Opioids and the immune system - friend or foe

Lisanne Mirja Plein, Heike L. Rittner

Dept. Anaesthesiology and Critical Care, University Hospital Wuerzburg

Corresponding author:
Heike Rittner, Dept Anaesthesiology and Critical Care, University Hospital Wuerzburg, Oberdürrbacher Strasse 6, D-97072 Wuerzburg, Germany,
Phone: +49-931-20130254, Fax: +49-931-20130023, Email: rittner_h@ukw.de

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Abstract

Systemically administered opioids are among the most powerful analgesics for treating severe pain. Several negative side-effects (respiratory depression, addiction, nausea, confusion) and the risk of opioid-induced hyperalgesia accompany opioid administration. One other side effect is the potential of opioids to suppress the immune response and thereby to increase the vulnerability for infections. Several studies have investigated the link between opioids and immunosuppression *in vitro*, *in vivo* as well as in patients with divergent results: Exogenous opioids such as morphine and fentanyl can impair macrophage and natural killer cell as well as T cell function and weaken the gut barrier *in vitro* and in animal studies. In epidemiological studies, high doses and the initiation of opioid therapy for non-malignant pain correlate with a higher risk of infectious diseases such as pneumonia. In addition, immune cells including neutrophils, macrophages and T cells can secrete endogenous opioid peptides relieving inflammatory and neuropathic pain via binding to peripheral opioid receptors. Apart from cytokines, hormones and bacterial products, the release of opioid peptides is stimulated by application of exogenous opioids. In summary, there is a reciprocal interaction between the immune system and endogenous as well as exogenous opioids. In addition to the existing epidemiological studies, controlled clinical studies are necessary in the future to delineate the role of the opioid-immune system interaction in patients and estimate the clinical relevance of it.

Targets	
Catalytic receptors	**GPCRs**
MHC II	MOP receptor
TLR	KOP receptor
Enzymes	DOP receptor
PI3-K	**Other protein targets**
p38 MAPK	TNF-α

Ligands	
FMLP	DAMGO
IL-2	DPDPE
IL-23	U50
morphine	methylnaltrexone
fentanyl	met-enkephalin
oxycodone	β-endorphin
hydromorphone	dynorphin A
codeine	
sufentanil	

These Tables of Links list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016), and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e]Alexander et al., 2015a,b,c,d,e).*

Abbreviations:

APC:	antigen-presenting cell
CREB1/CREB5	cAMP response element-binding protein 1/ 5
CD4+/CD8+ Cells:	cluster of differentiation 4 positive cells/ cluster of differentiation 8 positive cells
CFA:	complete Freud´s Adjuvant
CTX:	cyclophosphamide
GATA3:	trans-acting T-cell-specific transcription factor GATA-3
MHC II:	major histocompatibility complex class II
MiRNA	micro Ribonucleic acid
MOP receptor:	mu opioid receptor
LPS	Lipopolysaccharides
OVACD4+ cells:	ovalbumin cluster of differentiation 4 positive cells
TH1/ TH2:	T-helper cell type 1/ 2
TLR2/4/9:	toll-like receptor 2/ 4/ 9
FMLP	N-formyl-methionyl-leucyl-phenylalanine
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase

Introduction

In this review, we will discuss the influence of opioids on the innate and adaptive immune system. We will delineate immunosuppressive effects depending on the type of opioid in *in vitro* and *in vivo* as well as clinical studies. The second part of this review focusses on analgesic properties of endogenous opioid peptides produced in immune cells. Thirdly, we will discuss recent findings on the interaction of endogenous and exogenous opioids for peripheral analgesia.

A connection between prolonged opioid administration and increased susceptibility to bacterial infection has been suspected since the late 1800´s (Vallejo, de Leon-Casasola & Benyamin, 2004). Systemic morphine treatment lowered the resistance of guinea pigs to various bacterial agents and also abolished the local recruitment of macrophages to the area of infection. Since then, various *in vitro* and *in vivo* studies have aimed to elucidate the exact relationship between opioids and increased susceptibility to infection (Bhaskaran et al., 2001; Casellas, Guardiola & Renaud, 1991; Lugo-Chinchilla, Baez, Velez, Ildefonso & Renaud, 2006; Menzebach, Hirsch, Nost, Mogk, Hempelmann & Welters, 2004; Wang et al., 2005). Despite these studies there is still some controversy remaining. For example, many studies focus solely on morphine without broadening their investigation to other opioids. Furthermore, the immunosuppressive effect of morphine seems to be dependent on dosage and number of administrations (Borman, Vick, Dattilo, Tarpley & Mitchell, 2009; Saurer, Ijames & Lysle, 2006) as well as the mouse strain used (Plytycz & Natorska, 2002).

