured by changes in splenic inducible NO synthase and plasma nitrate/nitrite levels in response to LPS challenge [83, 84]. Collectively, these findings paint a complicated picture of opioid tolerance and its relationship with the peripheral immune system and the CNS.

Quantitative Systems Pharmacology: a Potential Approach for Managing Pain and Opioids

Pain and opioid management involve complex processes that are influenced by the pharmacokinetics/pharmacodynamics of analgesics, the development of opioid tolerance and addiction, disease progression/recovery, and patient behavioral and psychosocial factors. In this review, various opioids effects on different systems, including the nervous systems, peripheral immune system, and the immune cells in the CNS, were discussed (Fig. 1). However, little is known about how these effects may interact with each other and contribute to opioid tolerance. Also, there are many other factors that may influence opioid therapy. For example, the release of anti-opioid peptides versus immune cell-derived opioid peptides can further contribute to the variability of pain levels [85]. Morphine appeared to increase the release of cholecystokinin in the spinal cord. Cholecystokinin acts as an anti-opioid peptide and reverses the effect of morphine. On the contrary, the activation of leukocyte opioid receptors was found to increase the release of beta-endorphin, met-enkephalin, and dynorphin. These opioid peptides can then suppress pain transmission.

Interestingly, chronic opioid use appeared to induce anti-opioid immunoglobulin M (IgM) antibodies, which affect the opioid dose requirement [86]. Additionally, many cytokines play a role in critically ill patients in the response to injury and infection [87]. Different cytokine levels among patients could result in significantly different opioid needs. In fact, serum cytokines have also been shown to correlate with pain severity in patients with cancer and inflammatory disease [88]. The accumulation of endogenous factors such as pro-inflammatory cytokines in injured tissues could also result in the activation of surrounding nociceptors, which lead to increased pain sensitivity [89].

To understand the collective impact of various factors on opioid use, an integrated approach such as quantitative systems pharmacology (QSP) is required. A QSP approach quantitatively analyzes the dynamic interactions between drugs and a biological system, providing a better understanding of the behavior of the system rather than the individual components. This approach aims to integrate the biological components horizontally (e.g., opioid-induced peripheral versus central immune response) and vertically (e.g., opioid effects on cells versus organs versus patients). A better understanding of how various components within the biological system interact with each other can further help identify biomarkers that predict disease severity and treatment outcome. Goulooze and colleagues [90] published an overview of how a QSP approach may integrate various components (e.g., pain assessment, psychosocial factors, neurophysiological response, and genomics) that contribute to patient-to-patient variation in pain and treatment response and help personalize pain pharmacotherapy. This approach may be further extended to integrate several components that contribute to the development of opioid tolerance.

Conclusions

Opioid effects on the CNS and the peripheral immune system have been studied extensively; however, the integrated effects of opioids on tolerance development are yet to be explored. Opioid induces central immune signaling, which contributes to opioid tolerance by enhancing neuron excitability. On the contrary, opioids exert immunosuppressive effects in the peripheral immune cells. Increasing evidence have shown that the peripheral immune system plays a significant role in CNS diseases and neuroinflammation. Further understanding of the integrated/interactive effects of opioids on peripheral immune cells and in the CNS is required so that their interactions may be exploited for the identification of new therapeutics and biomarkers. These integrated effects and several other factors that contribute to pain and opioid tolerance may also be used to support a QSP model, which aims to help personalize opioid therapy and assist the development of different strategies to avoid opioid tolerance and addiction.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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