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Immunomodulatory effects of opioids

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Abstract

Objective – To review the immunomodulatory effects of opioids.
Data Sources – Original research publications and review articles using the PubMed search engine with the following keywords – opioids, morphine, immuomodulation, and immunosuppression.
Veterinary and Human Data Synthesis – Opioids have been shown to modulate the immune system in animal models by affecting both the acquired and innate arms of the immune system. Natural killer cell activity, T-cell proliferation, antibody production, phagocytic cell function, and cytokine production have all been shown to be affected by opioids. Many of these effects are reversed by opioid antagonists. Opioids have also been shown to induce sepsis in laboratory animals. Opioid administration alters immune parameters in healthy humans at analgesic doses and may increase the risk of infection in some patient populations.
Conclusions – While opioids remain the most powerful and widely used analgesics available, their negative effects on the immune system are well established in the laboratory setting. Thoughtful consideration should be given to the use of certain opioids in critically ill patients, especially those with pre-existing immunocompromise.

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Keywords: HPA axis, immunosuppression, intravenous drug users, morphine, sepsis

Introduction

The term opioid refers to any directly acting compound that is stereospecifically antagonized by naloxone.[1] The clinical use of opioids stems from more than 5000 years of medicinal use of opium, which is derived from the unripe seed capsule of poppy *Papaver somniferum*. Morphine, a pure mu receptor agonist opioid, was isolated from opium in 1805; it is also known as an opiate as it is not a synthetically compounded drug. Since that time other semisynthetic and synthetic opioids have been developed in an attempt to produce more efficacious compounds with reduced abuse potential and adverse effects.[1]

Opioids are the most powerful and effective analgesic drugs used in clinical medicine. They make up the backbone of pain management in human and veterinary patients and are used for the management of moderate to severe pain.[2,3] They are potent analgesics, have few clinically apparent adverse effects on other organ systems, and have consistent pharmacokinetics.[4] Opioids are naturally occurring alkaloids, related synthetic/semisynthetic compounds, and endogenous opioid peptides (enkephalins, endorphins, and dynorphins).[5] The exact physiologic function of endogenous opioids includes modulation of stress-induced analgesia and neurotransmitter, neuromodulator, and neurohormonal activity.[6] In addition to analgesic properties, opioid receptor agonists and antagonists modulate the immune system by interacting with opioid receptors in the central nervous system (CNS) and on immune cells.

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Pharmacology

Opioid receptors are named for their endogenous ligands and identified by a numerical subscript corresponding to the chronological order of discovery by cloning and sequencing.[1] The receptors for which all opioids act as agonists have a generic designation of OP (Table 1). The opioid receptor is made up of an extracellular N-terminal domain, 7 transmembrane guanine domains connected by 3 extracellular and 3 intracellular loops and an intracellular C-terminal tail.[7,8] Each

Table 1: Opioid nomenclature

International Union of Pharmacology recommendation	Pharmacology nomenclature	Molecular biology nomenclature
OP_1	δ	DOR
OP_2	κ	KOR
OP_3	μ	MOR

Adopted from Dhawan BN et al.[145]
DOR, delta opioid receptor; KOR, kappa opioid receptor; MOR, mu opioid receptor.

receptor has specific subtypes that have not been completely defined.[9,10] These subtypes may dictate the physiologic response to endogenous and exogenous opioids and explain variable analgesic and physiologic responses associated with OP_3 receptor opioids.[11]

The frequency and distribution of opioid receptors is organ and species dependent and nonuniform.[5,8,12] The opioid receptor has been shown to be distributed in many sites throughout the CNS including the cerebral cortex, thalamus, periaqueductal gray matter, and the spinal cord dorsal horn. In addition, opioid receptors have been demonstrated on peripheral sensory neurons following inflammation and nonneurologic tissue including the heart, gastrointestinal tract and cells of the immune system.[6,9,10,13,14] Opioid receptors in these different areas all exhibit similar molecular structure.[13]