Effects of morphine on the immune system were investigated in patients with prolonged opioid use or people with a history of opioid abuse (Roy et al., 2011). The latter patients are far more susceptible to various infectious diseases of the skin, soft tissue, bones and joint as well as pulmonary and sexually transmitted diseases. The prevalence of HIV, hepatitis B and C tetanus and malaria is also higher in these patients. Therefore, these drug abusers might not be a suitable group to evaluate the immunosuppressive potential of opioids *per se* because of too many other contributing factors. In addition, the majority of prescriptions are given to patients with chronic cancer and non-cancer pain Therefore, studies in cohorts of patients with non-malignant pain would focus on a large group of patients with long-term opioid intake (Werber, Marschall, L'Hoest, Hauser, Moradi & Schiltenwolf, 2015).

Impact of exogenous opioids on the innate and adaptive immune system

Immunity of an organism is defined as the resistance to infectious diseases (Abbas, Lichtman & Pillai, 2014), which is a broad and fast response of the body to intrusion of microbes, and a later, more specialized response to individual pathogens, the adaptive immune system. Opioids modulate both branches of the immune system by binding to the mu opioid receptor (MOP receptor) and ultimately leading to an impaired ability of the host organism to clear pathogens (**Figure 1**) (Abbas, Lichtman & Pillai, 2014). Parts of the innate immune system are epithelial barriers, phagocytes, dendritic cells and natural killer cells. The cells of the innate system recognize and respond to pathogens in a generic way, but, unlike the adaptive immune system, the system does not confer long-lasting or protective immunity to the host. The innate immune system fulfils the following functions: Recruiting immune cells to sites of infection through the production of cytokines and chemokines, activation of the complement cascade to promote clearance of antibody complexes or dead cells, as well as activation of the adaptive immune system through a process known as antigen presentation. Furthermore, it acts as a physical and chemical barrier to infectious agents (Abbas, Lichtman & Pillai, 2014; Roy et al., 2011).

The adaptive or acquired immune system is a more differentiated answer to pathogens. It involves T- and B-lymphocytes and their products such as antibodies. Adaptive immunity creates immunological memory after an initial response to a specific pathogen, and leads to an enhanced response to subsequent encounters with that pathogen. Like the innate system, the adaptive system includes both humoral immunity components and cell-mediated immunity components (Abbas, Lichtman & Pillai, 2014).

Impact on the innate immune system

Innate immunity consists of macrophages, neutrophils, mast cells, natural killer cells and dendritic cells. All of these are impaired by certain opioids (Roy et al., 2011). Morphine reduces the number of **macrophages** responding to an infection by firstly decreasing the proliferative capacity of macrophage progenitor cells and lymphocytes and secondly by inhibition of the recruitment of these cells into the tissue. Activation of MOP receptor triggers phosphorylation and desensitization of chemokines receptors (e.g. CCR1, CCR2, CXCR1 and CXCR2) on macrophages leading to receptor insensitivity. Additionally, chronic morphine inhibits the ability of macrophages to ingest opsonized pathogens (phagocytosis) (Ninkovic & Roy, 2013), and to kill bacteria by releasing nitric oxide and superoxide

