MINIREVIEW

The Relevance of Opioids and Opioid Receptors on Immunocompetence and Immune Homeostasis[1] (44056)

DANIEL J. J. CARR,*,[2] THOMAS J. ROGERS,† AND RICHARD J. WEBER‡

Department of Microbiology, Immunology, and Pharmacology, LSU Stanley S. Scott and Neuroscience Centers, LSU Medical Center, New Orleans, Louisiana 70112-1393; Department of Microbiology & Immunology,† Temple University, Philadelphia, Pennsylvania 19140; and Department of Immunopharmacology and Microbiology,‡ University of Illinois College of Medicine at Peoria, Peoria, Illinois 61656*

Abstract. **Since the previous review on the role of opioids in the immune system, numerous investigative teams have contributed to the growing pool of information illustrating the tangible relationship between opioids and immune function, particularly as this association pertains to bacterial and viral pathogens. In addition, the recent cloning of both neural- and immune-derived opioid receptors will ultimately facilitate the identification of molecular events that are responsible for the immunomodulatory effects that are mediated by receptor ligation. Specifically, the administration of opioids *in vivo* can potentially affect the immune system either through direct interaction with receptors on the effector cells or indirectly, through the ligation of receptors found within the central nervous system. This indirect routing is hypothesized to involve secondary pathways including the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system ultimately resulting in immunomodulation. Consequently, a portion of this review addresses the recent data on leukocyte-derived opioid receptors and the potential immunoregulatory role relative to opioid receptors found within the central nervous system. In addition, recent observations on the effects of opioids and immunocompetence is reviewed from both a molecular and cellular perspective. Finally, the consequence of opioid exposure on the competence of the host immune system to microbial pathogens is summarized.**

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Direct and Indirect Effects of Opioids on Immune Function

Evidence for the existence of opioid receptor expression on cells of the immune system stemmed from the observations showing leukocytes could respond specifically to opioid ligands (1). Since these initial observations, the significance of opioid receptor expression on leukocytes has been under intense investigation. The direct effects of opioids on cells of the immune system have most recently been studied measuring macrophage activation and antibody production. Specifically, the prototypic μ agonist morphine and μ-selective agonist [D-Ala^2, MePhe^4, Gly-ol^5]enkephalin (DAMGO), κ-selective agonist U50,488, and δ-selective agonist [D-Pen^{2,5}]enkephalin (DPDPE) have been shown to suppress peritoneal phagocytosis of *Candida albicans* through selective opioid antagonist-reversible mechanisms (2, 3). Granulocyte chemotaxis or phagocytosis has also been shown to be suppressed in the presence of morphine

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[2] To whom requests for reprints should be addressed at Department of Microbiology, Immunology, and Parasitology, Box P6-1, LSU Medical Center, 1901 Perdido Street, New Orleans, LA 70112-1393.

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(4, 5). Conversely, other results show that the endogenous opioid peptides dynorphin A, [met]- and [leu]-enkephalin, and β-endorphin enhance macrophage activation measuring tumoricidal activity, and the augmentation is antagonized by naloxone (6). Since the parameters measured are distinct, it is difficult to speculate as to why the discrepancies exist.

Opioids have also been shown to suppress antibody production. The original observations showing the κ agonists (U50,488 and U69,593) inhibited antibody production *in vitro* (7) could be mimicked by pretreating either T lymphocytes or macrophages with U50,488 prior to the *in vitro* plaque-forming assays (8). The inhibition could be blocked with naloxone, suggesting the direct effect of the agonist on the lymphocyte or macrophage. Similar to the *in vitro* effects of κ agonists, the administration of the κ agonist MR2034 *in vivo* has been shown to suppress the antibody response to sheep red blood cells *in vitro* (9, 10). Moreover, this effect was antagonized by peripheral administration of quaternary naltrexone, a compound that does not readily cross the blood-brain barrier (11). The effects of opioids on humoral immunity may be related to the modification to cytokine specific synthesis by T cells and macrophages following stimulation (12–15). The T-dependent nature of opioid-induced suppression of humoral immunity is supported by data showing the active stereoisomer of morphine ([−]morphine) has no effect on the humoral immune response to the T-independent antigen TNP-ficoll (16). Similarly, morphine has been shown to suppress the primary but not the secondary humoral immune response to cholera toxin in mice (17). These results are relevant in light of efforts to stimulate protective mucosal immune responses in AIDS vaccine recipients, a fraction of whom are heroin abusers.