Opioid receptors signal through a second messenger system (cyclic AMP) or ion channel (K^+).[6] They work by reducing intracellular calcium concentrations leading to a decrease in presynaptic neurotransmitter release.[6,10] They may also enhance efflux of potassium leading to hyperpolarization of postsynaptic neurons.[6] Opioids inhibit γ-aminobutric acid (GABA)ergic transmission in a local circuit, ultimately preventing GABA inhibition of descending antinociceptive pathways.[6,10] Binding of endogenous and exogenous opioid ligands to the opioid receptor results in receptor activation and a variety of effects, including analgesia, euphoria, feeding, hormone secretion, respiratory depression, inhibition of gastrointestinal motility, and anxiolysis.[8]

Opioids may interact with receptors as agonists, antagonists, or as partial agonists. Morphine is the prototypical agonist of the OP_3 receptor and is standard of comparison for other opioid analgesics.[6,15,16] Other drugs that act as agonists at this receptor include hydromorphone, oxymorphone, methadone, fentanyl, and meperidine (Table 2). Buprenorphine has traditionally been described as a partial agonist at the OP_3 receptor and an antagonist at the OP_2 receptor.[17] Opioid antagonists lack in vivo or in vitro agonist activity and may be used to reverse the effect of opioid antagonists.[12] Naloxone, naltrexone, and nalmephine are opioid antagonists that block central and peripheral opioid effects.[12] In addition, specific peripheral opioid antagonists have been developed and are used to block undesired peripheral effects (ie, altered gastrointestinal motility) without reversing central analgesic effects of the drugs.[12]

Immunomodulatory effects of Opioids

As early as the late 19th century, the immunosuppressive effects of opioids were recognized. Both exogenous and endogenous opioid peptides have been shown to cause immunosuppression or immunostimulation.[23–25] Morphine-induced immunomodulation has been investigated most extensively. However, other opioids have immunomodulatory properties.[26]

The immunosuppressive effects of opioids are independent of their antinociceptive properties and appear to be related to the molecular structure of the opioid. Some opioids (morphine, fentanyl, methadone, codeine) are more immunosuppressive than others (hydromorphone, tramadol, hydrocodone, and oxycodone) (Table 3).[26–28] Buprenorphine produces little to no negative immune alterations and may enhance immune function.[26,27,29–31] Antagonists at the OP_3 receptor also appear to enhance immune function.[13,23,32] Opioids

Table 2: OP_3 receptor agonists and their relative potencies to morphine

OP_3 receptor agonist	Administration route	Relative potency to morphine	Additional comments
Hydromorphone	IV, IM, SQ, PO	5–10[18]	May cause panting in dogs. Minimal to no histamine release
Oxymorphone	IV, IM, SQ, PO	10[19]	Expensive. Minimal to no histamine release
Fentanyl	IV, TD	80–100[20]	Short acting. Usually given as a constant rate infusion to attain prolonged therapeutic effects. Transdermal application takes 12–24 hours to reach therapeutic levels
Methadone	IV, IM, SQ, PO	3.4–10[21,22]	Also has NMDA antagonist properties.

IV, intravenous; IM, intramuscular; SQ, subcutaneous; TD, transdermal; PO, oral; NMDA, *N*-methyl-D-aspartic acid.

Table 3: Immunomodulating properties of selected opioids

Opioid	Primary receptor activity	HPA axis	Corticosteroid secretion	NK cell activity	Additional information
Morphine	OP_3 agonist	Stimulates[31,34]	Increases[31,34]	Decrease[28,31,35]	Generally upregulates production of pro-inflammatory mediators and suppresses the production of anti-inflammatory mediators. Suppresses immune cell proliferation[31,33]
Fentanyl	OP_3 agonist	Stimulates[34]	Increases[34]	Decreases, has also been reported to increase. May be dose dependent[29,36,37]	Does not stimulate the release of nitric oxide.[38] Suppresses T cell proliferation, IFN-γ and IL-2 production[29,39]
Hydromorphone	OP_3 agonist	No known reported effect	No known reported effect	No effect[33]	Has no effect on immune cell proliferation or IL-2 production
Buprenorphine	OP_3 partial agonist	No effect[31,34]	No effect, decreases[29,31]	No effect[29,31]	No effects on immune cell proliferation or cytokine activity[29]
Naloxone	OP_3 antagonist	Variable and dose dependent[40]	Variable[40]	Increase, decrease, or no effect[41,42]	Not well studied. Decreases IL-4 Increases the production of IL-2 and IFN-γ. Increases T lymphocyte proliferation[42]
Naltrexone	OP_3 antagonist	Variable and dose[40] dependent	Variable[40]	Increase, decrease, or no effect[41]	Not well studied. Effects likely similar to naloxone