intermediates, overall reducing the ability to fight off invading pathogens *in vitro* and *in vivo* (Bhaskaran et al., 2001; Casellas, Guardiola & Renaud, 1991; Menzebach, Hirsch, Nost, Mogk, Hempelmann & Welters, 2004; Wang et al., 2005). The effect of morphine on macrophages depends on the dosage. Lower to moderate dosages can induce impairment of phagocytosis, higher dosages will lead to morphine-induce apoptosis of macrophages via toll like receptor 9 (TLR9) and the p38 MAPK pathway. The microRNA miR-873 is also suppressed by morphine and significantly less expressed in peritoneal macrophages from mice treated with various dosages of morphine (20 mg/kg to 140 mg/kg). MicroRNAs (miRNAs) are short (20-40 base pairs) of single stranded RNA molecules, that can regulate protein expression within the cell. Macrophages transfected with miR-873 mimics, show a significant reduction in apoptosis rate when exposed to morphine. Although the mechanism is not fully understood, it is suggested that miR-873 also acts via the TLR signalling pathway (Li, Yu, Yu, Chi & Xiang, 2015). Priming macrophages with lipoteichoic acid, a bacterial product of gram-negative bacteria together with morphine results in decreased phagocytosis via TLR messaging (Ninkovic & Roy, 2013). Further effects of morphine treatment include: suppression of NFκB, reduced release of the chemokine CXCL2, (CXCR2-ligand) and NFκB-dependent gene-transcription after infection with S. pneumonia infection in mice. Consequently, patients using opioids should be more prone to infections with gram-negative bacteria. However, clinical data supporting this is lacking. A recent study has further investigated the underlying mechanism of opioid-induced immunosuppression with focus on human peripheral blood monocytes (Long, Li, Qiu, Liu, He & Peng, 2016). They could show, that two miRNAs, miR 582-5p and miR-590-5p, were decreased in monocytes from heroine abusers compared to monocytes from healthy controls. Both target cAMP response element-binding protein 1 (CREB1) and cAMP response element-binding protein 5 (CREB5) respectively. Downregulation of both miRNAs leads to a decrease in CREB1/CREB5 which in turn reduces NFκB-phosphorylation and TNF-α levels in monocytes. The study therefore underlines previous findings, stating that opioid-induced immune-suppression is dependent on the NFκB-pathway but adds miRNAs as additional factors to it. Selected opioids decrease **neutrophil** bactericidal function by inhibiting the production of superoxide (Roy et al., 2011). Similar to macrophages, the migration of the neutrophils to the area of pathogen´s invasion diminishes after morphine treatment (Sharp, Keane, Suh, Gekker, Tsukayama & Peterson, 1985; Simpkins, Alailima, Tate & Johnson, 1986). Morphine inhibits **mast cell** activation via a negative cross talk between opioid receptor and TLR4 signalling pathways (Meng et al., 2013). Additionally, morphine leads to an increase in gut barrier permeability,

allowing pathogens to cross the gut barrier more freely (Harari, Weisbrodt & Moody, 2006) (see below). Based on previous research (Granger, Zimmerman, Sekizuka & Grisham, 1988; Harari, Weisbrodt & Moody, 2000; von Ritter, Sekizuka, Grisham & Granger, 1988) they demonstrated that N-formyl-methionyl-leucyl-phenylalanine (FMLP), a chemotactic peptide similar to gram- negative bacteria, increases the permeability of the mucosal barrier of the ileum, which was lost in mast cell deficient mice. FMLP-induced permeability was accompanied by an elevated amount of histamine and serotonin in the intestinal lumen. Both of these inflammatory agents are stored in mast cells, linking this cell type to gut barrier permeability. Morphine inhibited the increase in histamine and serotonin by FMLP. Thus, while mechanistically not fully understood, the effect is dependent on the presence of functional mast cells in the animal. Suppression of the innate immune response via morphine-dependent inhibition of mast-cell activity is not solely limited to morphine (Molina-Martinez, Gonzalez-Espinosa & Cruz, 2014). When administered to male Swiss-Webster mice, fentanyl inhibits Lipopolysaccharide (LPS)-produced TNFα production in intraperitoneal mast cells proportionally to its antinociceptive effect. This effect was dependent on the presence of functional mast cells. In the case of fentanyl, repeated administration lead to loss of immunosuppressive effects and a sensitization to LPS-induced TNFα secretion. The later was characteristic solely for fentanyl. **Natural killer** cells are indirectly impaired by morphine activating opioid receptors in the central nervous system, especially MOP receptors in the periaqueductal grey (Nelson, Schneider & Lysle, 2000; Saurer, Carrigan, Ijames & Lysle, 2006; Saurer, Ijames & Lysle, 2006). **Dendritic cells** play an important role in linking the innate and adaptive immune system together. They detect, capture and present foreign antigens to T-cells (Banchereau & Steinman, 1998). Morphine treatment inhibits the presentation of the antigens to the T cells by dendrites via inhibiting IL-23 production (Wang, Ma, Charboneau, Barke & Roy, 2011).

Impact on the adaptive immune system

Similar to its impact on the innate immune system prolonged morphine treatment weakens the adaptive immune response (Roy et al., 2011), e.g. impaired T cell function, altered cytokine expression, suppressed T cell apoptosis and modified T cell differentiation as well as reduced B cell function via MOP receptor.

In professional antigen-presenting cells (APC), morphine treatment initiates down-regulation of the major histocompatibility complex class II (MHC-II) expression especially on **B cells**.