The production of opioid peptides by leukocytes during inflammation (18, 19) and the existence of opioid receptors on cells of the immune system seem to have a physiological consequence relative to antinociception (20, 21). The production of endogenous opioids may also contribute to autoimmune phenomena, which may develop as a part of the inflammatory response (22, 23). However, there does appear to be a mechanism in place to rapidly remove locally produced opioid peptides *via* aminopeptidases and ectopeptidases (24–26) which would considerably reduce the potential for pathological manifestations associated with the local production.

A considerable amount of evidence suggests that opioids administered *in vivo* modify the immune system indirectly. The HPA axis has been implicated in morphine-mediated suppression of primary humoral immune responses (27), Kuppfer cell and splenic macrophage phagocytosis of sheep red blood cells (28), thymic hypoplasia (29), phorbol myristate acetate-stimulated increase in $CD25^+$ expression on $CD4^+$ T lymphocytes (30), and splenic natural killer (NK) activity (31). Morphine has also been shown to activate adrenergic processes in suppression of splenic NK activity (32, 33) and mitogen-induced splenocyte proliferation (34). Using opioid receptor agonists administered intraventricularly, the μ-selective ligand DAMGO but not the δ-selective agonist DPDPE or the κ-selective agonist U50,488 was found to suppress splenic NK activity through a naltrexone-sensitive pathway (35). Other recent studies also suggest morphine-mediated effects on the immune system operate through central processes (36–38). However, there is an indication that the HPA axis is not necessarily involved in all opioid-mediated immunosuppressive effects since microinjection of opioid compounds into specific sites of the brain that result in a suppressive effect on immune function (e.g., lymphocyte proliferation or splenic NK activity) do not change the circulating levels of corticosterone (35, 36). The immunosuppressive effects of opioid agonists may be mediated through the central nervous system, however this does not preclude a role for direct *in vivo* effects of opioids on cells of the immune system. The overall effect of *in vivo* administration of opioids may be suppression due to central actions which override direct peripheral actions.

Collectively, these results provide convincing evidence for the local and systemic activity of opioids on immunocompetence and immune homeostasis. Definitive proof of the existence of opioid receptors on cells of the immune system has recently been provided through the cloning of these receptors. The fact that the receptors cloned from leukocytes are highly homologous with those identified in neural tissue substantiates the previous studies showing biochemical and pharmacological evidence for opioid receptors on cells of the immune system (39).

Molecular Characterization of Leukocyte Opioid Receptors

Each of the major opioid receptor classes have now been cloned from neuronal cells and fully sequenced. These proteins are seven-transmembrane receptors and share homology with the somatostatin receptor (40). Analysis of the δ-opioid (41, 42), κ-opioid (43–47), and μ-opioid (48, 49) sequences show a high degree of amino acid homology among the opioid receptors. Northern blot analysis has shown that the δ-opioid receptor mRNA varies in size between 1.4 and 9 kb (41). In a similar fashion, the κ-opioid receptor mRNA isolated from brain tissue is quite large (5.2–6.0 kb) (43, 47), as is the μ-opioid mRNA (>10

kb) (50). The large size of these transcripts is due to a long 3′ untranslated region in each case.

The genomic organization of the opioid receptors is now being clarified. Both the μ- and δ-opioid receptors appear to possess three exons with multiple transcription initiation sites identified (51, 52). The κ-opioid receptor was first reported to be composed of three exons (53), however, more recent reports have clearly established the existence of an additional exon 5′ of the exon containing the translation start site (54–56).

In the course of the examination of cDNA clones while involved in the cloning of the μ-, κ-, and δ-opioid receptors, several investigators have cloned and sequenced an opioid-like receptor which fails to bind to the opioid agonists commonly employed to characterize the classical opioid receptors (57, 58). This receptor possesses homology with the other opioid receptors and was originally termed the "orphan" opioid receptor. More recently the natural ligand for this receptor was identified as a heptadecapeptide which resembles dynorphin A and has been termed nociceptin (59, 60). The genomic structure of the nociceptin receptor is organized into three exons, and the translated sequence is approximately the same size as the cloned opioid receptors (53).

