British Journal of Pharmacology

British Journal of Pharmacology (2018) **175** 2717–2725 2717

Themed Section: Emerging Areas of Opioid Pharmacology

REVIEW ARTICLE

Opioids and the immune system – friend or foe

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Received 10 November 2016; **Revised** 6 February 2017; **Accepted** 8 February 2017

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Systemically administered opioids are among the most powerful analgesics for treating severe pain. Several negative side effects (respiratory depression, addiction, nausea and 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 to infections. The link between opioids and immunosuppression has been investigated both *in vitro* and *in vivo* as well as in patients. However, the results are inconsistent: Exogenous opioids such as morphine and fentanyl have been found to impair the function of macrophages, natural killer cells and T-cells and to 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 have been correlated with a higher risk of infectious diseases such as pneumonia. However clear randomized controlled studies are missing. Furthermore, immune cells including neutrophils, macrophages and T-cells have been shown to secrete endogenous opioid peptides, which then bind to peripheral opioid receptors to relieve inflammatory and neuropathic pain. In addition to cytokines, hormones and bacterial products, the release of opioid peptides is stimulated by the application of exogenous opioids. In summary, there is a reciprocal interaction between the immune system and endogenous as well as exogenous opioids. Further to the existing epidemiological studies, controlled clinical studies are needed in the future to elucidate the role of the opioid–immune system interaction in patients and to determine its clinical relevance.

LINKED ARTICLES

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Abbreviations

APC, antigen-presenting cell; CD4+/CD8+ cells, cluster of differentiation 4 positive cells/cluster of differentiation 8 positive cells; CFA, complete Freud's adjuvant; CREB1/CREB5, cAMP response element-binding protein 1/ 5; MiRNA, microRNA; TH_2, T-helper cell type 2

DOI:10.1111/bph.13750

Tables of Links

TARGETS	
Other protein targets[a]	**Catalytic receptors**[d]
TNF-α	MHC II
GPCRs[b]	TLR4
δ receptor	TLRs
κ receptor	**Enzymes**[e]
μ receptor	PI3K
Ligand-gated ion channels[c]	p38 MAPK
IP_3 receptor	

LIGANDS	
β-endorphin	IL-2
Codeine	IL-23
DAMGO	Methylnaltrexone
DPDPE	Met-enkephalin
Dynorphin A	Morphine
Fentanyl	Oxycodone
FMLP	Sufentanil
Hydromorphone	U50488

These Tables list key protein targets and ligands in this article which 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).

Introduction

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

A connection between prolonged opioid administration and increased susceptibility to bacterial infection has been suspected since the late 1800s (Vallejo *et al.*, 2004). Systemic morphine treatment lowers the resistance of guinea pigs to various bacterial agents and also abolishes 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 (Casellas *et al.*, 1991; Bhaskaran *et al.*, 2001; Menzebach *et al.*, 2004; Wang *et al.*, 2005; Lugo-Chinchilla *et al.*, 2006). Despite these studies, there is still some controversy about this relationship. For example, many studies have focussed solely on morphine without broadening their investigation to other opioids. Furthermore, the immunosuppressive effect of morphine seems to depend on the dose and number of administrations of the opioid (Saurer *et al.*, 2006b; Borman *et al.*, 2009) as well as the mouse strain (Plytycz and Natorska, 2002).

The effects of morphine on the immune system have been investigated in patients with prolonged opioid use or people with a history of opioid abuse (Roy *et al.*, 2011). The latter group are far more susceptible to 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 people. Therefore, drug abusers might not be a suitable group to evaluate the immunosuppressive potential of opioids *per se* because there are 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 could focus on a large group of patients with long-term opioid intake (Werber *et al.*, 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 *et al.*, 2014), which is a broad and fast response of the body to the 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 μ receptor (also known as the MOP receptor), which ultimately leads to an impaired ability of the host organism to clear pathogens (Figure 1) (Abbas *et al.*, 2014). The innate immune system consists of epithelial barriers, phagocytes, dendritic cells and natural killer (NK) cells. The cells of the innate system recognize and respond to pathogens in a generic way, but, unlike the adaptive immune system, it does not confer long-lasting or protective immunity to the host. The innate immune system fulfils the following functions: recruits immune cells to the sites of infection through the production of cytokines and chemokines, activates the complement cascade to promote the clearance of antibody complexes or dead cells and activates the adaptive immune system through a process known as antigen presentation. Furthermore, it acts as a physical and chemical barrier to infectious agents (Roy *et al.*, 2011; Abbas *et al.*, 2014).