This downregulation in turn causes an attenuation of the APC´s central function: the activation of **T cells**. Additionally, lower MHC-II levels impair T cell proliferation. When administered, morphine will bind to the MOP receptor on the T cells and drive T cell towards the TH2 phenotype. MOP receptor activation will lead to superactivation of adenylyl cyclase, an increase cAMP intracellularly, an activation of p38 MAPK leading CREB phosphorylation, GATA3 activation and shift to the TH2 phenotype, a helper T cell secreting IL-4, IL-5 as well as IL-10 and being effective against helminths. This intracellular switch towards TH2 is the functional step considered to impair the immune response. However, in the light of the complexity of T cell immunology the functional consequences need to be determined.

Immunomodulative effects depend on the type of the opioid

Immunosuppressive activity depends on the type of the opioid independent of the potency or the duration of action. For example, hydromorphone is highly potent, short acting and not immunosuppressive. Morphine sulphate possesses also a high potency and a short action but is immunosuppressive. The immunosuppressive action of morphine has been examined most extensively and thereby supported by numerous studies (Ninkovic & Roy, 2013). Direct comparative studies of opioids are seldom. Nevertheless, the comparison of fentanyl, morphine and sufentanil revealed an impairment NK cell activity if given during surgery in animals and patients, however the impact of this finding is unclear (Beilin, Martin, Shavit, Gale & Liebeskind, 1989; Beilin, Shavit, Cohn & Kedar, 1992; Beilin et al., 1996). One comparative study evaluated the immunosuppressive effect of several opioids in male Swiss mice (Sacerdote, Manfredi, Mantegazza & Panerai, 1997). Morphine and oxycodone impaired splenocyte proliferation, natural killer cell activity and IL-2 production while hydromorphone and codeine treatment resulted in no significant effects. Therefore, these two opioids are considered not immunosuppressive. The reason for this diversion of immunosuppressive effects in two opioids (morphine, oxycodone) and not in others is rooted within the structural attributes of the molecule itself. Substitution of the carboxylgroup at C6, a single bond between C7 and C8 and a hydroxylgroup within the molecule lead to blockage of the immunosuppressive effect (Sacerdote, Manfredi, Mantegazza & Panerai, 1997).

Opioid-induced mucosal barrier impairment and microbe composition

Morphine can impair intestinal barrier function thereby promoting systemic infections by increasing the sensitivity of gut epithelial cells to TLR activation allowing a translocation of

gut bacteria from the lumen (Meng et al., 2013). *In vivo* as well as *in vitro* morphine impairs barrier function of gut epithelial cells due to a disrupted distribution of tight junction proteins (occluding, ZO-1) in the gut epithelial cells in mice. This disruption is mediated by activation of TLR2 and TLR4 by MOP receptor agonists as shown by a lack of effect in TLR2/4 and MOP receptor KO mice. As a result, translocation of E. coli bacteria in the mesenteric lymph node and liver tissue of mice increases. In addition, chronic morphine treatment significantly alters the gut microbial composition and induces preferential expansion of gram-positive pathogenic and reduction in bile-deconjugating bacterial strains. Morphine-induced microbial dysbiosis and gut barrier disruption can be rescued by transplanting placebo-treated microbiota into morphine-treated animals (Banerjee et al., 2016). In summary, impairment of the intestinal barrier and the microbiome alterations can promote translocation of harmful bacteria and systemic infections.

Clinical Studies

Although many studies have confirmed the immunosuppressive effect in animal studies, there is hardly any evidence of the relevance in patients, because large randomized controlled studies with clinical endpoints (e.g. rate of infection and mortality) are lacking – especially in patients with non-malignant pain, who constitute the major group of opioid prescription. Studies of Dublin et al. (2011) and Wiese et al. (2016) have investigated the correlation between opioid use and risk of infections and pneumonia. Dublin et al. (2011) conducted a chart review of community-acquired pneumonia older adults. They found a higher risk of pneumonia in opioid-users with the highest risk in adults, who had just begun opioid treatment in the last 14 d prior to the infection and took longer lasting and more immunosuppressive opioids. The study of Wiese et al. (2016) analysed patients at risk with immunosuppression due to autoimmune disease. It consisted of a self-controlled case series analysis on a retrospective cohort of 13,796 patients with rheumatoid arthritis enrolled in Tennessee Medicaid ~~in~~ between 1995–2009. Within-person comparisons of the risk of hospitalization for serious infection during periods of opioid use versus non-use were performed. Within this patient group, the risk of hospitalization due to infection was higher during periods of active opioid intake. Higher risks were also associated with longer-acting and potentially immunosuppressive opioids as well as a daily intake equal or more than 60 mg morphine equivalent. On the other hand, a recent in depth analysis of opioid use in non-cancer pain and treatment recommendation (S3 guideline) did not find an increased incidence of infection as a side effect of long-term treatment (Hauser et al., 2015). In summary, current

evidence is not strong enough to argue for a clinical relevance. It might be beneficial to prefer non-immunosuppressive opioids in high risk patients including already immunosuppressed patients and always to follow current guidelines in the prescription of opioids (Dowell, Haegerich & Chou, 2016).