Efforts have recently been made to examine the molecular structure of the opioid receptors expressed by cells of the immune system. The evidence reviewed above suggested that the opioid receptors expressed in these cells may possess unique features. A partial sequence for the δ-opioid receptor was recently obtained by reverse transcription–polymerase chain reaction (RT-PCR) from monkey lymphocytes (61). Examination of the partial sequence of this receptor revealed essentially complete identity with the brain δ-opioid receptor. A partial sequence for the μ-opioid receptor has also been reported for rat peritoneal macrophages (62) and monkey lymphocytes (63). Here again, the sequence is essentially identical to the brain μ-opioid receptor. And, finally, a partial κ-opioid receptor sequence has been obtained from human and monkey lymphocytes (64). The results from each of these studies strongly support the presence of classical opioid receptors expressed by cells of the immune system.

A recent study (56) represents the first report of a complete opioid receptor expressed by cells of the immune system. These investigators employed the immature T cell lymphoma cell line R1.1 as a source of mRNA for RT-PCR analysis and identified the presence of the κ-opioid receptor sequence (Fig. 1). This cell line has been shown previously to possess typical κ-opioid receptors based on pharmacological analyses (65–67).

RT-PCR was performed with RNA from the R1.1 cell line using several oligonucleotide pairs permitting analysis of the full-length sequence, as well as the sequence of individual regions of the open reading frame. Analysis of overlapping RT-PCR fragments and the full-length product revealed a surprising degree of heterogeneity at the 5′ end of the coding region. Nucleotide sequences of multiple clones of the PCR products from the R1.1 thymoma cells were determined, and assembly of the individual overlapping PCR products and the sequence of multiple full-length clones confirmed the heterogeneity in the region of the κ-opioid receptor near the start codon. Clones were observed with a sequence which is essentially identical (99.8% nucleotide homology; 100% amino acid homology) to that of the reported murine brain κ-opioid receptor (43). Clones were also identified with a 30-bp insertion 15 bp upstream of the initiation codon. This 30-bp insertion is present in the cDNA of the rat brain κ-opioid receptor (44).

The presence of the 30-bp insertion in the 5′-noncoding region were somewhat surprising given the initial reports of the genomic structure of the mouse μ-, κ-, and δ-opioid receptors (51–53). Within the coding regions, there are two introns in the δ and κ receptors and three introns in the μ receptor. The 30-bp insertion suggested alternative intron-exon splice variation which could only occur if an additional exon 5′ of the exon containing an upstream transcription initiation site is present in the genomic sequence. More recent reports have clearly identified the sequence of this fourth exon in the κ-opioid receptor (53).

These results suggest that multiple κ-opioid receptor mRNA species are present in the R1.1 cell line, and either the κ-receptor or the cell population may be unique in this regard. The impact of these inserted sequences in the 5′-noncoding region on expression of the κ-opioid receptor remains uncertain at this time. Additional analyses of other cell lines as well as primary cells to determine whether any differences are seen in the sequences of the opioid receptors of these cells may provide more information on the interaction seen between the brain and immune system.

Further analysis of the R1.1 cell line has resulted in the identification of an additional intron-exon splice variant (Belkowski S, Alicea C, Zhu J, Liu-Chen L-Y, Eisenstein T, Adler M, Rogers T, *submitted for publication*). This splice variant fails to utilize any part of the second exon for the mature transcript. This alternate splice variant was detected in the R1.1 cell line as well as primary macrophages and brain tissue. The level of expression of this truncated transcript relative to the full length transcript appears to vary among tissues. The primary macrophages appear to express predominantly the truncated transcript, while the brain expresses primarily the full-length transcript. These splice variants may provide a source of protein hetero-

