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Opioid-induced immunosuppression: is it centrally mediated or peripherally mediated?

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Abstract

Opioid compounds are commonly used pain medications. However, their administration is associated with a number of side-effects. Among them, opioid-induced immunosuppression is a significant medical problem, which is evidenced by a strong association between the use of opioids and exacerbated infections, including AIDS. Research data have demonstrated the effects of opioids to be suppressive on phagocytic, natural killer (NK), B and T cells. However, these immunosuppressive effects may be mediated by mechanisms different from those for antinociceptive actions. This article reviews possible central and peripheral mechanisms of opioid-induced immunosuppression. To the extent that peripherally mediated immunosuppressive effects play a significant role in opioid-induced immunosuppression, novel peripheral opioid antagonists may have a therapeutic role in attenuating opioid-induced immunosuppression without affecting analgesia.

Keywords: Opioid; Immunosuppression; Centrally mediated; Peripherally mediated; Morphine; Naloxone; Naltrexone; Methylnaltrexone

1. Introduction

Opioid medications are widely used clinically for relieving pain and as antidiarrheals and antitussives. Opioid agonists consist of a group of natural, semisynthetic, or synthetic compounds acting on a series of receptors, such as μ-, κ-, and δ-receptors. Concomitant with the ability to relieve pain, these drugs can have adverse effects. Side-effects of opioid treatment include nausea, vomiting, respiratory suppression, fatigue, sweating, difficult micturition, constipation, psychomimetic disturbance, and dependence. Another less well understood adverse effect of opioids is immunosuppression. Although well described as a laboratory phenomenon in numerous animal experiments and clinical studies [1], its overall importance as an adverse effect of opioid use has not been fully appreciated by physicians. The exact mechanisms of action of opioid effects on immunomodulation are incompletely understood, but several studies have suggested that these immunomodulatory effects may be mediated via mechanisms different from those responsible for analgesia.

The introduction of an antagonist is a traditional element in the pharmacological proof of the receptor. Naloxone, naltrexone, and nalmephene are clinically prescribed opioid antagonists. These non-selective opioid receptor antagonists block both central analgesia and adverse effects of opioid medications, and therefore cannot discriminate between the analgesic and immunological effects. The recent development of peripheral opioid antagonists may permit greater understanding of the mechanisms of immunosuppression and be therapeutically relevant. Selective opioid antagonists have a potential for blocking undesired side-effects of opioids predominantly mediated by peripherally located receptors, while preserving beneficial analgesic effects [2,3]. This article reviews studies of possible sites of action of opioid-induced immunosuppression. If peripheral mechanisms do indeed play a significant role in opioid-induced immunosuppression, peripheral opioid antagonists may have a therapeutic role in clinical medicine.

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Abbreviations: NK cell, natural killer cell; PAG, periaqueductal gray matter; HPA axis, hypothalamic–pituitary–adrenal axis.

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2. Opioid-induced immunosuppression

Animal and human studies have shown that opioids have profound effects on the immune system, a drug-induced immunological compromise. Increased rates of infection in animals treated with opioids [4–6], as well as among heroin addicts [7–9], have been demonstrated. Narcotic addicts are reported to have a markedly increased incidence of viral hepatitis, bacterial pneumonias, endocarditis, tuberculosis, and soft tissue and CNS infections [7,8,10,11], although confounding variables, such as nutrition and access to care, may make such correlations inexact.

Several studies in healthy normal individuals exposed to opioids have demonstrated the effect of opioids on immunomodulatory function [12,13]. Hamra and Yaksh [14] observed that morphine inhibited lymphocyte proliferation, decreased splenic lymphocyte number, and altered phenotypic expression of cell surface markers. Perhaps more importantly, chronically exposed individuals showed a series of changes in their ability to respond to immunological challenges. Narcotic addicts, patients, and animals receiving opioids exhibit abnormalities in many immunological parameters including decreased NK cell cytolytic activity, blood lymphocyte proliferation responses to mitogen, and alterations in more complex immune responses including antibody-dependent cell-mediated cytotoxicity [15–17] and antibody production [18–20]. Opioids also have suppressive effects on hematopoietic cell development, resulting in atrophy of both the thymus and the spleen [21–23], and reduced numbers of macrophages and B cells in the murine spleen [24].