Analgesia by endogenous opioid peptides from immune cells of the innate and adaptive immune system

Several cell types in the innate immune system (Brack et al., 2004a; Brack et al., 2004b; Labuz et al., 2006; Labuz, Schmidt, Schreiter, Rittner, Mousa & Machelska, 2009; Rittner et al., 2009a; Rittner et al., 2009b; Rittner et al., 2007; Sauer et al., 2014; Wang, Gehringer, Mousa, Hackel, Brack & Rittner, 2014; Zollner et al., 2008) as well as the adaptive immune system (Boue, Blanpied, Djata-Cabral, Pelletier, Vergnolle & Dietrich, 2012) have either the capability to enhance the synthesis or release of endogenous opioid peptides (**Figure 2**). Opioid peptides bind to peripheral opioid receptors (Mambretti et al., 2016). Messenger RNA for β-endorphin and other proopiomelanocortin-derived peptides as well as proenkephalin has been found to be expressed by blood splenic cells, lymphocytes and macrophages. Immunosuppression due to cyclophosphamide (CTX) injection leads to increased mechanical and thermal hyperalgesia in complete Freund´s Adjuvant (CFA)-induced inflammation (Sauer et al., 2014) supporting a role of immune cells in endogenous tonic analgesia.

Macrophages, in particular anti-inflammatory macrophages, generate and release opioid peptides in inflammatory and neuropathic pain. Release is mediated by TLR4 signalling *in vitro* and *in vivo*: The analgesic effect of leukocyte-dependent opioid peptide release in CFA models is elicited by lipopolysaccharide, a TLR4 ligand. When a TLR4 inhibitor is injected *in vivo* hyperalgesia further worsens (Sauer et al., 2014). *In vitro*, alternatively activated macrophages, M2-polarized macrophages contain and release more endogenous opioids than other macrophage types (M0-unpolarized and classically activated M1-polarized) (Pannell et al., 2016). *In vivo*, adoptive transfer of M2 macrophages leads to reduction of mechanical but not heat-induced hyperalgesia in neuropathy. This shows that macrophage subtypes have an important role in attenuating nociception.

Several other studies investigated opioid peptide release from **neutrophils** in CFA inflammation (Rittner et al., 2009a; Rittner et al., 2006). When stimulated with mycobacteria *in vitro* only neutrophils but not monocytes release Met-enkephalin and β-endorphin. The release of opioid peptides from neutrophils is dependent on intracellular Ca^{2+} mobilization

and PI3K activation but most importantly on activation of formyl peptide receptors but not TLRs *in vitro* and *in vivo*.

Within the adaptive immune system **T-helper cells** synthesize and release β-endorphin and met-enkephalin in inflamed tissue (Boue, Blanpied, Brousset, Vergnolle & Dietrich, 2011; Labuz, Schreiter, Schmidt, Brack & Machelska, 2010; Vallejo, de Leon-Casasola & Benyamin, 2004), although the contribution of β-endorphin has recently been challenged (Basso et al., 2016). The antinociceptive effect is mediated by MOP receptor and DOP receptor on the sensory neurons in the periphery or the CNS. In their study Boué et al. (2012) concentrated on the contribution of the adaptive immune e.g. T cell system to analgesia in inflammatory pain. Only after activation and proliferation into their respective specialized phenotypes, the naïve CD4+ and CD8+ T cells produce opioid peptides and release it at the site of inflammation. No difference in opioid synthesis or release was found between TH1 and TH2 lymphocytes, indicating that induction of analgesia is a fundamental property of the adaptive immune system. This role was confirmed *in vivo:* Nude mice immunized with OVACD4+ cells showed prolonged analgesia compared to WT mice. Analgesic properties of CD4+/CD8+ cells depend on activation of the MOP receptor on sensory afferent neurons in the periphery (Boue, Blanpied, Djata-Cabral, Pelletier, Vergnolle & Dietrich, 2012). In summary both innate and adaptive immune system cells have the capacity to release opioid peptides and play a critical role in establishing analgesia in the periphery in inflammatory pain.