HPA, hypothalamo-pituitary axis; NK, natural killer; IL, interleukin; IFN, interferon.

with no immunosuppressive activity have a carbonyl substitution at C_6, a single bond between $C_{7–8}$ and a hydroxyl group at C_{14}.[27,33] Molecules like morphine and fentanyl that carry the hydroxyl group at both C_3 and C_6 have the greatest immunomodulatory effects; the mechanism by which these structural differences dictate immune response is unknown.[33]

Mechanisms of Immunomodulation

The mechanism by which opioids affect the immune system is complex and incompletely understood.[43] Opioids alter immune response through their actions in the CNS and in the periphery. Central mechanisms involve interaction of opioids with opioid receptors in the CNS, which leads to changes in neuroendocrine and autonomic function.[44] The OP_3 receptor is primarily responsible for the central immunomodulatory effect of opioids; OP_3 receptor knockout mice are protected from these immunomodulatory effects.[23,45,46] Centrally mediated suppression is responsible for reduction in natural killer (NK) cell activity (associated with the sympathetic nervous system), reduction in lymphocyte proliferation and interferon (IFN)-γ activity.[47,48] Direct stimulation of OP_1 and OP_3 receptors on immune cells including B lymphocytes, monocytes, and macrophages is primarily responsible for peripheral immunosuppression, although a naloxone-insensitive morphine receptor may also play a role.[23]

Centrally mediated immunomodulation

Several studies have demonstrated a centrally mediated mechanism for opioid-related immunosuppresion.[49–52] Hernandez et al[49] demonstrated the role of the CNS by showing that systemic administration of morphine, which crosses the blood brain barrier, suppressed lymphocyte activity. In contrast, *N*-methylmorphine, an active morphine analog that does not cross the blood-brain barrier, did not produce any systemic changes in lymphocyte activity. The role of central OP_3 receptors was further demonstrated by the observation that injection of *N*-methylmorphine directly into the third ventricle suppressed peripheral lymphocyte and NK cell activity.[49,50]

The periaqueductal gray matter of the mesencephalon (PAG) is enriched with opiate receptors and endogenous opioids. Thus, it is not surprising that the PAG is also the primary area of the brain involved in opioid-induced immunomodulation.[31,47,53] Microinjections of morphine into the PAG cause rapid suppression of NK cell function, while injection into other neuroanatomical sites does not cause immunosuppression.[53] While there are OP_1, OP_2, and OP_3 receptors present in the PAG and in many areas of the CNS, OP_3 receptors appear to be primarily responsible for the central immunomodulatory effect of morphine.[51] Administration of high doses OP_1 and OP_2 receptor agonists into the CNS of mice only produced mild

suppression of blood lymphocyte proliferation in comparison to OP_3 agonists.[51]

While the role of opioid receptors in immunosuppression has been established, the pathway by which activation of central opioid receptors results in immunosuppression is debated.[54] It has been proposed that central opioid immunomodulation is either through the neuroendocrine (hypothalamic-pituitary-adrenal [HPA]) axis or the sympathetic nervous system.[53,55,56] Both acute and chronic administration of morphine appears to alter the immune response through different pathways. Acute administration of exogenous opioids primarily affects immune function through the sympathetic nervous system while chronic administration may activate the HPA axis.[55,56]

Activation of the HPA axis results in the activation of a hormonal cascade from the hypothalamus, pituitary (ie, CRH, ACTH) and the secretion of immunosuppressive hormones from the adrenal glands (ie, glucocorticoids) which exert their effect peripherally.[30,56,57] Importantly, opioid agonist administration has been shown to activate the descending pathways of the HPA and hypophysectomy, adrenalectomy, and the use of steroid antagonists abolish the immunosuppressive effects of morphine.[58–61]