The adaptive or acquired immune system is a more differentiated reaction 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, which then leads to an enhanced response to subsequent encounters with that pathogen. Like the innate system, the adaptive system includes both humoral and cell-mediated immune components (Abbas *et al.*, 2014).

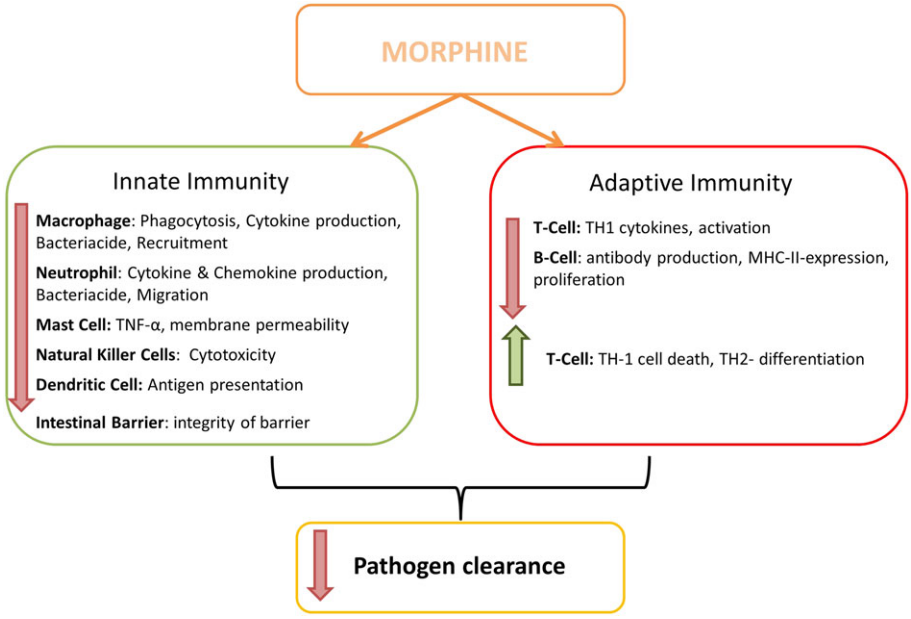

Figure 1

Overview of the immunosuppressive effects of morphine. Morphine impairs the innate and adaptive immune systems and opens the gut barrier (modified from that of Roy *et al.,* 2011).

Impact on the innate immune system

Innate immunity consists of macrophages, neutrophils, mast cells, NK 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 inhibiting the recruitment of these cells into the tissue. Activation of the μ receptor triggers the 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 and Roy, 2013) and to kill bacteria by releasing nitric oxide and superoxide intermediates, overall reducing their ability to fight off invading pathogens *in vitro* and *in vivo* (Casellas *et al.,* 1991; Bhaskaran *et al.,* 2001; Menzebach *et al.,* 2004; Wang *et al.,* 2005). The effects of morphine on macrophages depend on the dosage. Lower to moderate dosages can impair their ability to phagocytose; higher dosages will lead to morphine-induce apoptosis of macrophages via the toll-like receptor 9 (TLR9) and p38 MAPK pathway. The microRNA miR-873 is also suppressed by morphine and its expression is significantly less in peritoneal macrophages from mice treated with various dosages of morphine (20 to 140 mg·kg^{-1}). 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 *et al.,* 2015). Priming macrophages with lipoteichoic acid, a bacterial product of Gram-negative bacteria, together with morphine results in decreased phagocytosis via TLR messaging (Ninkovic and Roy, 2013). Further effects of morphine treatment include suppression of NF-κB, reduced release of the chemokine CXCL2 (CXCR2-ligand) and NF-κB-dependent gene-transcription in response to infection with S. pneumonia in mice. Consequently, patients using opioids are more likely to be prone to infections with Gram-negative bacteria. However, clinical data supporting this concept are lacking. A recent study has investigated the underlying mechanism of opioid-induced immunosuppression further by focusing on human peripheral blood monocytes (Long *et al.,* 2016). The findings show that two miRNAs, miR 582-5p and miR-590-5p, are decreased in monocytes from heroine abusers compared with monocytes from healthy controls. These miRNAs target cAMP response element-binding protein 1 (CREB1) and cAMP response element-binding protein 5 (CREB5) respectively. Down-regulation of both miRNAs leads to a decrease in CREB1/CREB5, which in turn reduces NF-κB-phosphorylation and TNF-α levels in monocytes. Therefore, these results corroborate previous findings, which showed that opioid-induced immune-suppression is dependent on the NF-κB-pathway, but miRNAs are additional factors that are also involved. Selective 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 *et al.,* 1985; Simpkins *et al.,* 1986). Morphine inhibits mast cell activation via a negative crosstalk between opioid receptors and the 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 *et al.,* 2006) (see below). Based on previous