Clinical studies

One recent study investigated the effect of peripherally administered morphine on post-surgical levels of nociception and possibly endogenous opioids via inhibition of peripheral opioid receptors for treatment of opioid-induced constipation (Jagla, Martus & Stein, 2014). Patients undergoing knee joint replacement surgery demanded a significantly higher amount of morphine (about 40%) to achieve sufficient analgesia when treated with the peripheral opioid receptor antagonist methylnaltrexone for opioid-induced constipation. Thus, peripheral opioid receptors and possibly endogenous opioid peptides significantly contribute to attenuation of post-surgical pain by systemically given opioids.

The connection between endogenous and exogenous opioids

In neuropathy, leukocytes can be activated by exogenous opioids (DAMGO, DPDPE and U50, 488H). Surprisingly, this leads to the release of endogenous opioids at the site (Celik et

al., 2016) (**Figure 3**). Exogenous opioids (agonists of MOP, KOP and DOP receptors) injected close to the peripheral nerve can induce analgesia via opioid receptors on immune cells. Activation of opioid receptors on leucocytes leads to the release of multiple endogenous opioid peptides (met-enkephalin, β-endorphin and dynorphin A). Endogenous opioid peptides in turn will then induce the analgesia at peripheral neuronal opioid receptors. Opioid-induced antinociception is reversed by pharmacological or genetic inactivation of endogenous opioids or by depletion of functional leucocytes lacking any opioid receptor. Impairment of leukocyte migration attenuates opioid-induced antinociception, which is inversed upon transfer of functional leukocytes (Celik *et al.*, 2016a). The exogenous opioid-induced endogenous analgesia by leukocytes is mechanistically dependent upon Gαi/o-coupled DOP, MOP and KOP receptors. The release of granules involves the Gβγ protein-phospholipase C-IP3 receptor-intracellular Ca^{2+}- regulated pathway with contribution of protein kinase C and some involvement of PKC (Celik et al., 2016). Enkephalin and β-endorphin release was thereby more governed by PLC than PKC, whereas dynorphin release relayed stronger on PKC. The activation of each leucocyte opioid-receptor subtype resulted in the release of all three types of endogenous opioid peptides and produced similar levels of analgesia.

Conclusion

Opioids are one of the most powerful analgesics for treating pain. When given systemically, they can have severe side effects. One potential side effect of opioids is their capacity for immunomodulation. Many studies have investigated the relationship between innate and adaptive immune cells and different opioids *in vitro*, *in vivo* and in epidemiological and clinical studies on various patient groups. *In vitro* studies and studies in animals have proven immunosuppression in the adaptive and innate immune system as well as damage to the mucosal barrier, but the clinical relevance remains to be elucidated by other than the two epidemiological studies cited above. One of the reasons of this discrepancy might be that the complexity of the observed effects is not accounted for in the current models. Furthermore, the time course in animal models (1-2 weeks) and in patients (months to years) is not comparable.

The innate and the adaptive immune system synthesize opioid peptides to control inflammatory and neuropathic pain. Interestingly, some of the exogenously mediated opioid effects are due to release of endogenous opioid peptides. Therefore, peripherally restricted exogenous opioids or boosting endogenous opioid-mediated antinociception could be future targets.

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Conflict of interest

The authors declare no conflict of interest.

Author Contribution

Lisanne M. Plein wrote the manuscript.

Heike L. Rittner wrote the manuscript.