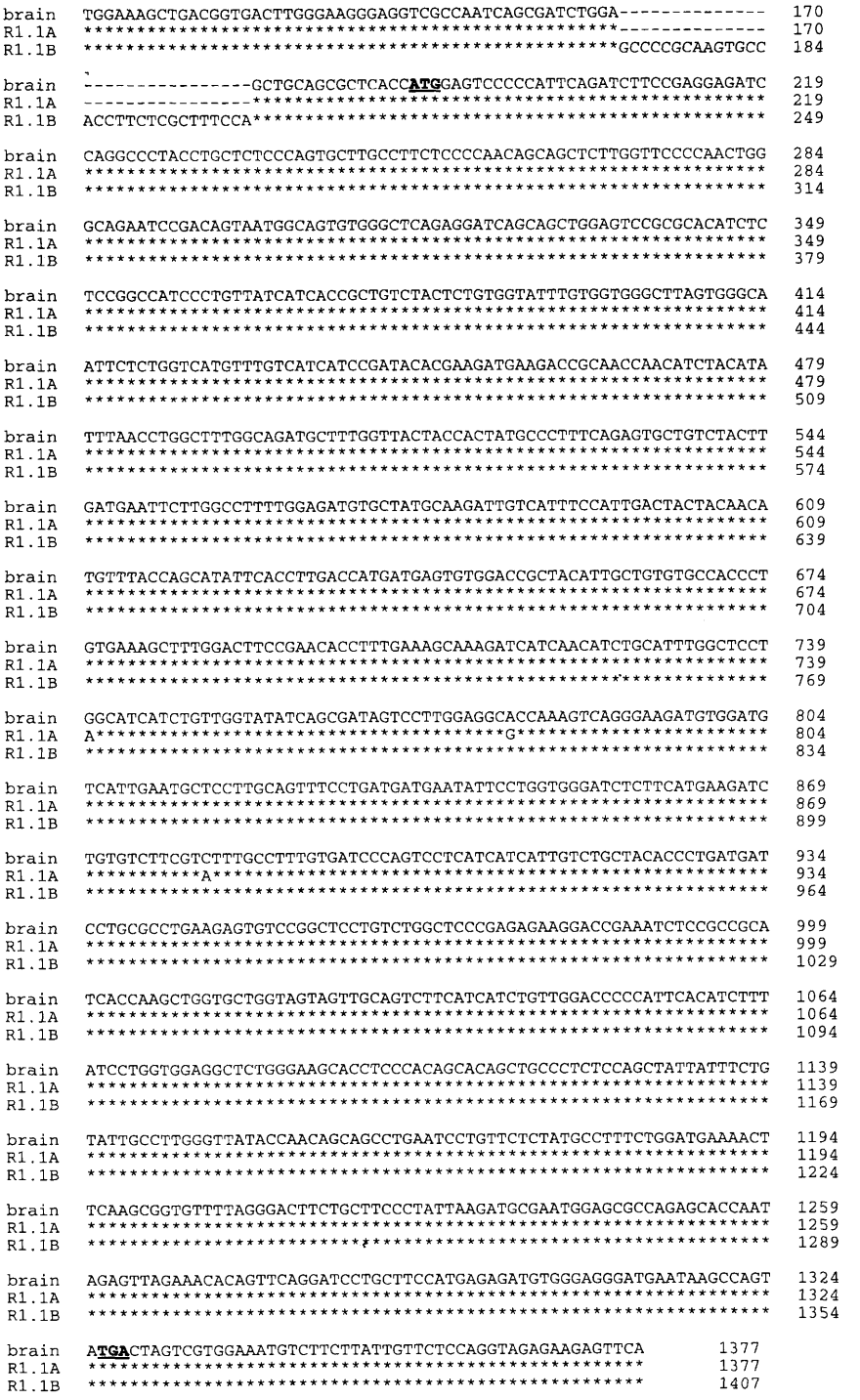

Figure 1. Comparison of κ-opioid receptor sequences for R1.1 cDNA with the cDNA of brain cells. Nucleic acids which are identical to brain κ-opioid receptor are indicated by asterisks. The sequence numbering of Yasuda *et al.* (43) is used for the brain cDNA sequence. The R1.1A sequence is 98% homologous to the brain sequence. The R1.1B sequence contains 30 bp in the region 5′ of the ATG translational start codon. (Reprinted with permission of the authors and the publisher [56].)

geneity and may provide the basis for some of the unusual binding properties by the immune cells.