The sympathetic nervous system is another pathway through which central opioid receptor activation translates to immunomodulation. Primary (eg, spleen, thymus) and secondary (eg, Peyer's patches, lymph nodes) lymphoid organs are primarily innervated by the sympathetic nervous system.[55] Opioids activate the sympathetic nervous system and induce catecholamine release, including epinephrine from the CNS and norepinephrine from the sympathetic nerve terminals and adrenal medulla. Catecholamines act on primary and secondary lymphoid organs and suppress lymphocyte proliferation, NK cell, and macrophage activity.[47,62–64] Alpha-adrenergic receptor activation is responsible for suppressing NK cell activity while beta-adrenergic receptor activation decrease lymphocyte activity.[47,65]

Peripherally mediated immunomodulation

Opioid receptors as well as nonclassical opioid-like receptors are expressed on the surface of immune cells. Additionally, there is evidence of opioid receptors that have yet to be cloned that are responsible for altered immune cell function. For example, novel morphine-selective receptors have been identified on lymphocytes. These opioid receptors are thought to exist in low density on a restricted population of lymphocytes.[25]

The OP_1 receptor is primarily responsible for peripherally mediated immunomodulation, although OP_2 and OP_3 receptors may also play a lesser role.[43] OP_1 receptors on T cells and macrophages are involved in the maintenance of immune homeostasis. Overstimulation of OP_1 opioid receptors by exogenous or endogenous opioids may alter the production cytokines (ie, enhancing or suppressing cytokine production depending on the agonist and the dose used) and decrease antibody production.[25,55,66]

Effects of opioids on specific cells of the immune system

Opioids mediate their immunosuppressive effects by acting on various cells of the immune system, affecting both the innate and the adaptive immune systems. Opioids interfere with the phagocytic activities of macrophages and neutrophils, inhibit B and T-cell antibody response, interfere with chemotaxis of immune cells and modulate inflammatory mediator production.[56,67–70]

Bone marrow progenitor cells: Roy et al[71] discovered in 1991 that bone marrow cells are differentially sensitive to chronic morphine treatment in vitro. Continuous in vivo morphine treatment compromised the ability of macrophage progenitor cells to proliferate in response to macrophage-colony stimulating factor (M-CSF) in mice. A 70% reduction in colony formation was seen as early as 36 hours after continuous morphine exposure although acute injection of morphine failed to suppress M-CSF induced colony formation. This effect was not permanent and M-CSF responsiveness returned within 5 days after cessation of morphine treatment.[56,71]

Macrophages: Morphine suppresses phagocytic functions of macrophages in vivo and in vitro. Acute and chronic exposure to morphine affects a variety of macrophage functions including phagocytosis, tumoricidal activity, nitric oxide (NO) production, superoxide formation, and cytokine expression.[56,72–76] Suppressed macrophage function is antagonized by OP_3 antagonists but not by OP_1 or OP_2 antagonists, emphasizing the importance of the OP_3 receptor in immunosuppression.[72] Morphine induced apoptosis in macrophages of mice, rats, and healthy human volunteers and this effect was reversed by naloxone.[77] Morphine-induced macrophage apoptosis may be mediated through the generation of NO, since the administration of NO-synthase inhibitors attenuated this effect.[77] NO is thought to promote macrophage apoptosis through the generation of p53.[78]

NK cells: Acute and chronic administration of morphine affects the function of human, monkey, and rodent NK cells.[56,79] Administration of morphine in rats and healthy human volunteers decreased splenic NK cell activity within 2–3 hours. This effect was completely antagonized by naltrexone.[48,79,80] The mecha-

nism by which morphine affects NK cell activity is thought to be mediated through OP_3 receptors in the CNS.[35,50,79] Morphine does not affect NK cell function in vitro and administration of *N*-methyl morphine, a morphine analog that does not cross the blood brain barrier, fails to inhibit NK activity in vivo.[50,61,81]