Bayer *et al*. [25] showed *in vivo* inhibition of lymphocyte proliferation by morphine, and this inhibition was completely antagonized by naltrexone pretreatment, suggesting involvement of opioid receptors. In a well-known study, Yeager *et al*. [26] observed that morphine administered intravenously inhibited NK cell cytotoxicity in volunteers. However, a subsequent study in healthy subjects after fentanyl administration yielded a different conclusion [27]. These divergent results lead one to question whether the response to morphine is compound specific or if the treatment regimen can be generalized to other opioids.

A recent observation provides a possible mechanism for opioid-induced immunosuppression. Apoptosis (cell death) of immune cells is accelerated by directly inducing Fas (a death receptor) expression [28]. In a subsequent study of cells exposed to clinically relevant opioid doses, Yin *et al*. observed that stress modulated the immune system through CD95 (Fas/APO-1)-medicated apoptosis dependent on endogenous opioids. These investigators showed that chronically stressed mice exhibited a significant reduction in splenocytes, a process likely mediated by apoptosis, and an increase in CD95 expression. These stress-induced changes in lymphocyte number and CD95 expression could be blocked by naloxone or naltrexone [29]. In addition, the reduction of splenocytes that they observed seemed to be independent of the HPA axis, since both adrenalectomized and sham-operated mice exhibited similar responses to chronic stress.

The immunosuppressive characteristics of opioids have come into greater focus with the increase in patients with AIDS. A large number of HIV-1-infected individuals are drug abusers [30], and data show that there is a correlation between drug abuse and HIV infection [31,32]. Morphine promotes the growth of HIV-1 in human peripheral blood mononuclear cell cultures [33,34]. Although the mechanism of increased HIV load in addicts is unclear, a recent study suggests a direct effect of opioids on CCR5 turnover. Li *et al*. [35] demonstrated that methadone in clinically relevant doses significantly enhances HIV infection of macrophages with the up-regulation of expression of CCR5, a primary co-receptor for macrophage-tropic HIV entry into macrophages. The relationship between opioid binding and CCR5 regulation remains to be further elucidated.

3. Is opioid-induced immunosuppression centrally mediated?

Although a peripheral effect of opioids on lymphocyte regulation and HIV uptake is likely, there is evidence that some elements of opioid-induced immunosuppression may be centrally mediated. An early study in rats demonstrated that a very low dose of morphine (20 or 40 μg) injected into the lateral ventricle suppresses NK cell activity, and this effect is blocked by naltrexone, a non-selective opioid antagonist [36]. Hernandez *et al*. [37] further examined whether the immunosuppressive effect of morphine is mediated by opioid receptors located at either peripheral or central sites. First, the effects of systemic morphine administration on analgesia, mitogen-stimulated lymphocyte proliferation, and corticosterone secretion were compared to those observed after the systemic administration of *N*-methylmorphine, a morphine analogue that does not cross the blood–brain barrier. In contrast to morphine, *N*-methylmorphine (20 mg/kg) did not show any effect on lymphocyte proliferation, plasma corticosterone concentrations, or analgesic responses. Second, the effects of morphine and *N*-methylmorphine after central administration were compared. With the microinjection of either morphine or *N*-methylmorphine into the third ventricle, blood lymphocyte responses were inhibited by 70%; plasma corticosterone concentrations were elevated significantly; and maximal analgesic responses were present at the same time. Interestingly, a dissociation of immunosuppressive effects with antinociceptive action was noted when morphine was injected into the anterior hypothalamus. Blood lymphocyte proliferation decreased 50%, without an analgesic effect or a significant increase in plasma corticosterone.

Several studies have attempted to identify the specific brain regions involved in opioid-induced immunoregula-

tion [38,39]. The PAG serves a variety of diverse autonomic functions and appears to be a candidate site for opioid action in the induction of immunosuppression. The PAG has been identified as a site of morphine-mediated naltrexone-sensitive suppression of rat splenic NK cell activity [39]. Opioid receptors and endogenous opioid peptides are present in the PAG, and endogenous opioids are released in the PAG during stress [40]. Further, microinjections of morphine into the PAG specifically result in a rapid suppression of NK cell activity, and prior systemic administration of naltrexone can block NK cell suppression. These findings demonstrate that opioid-induced suppression of NK cell function is mediated, at least in part, through opioid receptors in the PAG [39].