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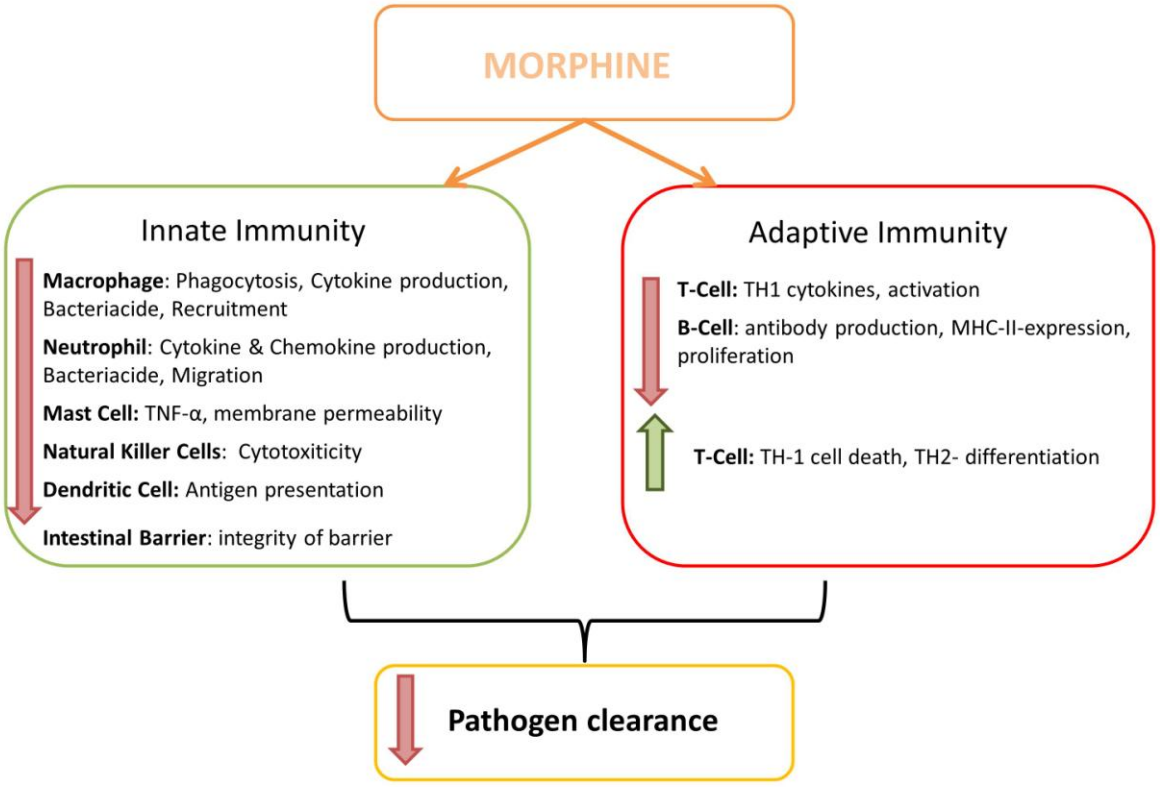

Figure 1 Overview of immunosuppressive effects. Morphine application impairs the innate as well as the adaptive immune system and opens the gut barrier (modified after (Roy et al., 2011))