A key aspect of NK cell function is the identification and eradication of neoplastic cells. Therefore, it is logical that opioid-induced NK suppression would lower defenses against neoplastic cell growth. However, in vivo evaluations of this phenomenon have yielded conflicting results. Ishikawa et al[82] demonstrated that morphine enhanced the growth of tumor cells in vivo and this effect was inhibited by naloxone. However, other investigators have demonstrated that morphine controlled metastasis and retarded the growth of tumors.[83,84] It is thought that the antitumor effect of morphine may be the result of analgesia.[84]

T cells: Chronic administration of morphine affects the function of T cells and their precursors, in part through the OP_3 receptor.[55,85,86] Chronic morphine administration interferes with the synthesis of interleukin (IL)-2 and IFN-γ, while the production of IL-4 and IL-5 are upregulated.[86,87] This ultimately leads to the differentiation of T helper (Th) cells toward Th2 effector cells, via killing of Th1 cells in a Fas/FasL-dependent manner, resulting in reduced cellular immunity.[86–88] Chronic morphine administration decreases CD4/CD8 ratio in the spleen and thymus of mice.[24,46] Morphine also decreases T-cell responses to the mitogen concanavalin A, in mice.[89]

Inflammatory mediators: In general, morphine increases production of proinflammatory cytokines and reduces production of anti-inflammatory cytokines, although this effect is dose dependent. The OP_3 receptor is involved in morphine induced reduction of tumor necrosis factor (TNF) synthesis while the role of this receptor in the modulation of IL-1β and IL-6 synthesis is unclear.[23,56,90] It is speculated that the modulation of IL-1β and IL-6 synthesis could be mediated by OP_2 or OP_3 receptors or through a naloxone-insensitive morphine receptor.[56] OP_1 selective agonist, U50,488 inhibits the synthesis of IL-1β and TNF but not IL-6 in a macrophage cell line.[25,91] Modulation of cytokine expression is thought to be through the nuclear factor-κB pathway.[92]

Morphine inhibits production of IFN-γ, an important T cell lymphokine responsible for enhancing the microbicidal activity of macrophages, peripheral blood mononuclear cells, and T lymphocytes.[93,94] Peng et al[95] demonstrated that morphine upregulated the production of proinflammatory cytokines, TNF, and IL-12, at the protein and the mRNA level, and naloxone blocked those effects. Morphine also inhibited the production of IL-10, an anti-inflammatory cytokine.[95] Morphine reduces IL-2 production while hydromorphone and the OP_3 antagonists, naloxone and naltrexone, increase or have no effect on IL-2 production.[33] In one in vitro study, morphine produced a dose dependent effect. Roy et al[92] demonstrated that high doses of morphine reduced the expression of inflammatory cytokines TNF and IL-6, while low doses of morphine increased their expression in vitro. Ultimately, the effect of morphine on inflammatory cytokine synthesis and secretion is variable depending on experimental conditions and the dose of morphine used.[56]

Opioids, infection, and sepsis

Certain opioids have been shown to increase infection rates in humans and animal models.[13,43] Morphine increased susceptibility to *Klebsiella pneumoniae* and *Candida albicans* infection in rodents, reduced splenic and thymic weights, and decreased T cell proliferative response to mitogens. Additionally, morphine promoted the translocation of intestinal bacteria into the peritoneal cavity inducing sepsis in mice.[14,23,44,96] The initial serum concentration of morphine attained in these mice was higher than those achieved with typical analgesia doses in clinical practice, although those concentrations could be attained if higher doses of morphine are used.[14] However, after 48–96 hours serum morphine concentrations were approximately 0.6 μg/mL, which is comparable to that obtained for analgesia in clinical practice.[14,97]

Along with inducing infection, morphine administration has detrimental consequences in experimental models of sepsis and endotoxemia. Cell-mediated immunity is vital to combat microorganisms during sepsis, and morphine attenuates cell-mediated immunity in murine models of sepsis.[14,98,99] Administration of morphine before administration of lipopolysaccharide (LPS) significantly enhanced development of hypotension, intravascular coagulation, leukocyte endothelial adhesion, and production of TNF, IL-1β, and IL-6 in rats.[99] Morphine hastened the progression of sepsis to septic shock in this group of rodents.[99]