The nociceptin (or orphan opioid) receptor has also been cloned by RT-PCR from mouse T cells (Fig. 2) (68). In comparison to previously characterized orphan opioid receptor cloned from rodent brain cDNA libraries (57), the lymphocyte orphan opioid receptor has 100% homology. Interestingly, a splice variant of the 1.5-kb lymphocyte opioid receptor (missing 15 bases between 378 and 392) was also identified in the brain receptor. However, the splice variant occurs in 45%–50% of the orphan opioid receptor species in lymphocytes whereas the variant occurs in only 25%–30% of the receptor species in brain. This alternative splicing may have important implications in intracellular signalling cascades since the missing amino acids constituting that portion of the first intracellular loop of the receptor may constitute a portion of tyrosine antigen recognition activation motif (68). An additional splice variant in this receptor has been identified in rat

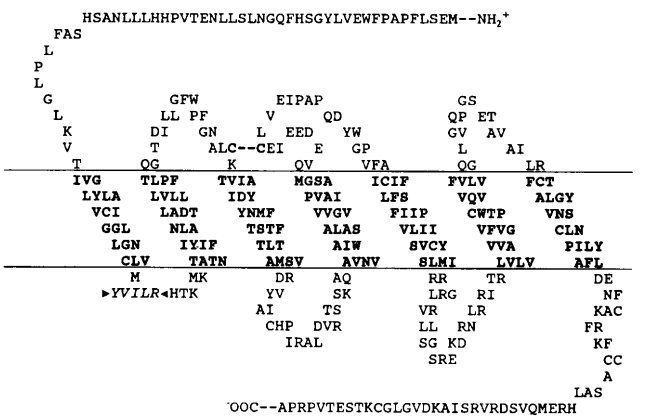

Figure 2. Proposed secondary structure of the lymphocyte orphan opioid receptor. Tyr^{71}-Arg^{75} are shown in a different font to indicate that they may be absent in some orphan opioid receptors due to alternative splicing of mRNA. Cys^{120}-Cys^{198} shown in bold-faced type, are thought to form a disulfide bridge by which the first and second extracellular loops of the orphan opioid receptor are covalently bound.

brain (49). In this case the alteration would be expected to yield a change in the third extracellular loop. The impact of these changes in the receptor sequence on the binding or signaling properties remains to be determined.

To explore the potential biological significance of the lymphocyte orphan opioid receptor, antisense experiments were carried out measuring *in vitro* polyclonal antibody production, lymphocyte proliferation, the generation of cytotoxic T lymphocytes (CTLs) in one-way mixed lymphocyte cultures, and IL-6 production by activated macrophages. Preliminary results show selective effects on the immune parameters measured (Table I). Specifically, orphan opioid receptor antisense oligonucleotides suppressed lipopolysaccharide (LPS)-induced lymphocyte proliferation and polyclonal IgM production (Table I) (68) but there was no observable effect on the generation of CTLs or LPS-elicited IL-6 production by macrophages (Table I). Given the recent identification of an endogenous ligand for the orphan opioid receptor (59, 60) termed nociceptin (59) which elicits a state of hyperalgesia, future studies on the role of this receptor (which is upregulated following mitogen-induced activation of lymphocytes [68]) in the immune system seem warranted.

The use of the recombinant opioid receptors expressed in transfected cell lines has permitted a more precise examination of the binding properties of the cloned receptor classes. In each case, however, the pattern of agonist and antagonist sensitivity is consistent with the established pharmacological behavior of these receptors (40). The availability of these transfected cells should permit a more extensive analysis of the signal transduction mechanisms following receptor activation.

The Relationship between Opioids and Infection

The concept that opioids have a significant biological role in modifying the immune system, thus predisposing opioid users (e.g., heroin addicts) to infectious pathogens, was not originally considered by physicians treating heroin addicts that presented with bacterial, protozoan, and viral infections in the early observations reported in the middle of this century (69–71). In fact, the increased incidence of infection was attributed to nonsterile needle use during the administration of the drug. Other studies noted that heroin addicts had immunologic abnormalities that may in part be due to the impurities in the acquired heroin or the result of the infection itself (72, 73). Currently, there is an active discussion as to the direct role of opioid exposure on acquiring infectious pathogens. Accordingly, this section reviews those studies that have used pharmacologically controlled conditions to evaluate opioid exposure and infection caused by microbial pathogens.