research (Granger *et al.,* 1988; von Ritter *et al.,* 1988; Harari *et al.,* 2000), 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; an effect that was lost in mast cell-deficient mice. FMLP-induced permeability was accompanied by an elevated concentration of histamine and 5-HT in the intestinal lumen. Both of these inflammatory agents are stored in mast cells, linking this cell type to gut barrier permeability. Morphine inhibited this FMLP-induced increase in histamine and 5-HT. Thus, while the mechanism of this opioid effect is not fully understood, it is dependent on the presence of functional mast cells in the animal. Suppression of the innate immune response via inhibition of mast cell activity is not solely limited to morphine (Molina-Martinez *et al.,* 2014). The administration of fentanyl to male Swiss–Webster mice inhibits LPS-induced TNF-α production in intraperitoneal mast cells in proportion to its antinociceptive effect. Again this effect was dependent on the presence of functional mast cells. In the case of fentanyl, repeated administration lead to a loss of immunosuppressive effects and sensitization to LPS-induced TNF-α secretion. This latter effect was characteristic solely for fentanyl. NK cells are indirectly impaired by morphine-induced activation of opioid receptors in the CNS, especially μ receptors in the periaqueductal grey (Nelson *et al.,* 2000; Saurer *et al*., 2006a,b). Dendritic cells play an important role in linking the innate and adaptive immune systems. They detect, capture and present foreign antigens to T-cells (Banchereau and Steinman, 1998). Morphine treatment inhibits the presentation of the antigens to the T-cells by dendrites by inhibiting the production of IL-23 (Wang *et al.,* 2011).

Impact on the adaptive immune system

Similar to its effect on the innate immune system, prolonged morphine treatment weakens the adaptive immune response (Roy *et al.,* 2011); for example, it impairs T-cell function, alters the expression of cytokines, suppresses T-cell apoptosis and modifies T-cell differentiation as well as reducing B cell function via the μ receptor.

In professional antigen-presenting cells (APCs), morphine treatment initiates a down-regulation of the expression of major histocompatibility complex class II (MHC-II) especially on B cells. This down-regulation 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 binds to the μ receptors on T-cells and drives T-cell towards the T-helper cell type 2 (TH_2) phenotype. The activation of μ receptors also results in the superactivation of adenylyl cyclase, an increase in intracellular cAMP, the activation of p38 MAPK leading CREB phosphorylation, the stimulation of the T-cell-specific transcription factor GATA3 and a shift of the TH_2 phenotype, to a helper T-cell that secretes IL-4, IL-5 and IL-10 and is effective against helminths. This intracellular switch towards TH_2 is the functional step that is 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 opioid