The immunosuppressive effects of acute morphine administration have been located to μ-opioid receptors in the mesencephalon PAG region [39,41]. Gomez-Flores and Weber [38] investigated the abilities of morphine and buprenorphine to influence immune function after central administration. Acute administration of morphine showed significant decreases in NK cell cytotoxic activity, T lymphocyte proliferative responses to various mitogens, and macrophage functions, which were associated with high glucocorticoid and catecholamine levels. However, buprenorphine, a partial opioid agonist, did not alter immune function and also failed to increase the peripheral production of plasma glucocorticoids and catecholamines. Morphine has been suggested to induce immunosuppression by mainly interacting with μ_2-opioid receptors [42], whereas buprenorphine has been observed to bind to μ_1- and κ-opioid receptors [43,44].

Although immune cells express μ-, δ-, and κ-receptors, which are functionally coupled with signal transductional mechanisms [45], evidence suggests that central μ-receptors play a role in immunomodulation, but neither δ- nor κ-opioid receptors are involved [46,47]. Schneider and Lysle [48] showed that intracerebroventricular administration of the μ-selective opioid agonist [D-Ala^2,*N*-MePhe^4,Gly^5-ol]-enkephalin (DAMGO) to rats increased the production by splenocytes of nitric oxide, a substance that may be linked to central immunomodulation, and this effect of DAMGO was blocked by prior methylnaltrexone injection. In contrast, intracerebroventricular administration of the κ-selective agonist (+)-(5α,7α,8β)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro [4,5] dec-8-yl] benzeneacetamide (U69,593) and the δ-selective agonist [D-Pen^2,D-Pen^5]-enkephalin (DPDPE) had no significant effect on the production of nitric oxide. Nowak *et al.* [49] also demonstrated that injection of SNC 80, a nonpeptidic δ-opioid receptor-selective agonist, in rats did not affect splenic NK cell activity. The notion that μ-opioid receptors within the CNS are responsible for the effect on immune function was further supported by another animal study, in which comparable results were obtained after administration of μ-, κ-, and δ-agonists to the ventricle [46]. Involvement of central μ-receptors in immunosuppression has also been observed in a recent study [50], in which rats received remifentanil, a pure μ-receptor agonist with a half-life of only several minutes. The animals showed immunosuppressive effects similar to those of other μ-receptor agonists.

While the immunological effects of opioids may be, at least in part, initiated centrally, there is evidence of a coordinated central and peripheral effect in mediating immunosuppression. Two possible pathways that have been implicated in the mediation of the immunomodulatory effects of morphine are (a) the HPA axis, and (b) the sympathetic nervous system. In this respect, signals from the CNS to the immune system are relayed primarily through the HPA axis or via sympathetic innervation of lymphoid organs. Thus, opioid action in the HPA axis through hypothalamic efferents or enhanced opioid activity in the PAG could cause an increase in peripheral sympathetic output [51], either of which could have an effect on NK cell activity [52]. The activation of the HPA axis results in the downstream production of glucocorticoids [53,54], which are immunosuppressives. On the other hand, activation of the sympathetic nervous system elicits the release of biologic amines, which have been demonstrated to suppress the immune system [55] by both a direct and secondary action on lymphocytes. While trying to reconcile these two hypotheses, it has been suggested that acute administration of opioids primarily alters peripheral immune function through the sympathetic nervous system, while chronic exposure to such compounds affects the immune system by activation of the HPA axis [47].

Investigators have utilized methylnaltrexone, a quaternary form of naltrexone that does not cross the brain–blood barrier, to separate central from peripheral effects. The compound was able to antagonize most of the immune alterations produced by systemic morphine injection when administered intracerebroventricularly, but failed to do so when administered subcutaneously in rats [56–58]. At first glance, this might be taken as proof that the CNS opioid receptors play an important role in the immune alterations by morphine. However, relatively low doses of methylnaltrexone were used in their *in vivo* studies, and receptor binding data showed that opioid receptor affinity of methylnaltrexone is approximately 20–100 times less than that of naltrexone [59,60]. In addition, small animals, such as rats and mice, demethylate methylnaltrexone over time as shown by the exhalation of $^{14}CO_2$ after the administration of [^{14}C-*methyl*]naltrexone methyl bromide [2].