Conversely, buprenorphine and opioid antag onists are beneficial in murine models of sepsis. Buprenorphine improved mean arterial blood pressure, pH, and base excess in endotoxemic rats and attenuated the development of fever after intrathecal injection of LPS in rats.[98,100] In pigs with *Escherichia coli*-induced sepsis, there was significant improvement in hemodynamic status when buprenorphine was administered.[101] Naltrexone reduced plasma TNF concentrations, improved microcirculation and reduced hepatic dysfunction in endotoxemic rats.[102] Additionally, administration of naltrexone protected mice from developing

LPS-induced shock by blunting TNF production.[103] The protective effect of naltrexone during endotoxemia was reversed when morphine was administered.[103] In human clinical trials, naloxone improved mean arterial blood pressure during septic shock.[104–106]

Evidence in humans

There is abundant evidence demonstrating the relationship between intravenous drug users (IVDU) and increased susceptibility to infectious disease.[57,107] Opioid exposure alone, in the absence of other confounding factors, markedly affects a wide variety of immune parameters in this population.[57,108] While a large percentage of infections in IVDU are associated with high-risk behaviors (eg, use of unsterilized needles) and lifestyle practices, IVDU also have an increased incidence of infections (eg, tuberculosis, pneumocystic pneumonia, systemic candidiasis) that cannot be attributed to high-risk behaviors alone.[57,108,109] Individuals that are infected with the human immunodeficiency virus (HIV) that are not IVDU have a lower frequency of infectious diseases and nonacquired immunodeficiency syndrome related deaths than HIV patients who are IVDU.[110]

Heroin users frequently develop lymphadenopathy, lymphocytopenia, hypergammaglobulinemia, and decreased monocyte adhesion and neutrophil function.[57,111] Additionally, IVDU develop opioid-induced endocrine and metabolic dysfunction.[112] Heroin, which activates the OP_3 receptor, attenuates the immune system and is thought to be a cofactor in the pathogenesis of HIV infection.[30,113–115]

Opioids have also been shown to affect the progression of disease in HIV infection. Opioids enhance immunodeficiency and increase the viral load in humans infected with HIV.[114,116–118] Cessation of IVDU in HIV-positive individuals resulted in a lower incidence of acquired immunodeficiency syndrome.[119] In vitro, morphine has been shown to promote production of HIV virus in lymphocytes.[114]

Healthy human volunteers exhibited a dose dependent reduction in NK cell activity 2 hours after receiving morphine at analgesic doses. This reduction in NK cell activity persisted for more than 24 hours.[79] Sacerdote et al[28] investigated the effect of morphine and tramadol in a group of human patients after abdominal tumor resection. Tramadol was shown to enhance NK cell activity while morphine suppressed lymphocyte proliferation in this population of patients. Opioids may also contribute to increased infection rates in hospitalized patients. For example, patients with mild-to-moderate burn injuries are more likely to develop infectious complications when treated with opioids.[120] In another study, men that underwent radical prostatectomy surgery were given either systemic opioids or epidural analgesia for pain control. Patients who had an epidural anesthesia were 57% less likely to have tumor reoccurrence when compared with those who received systemic morphine for pain control.[121] The authors speculated that the use of regional anesthesia reduces the neuroendocrine stress response to surgery, blocked the descending efferent activation of the sympathetic nervous system, and reduced the amount of general anesthesia required (all of which contribute to immunosuppression).[121] Regional anesthesia also provides adequate pain relief and may obviate the need for postoperative opioids and the consequent adverse effects on immune function and tumor growth.[121]

Naloxone has been shown to improve mean arterial blood pressure during septic shock in rats and human patients. Authors of a meta-analysis evaluating the use of naloxone in septic shock in humans concluded that naloxone administration may have hemodynamic benefits.[104] In one study, continuous infusion of naloxone decreased mortality but this effect has not been confirmed in subsequent studies.[104–106,122,123] The use of naloxone in septic shock is still controversial.