Immunosuppressive activity depends on the type of opioid and is independent of its potency or duration of action. For example, hydromorphone is a highly potent, short acting opioid that does not have immunosuppressant properties. Morphine sulphate is also highly potent and has a short duration of action but is immunosuppressive. The immunosuppressive effect of morphine has been most extensively investigated and, thereby, corroborated by numerous studies (Ninkovic and Roy, 2013). There are few direct comparative studies of the immunosuppressant effects of opioids. Nevertheless, a comparison of fentanyl, morphine and sufentanil revealed an impairment of NK cell activity when these were given during surgery in animals and patients; however, the relevance of this finding is unclear (Beilin *et al.,* 1989, 1992, 1996). One comparative study evaluated the immunosuppressive effect of several opioids in male Swiss mice (Sacerdote *et al.,* 1997). Morphine and oxycodone impaired splenocyte proliferation, NK cell activity and IL-2 production, while hydromorphone and codeine treatment resulted in no significant effects. Therefore, these latter two opioids are not considered to be immunosuppressive. The reason for this difference in the immunosuppressive effects of the two opioids (morphine and oxycodone) and not in others is rooted within the structural attributes of the molecule itself. Substitution of the carboxyl group at C6, a single bond between C7 and C8 and a hydroxyl group within the molecule lead to blockage of the immunosuppressive effect (Sacerdote *et al.,* 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). Morphine has been shown to impair the barrier function of gut epithelial cells, by disrupting the distribution of tight junction proteins (occluding, ZO-1) in gut epithelial cells, in mice both *in vivo* and *in vitro*. This disruption is mediated by activation of TLR2 and TLR4 by μ receptor agonists, as shown by a lack of effect of morphine in TLR2/4 and μ receptor KO mice. As a result, translocation of *Escherichia coli* bacteria in the mesenteric lymph node and liver tissue of mice is increased after morphine treatment. In addition, chronic morphine treatment significantly alters the gut microbial composition and induces preferential expansion of Gram-positive pathogens and a reduction in bile-deconjugating strains of bacteria. 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 alterations in the microbiome can promote the translocation of harmful bacteria and result in systemic infections.

Clinical studies

Although many studies have confirmed the immunosuppressive effect of opioids in animal studies, there

is hardly any relevant evidence in patients. There is a lack of large randomized controlled studies with clinical endpoints (e.g. rate of infection and mortality) – especially in patients with non-malignant pain, who constitute the main group receiving opioids on prescription. 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 in older adults. They found opioid users were at a higher risk of contracting pneumonia, with the highest risk in adults who had just begun opioid treatment in the last 14 days prior to the infection and had received longer lasting and more immunosuppressive opioids. Wiese *et al*. (2016) analysed patients at risk of immunosuppression due to autoimmune disease. Their study consisted of a self-controlled case series analysis on a retrospective cohort of 13 796 patients with rheumatoid arthritis enrolled in Tennessee Medicaid between 1995 and 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. A higher risk of infection was also associated with longer-acting and potentially immunosuppressive opioids as well as a daily intake equal to or more than 60 mg morphine equivalent. In contrast, in a recent in-depth analysis of opioid use for non-cancer pain (and treatment recommendation; S3 guideline) no increased incidence of infection as a side effect of long-term treatment was observed (Hauser *et al.,* 2015). In summary, the current evidence is not strong enough to establish the clinical relevance of opioid-induced immunosuppression. It might be beneficial to use non-immunosuppressive opioids in high-risk patients, which would include those already immunosuppressed, and always to follow the current guidelines when prescribing opioids (Dowell *et al.,* 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,b; Labuz *et al.,* 2006, 2009; Rittner *et al.,* 2007, 2009a, b; Zollner *et al.,* 2008; Sauer *et al.,* 2014; Wang *et al.,* 2014) and the adaptive immune system (Boue *et al.,* 2012) have the capacity to either enhance the synthesis of, or induce the release of, endogenous opioid peptides (Figure 2). Opioid peptides bind to peripheral opioid receptors (Mambretti *et al.,* 2016). The mRNA 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 injection leads to increased mechanical and thermal hyperalgesia in complete Freund's adjuvant (CFA)-induced inflammation (Sauer *et al.,* 2014) supporting a role for immune cells in endogenous tonic analgesia.

Macrophages, in particular anti-inflammatory macrophages, generate and release opioid peptides in inflammatory and neuropathic pain. This 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 LPS, a TLR4 ligand. When a TLR4 inhibitor is injected *in vivo*, the hyperalgesia is increased (Sauer *et al.,*