4. Is opioid-induced immunosuppression peripherally mediated?

Although there is evidence for centrally mediated opioid immunosuppression, there are also studies demonstrating that immunological dysfunction is mediated directly by opioid receptors located on immune cells. Morphine was found to decrease phagocytic activity of macrophages in a

concentration-dependent manner, and naltrexone completely blocked the effects of morphine in both *in vivo* and *in vitro* paradigms [61]. Bone marrow cells from mice implanted with morphine pellets showed a significant decrease in their developing capacity from macrophage precursors into viable colonies in response to macrophage colony stimulating factor, and this effect was inhibited by naltrexone [62]. Also, addition of morphine or β-endorphin to precursor cells of macrophages had a similar effect, showing that morphine acted directly on the precursor cells. Bayer *et al*. [25] observed that morphine inhibited concanavalin A-induced proliferation of both whole blood and splenic lymphocytes, although this inhibitory effect on the proliferation of lymphocytes could not be attenuated by co-incubation with naltrexone. The recent development of μ-opioid receptor knockout mice has failed to reveal the mechanism of opioid-induced immunosuppression. Roy *et al*. [63] demonstrated that morphine reduction of splenic and thymic cell number and mitogen-induced proliferation were unaffected in the μ-opioid knockout mice, suggesting non-μ-opioid or non-opioid actions on binding sites of immune cells.

Thomas *et al*. [64] reported that, after *in vitro* exposure to morphine and its metabolites, a number of immunosuppressive effects were observed in immune cells obtained from both laboratory animals and humans. Taub *et al*. [65] and Eisenstein *et al*. [66] showed that morphine and κ-agonists (U50,488H and U69,593) inhibited antibody formation when added to mouse spleen cells *in vitro*, indicating that the effects of these compounds act directly on immune cells. Furthermore, *in vitro* application of DAMGO, DPDPE, or U69,593 to splenocyte cultures did not alter the production of nitric oxide by splenocytes significantly. Thus, it seems unlikely that the suppression observed is mediated via the HPA axis or the sympathetic nervous system. Guan *et al*. [67] examined the effect of U50,488H when added *in vitro* to T cell- or macrophage-enriched fractions of normal mouse spleens and found that the compound inhibited the activity of both of these cell types. Additionally, the suppressive effects of a κ-agonist were observed on the plaque-forming cell antibody response in rats, whether given *in vivo* or *in vitro* [68]. In contrast, there is evidence showing that by the inhibition of the expression of CXCR4, a chemokine receptor, a κ-agonist has a suppressive effect on HIV-1 entry into $CD4^+$ lymphocytes that is time-dependent [69] and concentration-dependent [70].

Altogether, while κ-receptors may be responsible for peripherally mediated immunosuppression, the contribution from μ- or δ-receptors remains to be determined. At present, two peripheral opioid antagonists, methylnaltrexone and ADL 8-2698 (Alvimopan), are under clinical investigation [2,71]. However, unlike methylnaltrexone, Alvimopan is only available in oral formulation without gut absorption. To the extent that the immunosuppression is peripherally mediated, parenterally administered peripheral opioid antagonists, such as methylnaltrexone [72], may have a therapeutic role in reducing or eliminating the opioid immunosuppressive action without affecting analgesia.

5. Summary and future work

In addition to their widespread illicit use and their role in addiction, opioid medications are a mainstay of perioperative care and chronic pain management. It has become increasingly clear that many of the side-effects of opioids can be limiting factors of opioid use. While the focus has been on clinically apparent side-effects, such as respiratory suppression and constipation, immunosuppression may be even more problematic, particularly in targeted populations. Evidence indicates that a close relationship exists between the use of opioids and immunological responses and infections, including HIV. The maintenance of immunological competence in the surgical population is a special challenge for medical professionals. Although numerous studies have demonstrated the effects of opioids to be suppressive on phagocytic, NK, B and T cells in both animals and humans, the problem is complex as the site of action of the immunosuppressive effects of opioids remains controversial. The weight of evidence suggests that opioids can act within the CNS and alter immunological competency. Understanding the immunosuppressive effect of opioids is complicated by differences among organ systems, specific testing compounds, the precise experimental conditions, and differences of effect among species. Currently, the precise mechanism by which opioids modulate the immune response is incompletely understood. Important new tools may permit a more complete understanding of the anatomic and pharmacological targets of these immunomodulators. Such an important effect merits further study. If peripherally mediated immunosuppressive effects play a significant role in opioid-induced immunosuppression, the use of selective peripheral opioid antagonists in humans could potentially attenuate opioid-induced immunosuppression while preserving the beneficial analgesic effect.

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