Evidence in veterinary species

The effects of opioids on the immune system have primarily been studied in murine rodents. Opioid receptors are present in many species including dogs, cats, horses, cows, monkeys, and sheep.[124–127] There are few studies evaluating the effects of opioids on immunomodulation in other species. It is possible that other species will demonstrate the same response to opioids seen in murine and human models but more controlled studies need to be performed to establish the effects of opioids in other species.

The immunomodulatory properties of opioids have been evaluated in pigs and cats. Bearing in mind the limited evaluation, morphine appears to have similar immunomodulatory effects in pigs as it does in mice and humans. Administration of high-dose morphine (3.3 mg/kg) to pigs downregulates neutrophil and monocyte activity.[128,129] Morphine also reduces T lymphocyte and NK cell activity in pigs when administered before vaccination with the Bacille-Calmette-Guérin vaccine. This vaccine stimulates T lymphocyte proliferation in humans and mice and has the same effect in the pig.[46,79]

In cats, the impact of morphine administration and withdrawal on lentivirus-related disease progression has been evaluated.[130] Morphine-treated feline immunodeficiency virus (FIV)-positive cats did not experience increase incidence or severity of FIV-related diseases.[130] While this study did not demonstrate an opioid-related increase in susceptibility to FIV-related

diseases, the results should be interpreted with caution because of small sample size and large variation in viremia severity.

Clinical implications

Most opioids used in clinical practice affect the immune system to varying degrees. Many ICU patients are immunocompromised and it is important to select analgesic drugs carefully to avoid promoting further immunosuppression.[27] A healthy patient would likely tolerate immune modulations without clinically important consequences but there are situations (young, elderly, or immunocompromised patients) where the risks associated with opioid-related immunomodulation may be of clinical concern. In critically ill patients or patients with risk factors for immune dysfunction, opioids with minimal or no immunomodulatory properties (buprenorphine, hydromorphone, tramadol, oxycodone, and oxymorphone) may be more advantageous compared with opioids with known immunomodulatory properties (morphine, fentanyl, methadone, and codeine).

While the risks of immunosuppression with the use of opioids should be considered in the critical patient, the importance of adequate analgesia cannot be overstated. Untreated pain produces a generalized sympthathetic response, leading to tachycardia, increased cardiac output and peripheral vasoconstriction that may cause hypertension and contribute to hemodynamic instability in the critical patient.[131] In some cases, pain may cause a generalized vagal response consisting of bradycardia and systemic hypotension, which may produce end-organ damage as a result of poor perfusion.[132] Indeed, untreated pain alone may ultimately lead to immunosuppression.[133,134] Unfortunately, the ability of specific opioids to reverse pain-induced immunosuppression has not been assessed clinically. Because opioids are the most effective analgesic drugs available for treating pain, their use in the critical patient is still advocated when pain is recognized or suspected.

Multimodal analgesia, using a combination of different classes of analgesics is an important strategy to improve the efficacy of pain management. In addition, this approach has the potential to reduce the amount of opioids required for analgesia and thus may help minimize potential immunosuppressive effects associated with the use of opioids. However, it should be noted that many analgesic medications have been shown to alter immune responses so careful consideration of each medication selection is recommended.[135–138] *N*-methyl-D-aspartate antagonists, sodium channel blockers and nonsteroidal anti-inflammatory drugs have been used with great success in human and veterinary medicine to provide multimodal analgesia.[139,140] Neuraxial analgesia will also significantly reduce the amount of systemic opioids needed and should be utilized as often as possible when managing the critical patient. The use of multimodal analgesia in veterinary species has been reviewed elsewhere.[141–144]

While there is compelling evidence demonstrating the immunomodulatory effects of endogenous and exogenous opioids in animal models and humans, a consensus on the appropriate use of opioids in critical patients has not been reached. In light of the fact that there is little clinical evidence evaluating the impact of opioids on outcome, additional research is needed in the clinical veterinary patient population. In the meantime, patients should be treated for pain, using opioids when clinically appropriate. Opioids that cause minimal immunosuppression should be considered in favor of opioids that cause immunosuppression whenever possible.

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