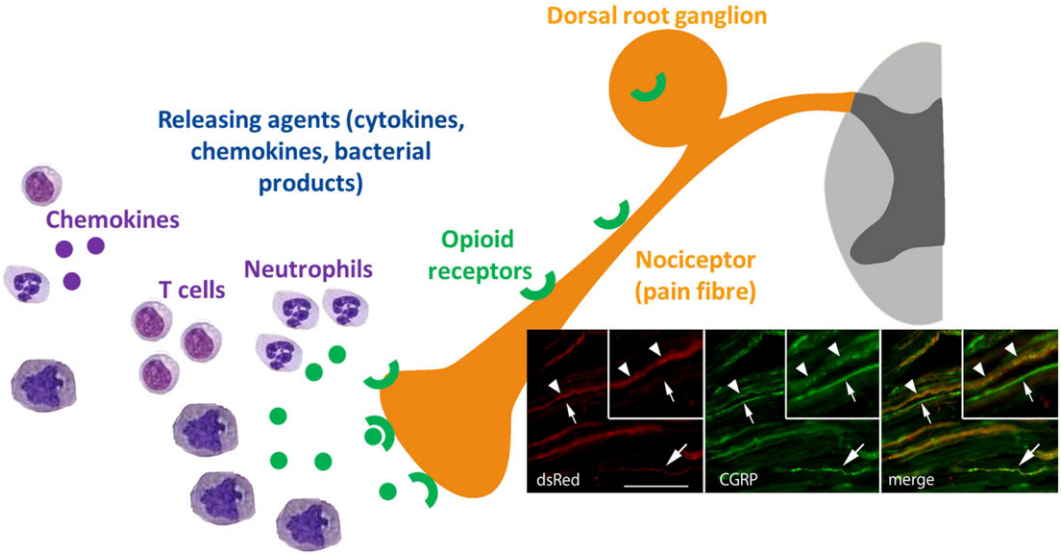

Figure 2

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 in response to 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. Inset: The presence and reactivity of peripheral μ receptors was shown via double immunostaining. DsRed mcherry immunolabelling of μ receptors in sciatic fibre bundles; green, sensory fibre marker CGRP.

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*, the adoptive transfer of M2 macrophages leads to a reduction in mechanical- but not heat-induced hyperalgesia in neuropathy. This indicates that macrophage subtypes have an important role in attenuating nociception.

Several other studies have investigated opioid peptide release from neutrophils in CFA inflammation (Rittner *et al.*, 2006, 2009a). 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, 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 (Vallejo *et al.*, 2004; Labuz *et al.*, 2010; Boue *et al.*, 2011), although the contribution of β-endorphin has recently been challenged (Basso *et al.*, 2016). The antinociceptive effect is mediated by μ and δ (also known as DOP) receptors on the sensory neurons in the periphery and CNS. In their study, Boue *et al.* (2012) concentrated on the contribution of the adaptive immune, for example the T-cell system, to analgesia in inflammatory pain. The naïve CD4+ and CD8+ T-cells produce opioid peptides and release them at the site of inflammation only after activation and proliferation into their respective specialized phenotypes. No difference in opioid synthesis or release was found between TH_1 and TH_2 lymphocytes, indicating that the induction of analgesia is a fundamental property of the adaptive immune system. This hypothesis was confirmed *in vivo*: nude mice immunized with ovalbumin-induced CD4+ cells showed prolonged analgesia compared with WT mice. The analgesic properties of CD4+/CD8+ cells depend on the activation of the μ receptor on sensory afferent neurons in the periphery (Boue *et al.*, 2012). In summary, cells of both the innate and adaptive immune system have the capacity to release opioid peptides and play a critical role in establishing analgesia in the periphery in inflammatory pain.

Clinical studies

In a recent study, the effect of peripherally administered morphine on post-surgical levels of nociception and the release of endogenous opioids via inhibition of peripheral opioid receptors for the treatment of opioid-induced