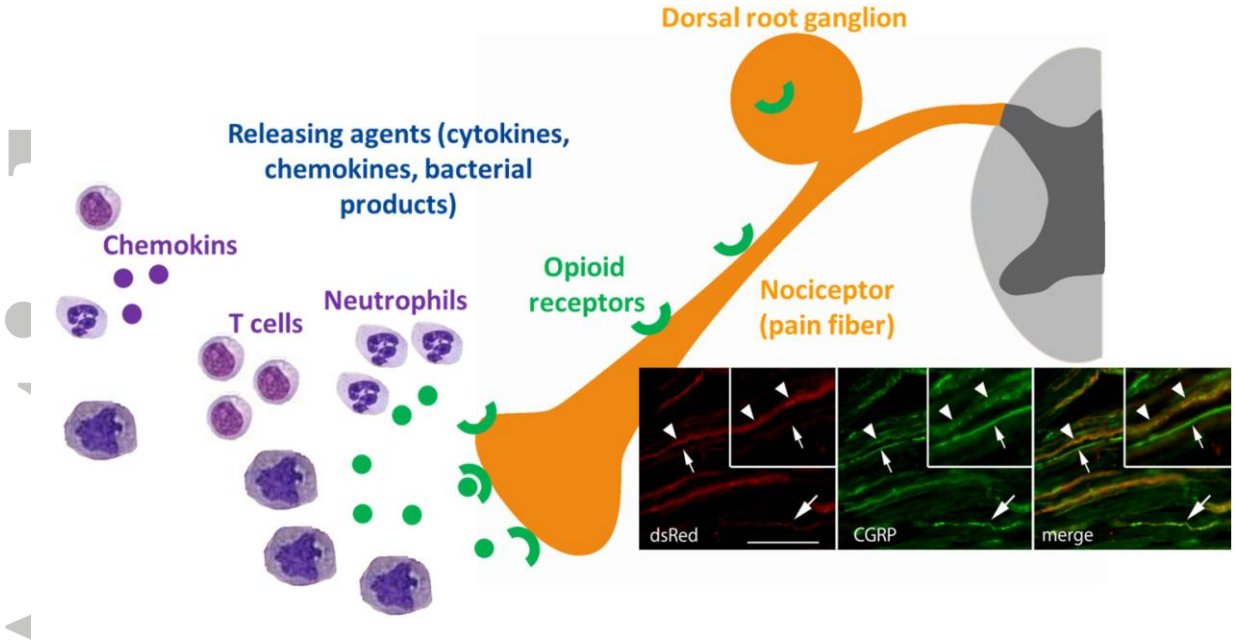

Figure 2 Schematic depiction of endogenous opioid peptide release from immune cells of the innate and adaptive immune system. Neutrophils, monocytes/macrophages and T cells migrate into inflamed tissue governed by chemokines. Release of opioid peptides (green circles) is triggered by cytokines, chemokines and bacterial products. Opioid peptides bind to opioid receptors (green) expressed in peripheral sensory neurons (yellow) (Mambretti et al., 2016). This cascade causes peripheral antinociception. (Peripheral MOP receptor presence and reactivity was shown via double immunostaining. DsRed = mcherry immunolabelling of MOP in sciatic fibre bundles, green = sensory fibre marker CGRP).

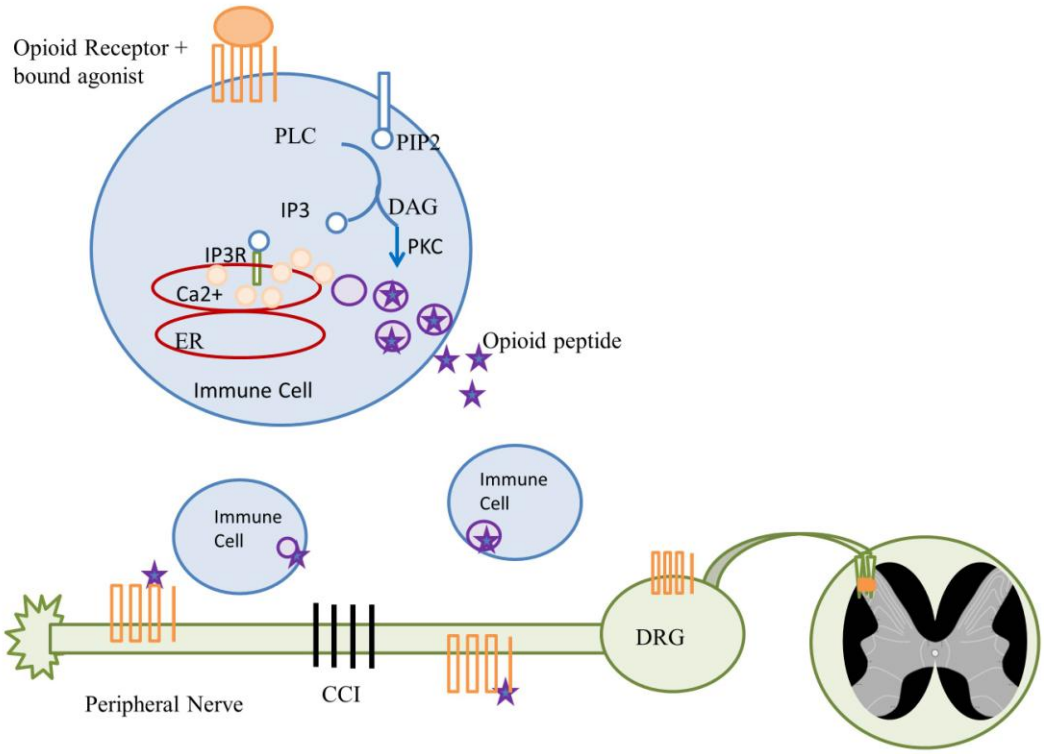

Figure 3 The connection between exogenous and endogenous opioids. Immune cells (blue) within the blood vessels (red) release endogenous opioids when exogenous opioids (not shown) are present. Stimulation of MOP receptor (orange) induces activation of phospholipase C (PLC). This triggers the formation of diacylglycerol (DAG) activating protein kinase C (PKC) and the formation of inositol-3 phosphate (IP3). Binding of IP3 to its receptor releases Ca from its intracellular stores in the endoplasmatic reticulum (ER) promoting the release of opioid peptides (purple star). Opioid peptides bind to opioid receptors on nociceptors (green) inhibiting neuropathic pain in chronic constriction injury (modified after (Celik et al., 2016; Rittner et al., 2006)).