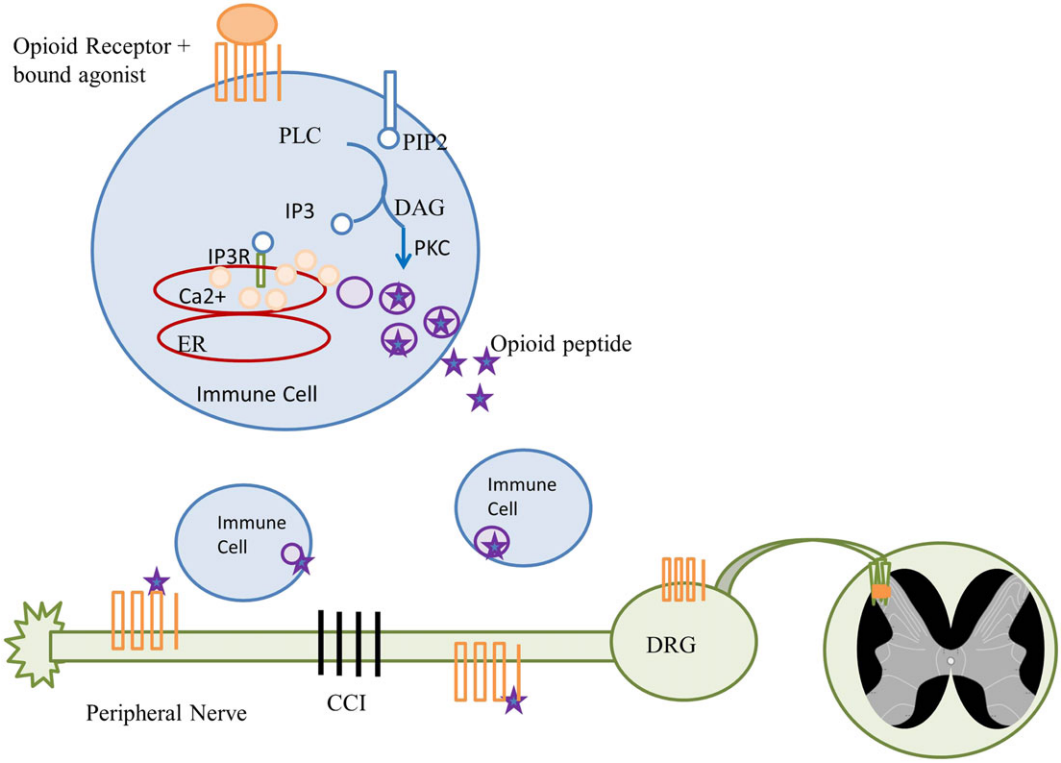

Figure 3

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 μ receptors (orange) induces activation of PLC. This triggers the formation of diacylglycerol (DAG), which activates PKC and results in the formation of inositol-3 phosphate (IP3). The binding of IP3 to its receptor releases Ca^{2+} 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 the neuropathic pain evoked by chronic constriction injury (CCI) (modified version of those presented by Rittner *et al.*, 2006 and Celik *et al.*, 2016). DRG, dorsal root ganglion.

constipation were investigated (Jagla *et al.,* 2014). Patients undergoing knee joint replacement surgery need a significantly higher amount of morphine (about 40%) to achieve sufficient analgesia when also treated with the peripheral opioid receptor antagonist methylnaltrexone for opioid-induced constipation. Thus, peripheral opioid receptors and possibly endogenous opioid peptides significantly contribute to the attenuation of post-surgical pain mediated 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 of administration (Celik *et al.,* 2016) (Figure 3). Exogenous opioids (agonists of μ, κ (also known as KOP) and δ 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 analgesia at peripheral neuronal opioid receptors. Opioid-induced antinociception is reversed by pharmacological or genetic inactivation of endogenous opioids or by depletion of functional leukocytes. Impairment of leukocyte migration attenuates opioid-induced antinociception; this effect is reversed upon transfer of functional leukocytes (Celik *et al.*, 2016). The exogenous opioid-induced analgesia mediated by leukocytes is mechanistically dependent upon Gαi/o-coupled δ, μ and κ receptors. The release of granules involves the Gβγ protein-PLC-IP_3 receptor-intracellular Ca^{2+}-regulated pathway with some involvement of PKC (Celik *et al.,* 2016). PLC was found to be more involved in the release of enkephalin and β-endorphin release than PKC, whereas dynorphin release is more dependent on PKC. The activation of each leukocyte 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 available to treat pain. However, when given systemically, they can have severe side effects. One potential side effect of opioids is due to their ability to affect the immune system. 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 shown that opioids induce immunosuppression in the adaptive and innate immune system as well as damage to the mucosal barrier, but the clinical relevance of these effects remain to be elucidated, as the results from the two epidemiological studies cited above are inconclusive. One of the reasons for the discrepancies in the findings might be that the complexity of the effects is not accounted for in the current models. Furthermore, the time courses of the studies in the animal models (1–2 weeks) and in patients (months to years) are not comparable.

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

Acknowledgement

This work was supported by funds from the graduate school 'DoloRes' supported by 'Evangelisches Studienwerk Villigst, Germany'.

Author contributions

L.M.P. and H.L.R. wrote the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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