The immunosuppressive qualities of opioid alkaloids on phagocytosis by macrophages and neutrophils as well as antigen-specific antibody production by B

Table I. Orphan Opioid Receptor Antisense Oligonucleotide Effects on Selected Immune Parameters[a]

Immune parameter tested	Concentration range of antisense oligo (μg/ml)	Effect
CTL generation[b]	0.5–5.0	No effect
IL-6 production[c]	1.0	No effect
Lymphocyte proliferation[d]	1.0	50% suppression
Polyclonal antibody production[e]	1.0–5.0	50–70% suppression

[a] Antisense oligonucleotide was prepared against the 5′ untranslated region of the lymphocyte orphan with the sequence 5′-AGCCACTCAGTACAGTTC-3′. As a control, a scrambled sequence of the orphan opioid receptor was generated as well (i.e., 5′-ATCCCTTAATCGCGCAAG-3′). The antisense and scrambled oligonucleotides were administered to cultures *in vitro* at the time of culture or up to 24-hr prior to the activation of cells.
[b] A one-way mixed lymphocyte reaction was initiated using 6×10^6 C57BL/6 ($H\text{-}2^b$ haplotype) splenic lymphocytes and 4×6^6 DBA/2 ($H\text{-}2^d$ haplotype) irradiated (900 rads) splenic lymphocytes in 2 ml of media. The oligonucleotides were added at the initiation of culture. Following a 5-day incubation period, the cells were harvested and assayed for CTL activity using P815 ($H\text{-}2^d$ haplotype) in a 4-hr ^{51}Cr-release microcytoxicity assay.
[c] Peritoneal macrophages were cultured for 18–24 hr and 1.0 μg/ml of oligonucleotide along with LPS was added. Following an 18-hr incubation period, supernates were collected and assayed for IL-6 production by ELISA. In some experiments, the oligonucleotides were incubated with the cells for 24 hr prior to the addition of the stimulus (LPS).
[d,e] See Ref. 68 for details.

lymphocytes (plasma cells) would logically lead one to predict that these drugs would have detrimental effects on the capacity of immune cells to clear bacterial and fungal infections. To this end, one study has found that resident peritoneal macrophages obtained from morphine pellet (75 mg)–treated mice have a significantly reduced phagocytic index capacity against *C. albicans* as measured *in vitro* (2). These results support earlier work showing that *C. albicans*–infected mice that were subsequently exposed to morphine (25 mg/kg, sc) 3, 24, and 48 hr postinfection succumbed to the infection more rapidly and in greater numbers (74). Interestingly, naltrexone pellet (30 mg) implantation in mice blocked the morphine-mediated suppression of the phagocytic index to *C. albicans* (2) (suggesting the event was mediated through opioid receptors) whereas the administration of naloxone (1–4 mg/kg/day) had no effect on the mean survival time of morphine-treated mice infected with the pathogen (74). The discrepancy may be due to the amount of opioid antagonist employed, the form (pellet versus multiple injections) of morphine and opioid antagonist exposure, and the potency of the opioid antagonist. The immunosuppressive effect or morphine exposure *in vivo* on the phagocytosis and killing properties of macrophages and neutrophils measuring *C. albicans* may be time dependent, since a recent report has shown an initial rise (20 min post morphine administration) and subsequent reduction (24 hr post morphine administration) in the killing capacity of peritoneal leukocytes on *C. albicans* organisms following an acute administration of morphine (20 mg/kg, sc) but not methadone (12.5 mg/kg, sc) administration (75). Transient changes in the killing capacity of polymorphonuclear cells measuring *C. albicans* blastospores have also been noted in morphine-treated (3–5 mg/kg, three times/day) rhesus monkeys (4).

Opioid influences on the incidence of viral infections in iv drug users has been well documented (76, 77). However, the polydrug use of the patient population as well as personal hygiene, adulterous drugs, and sharing of needles have all been considered in the explanation of the prevalence to viral infections in the iv drug-use population (77). One of the earliest laboratory controlled studies showed that morphine pellet (50 mg) implantation of mice resulted in an increased incidence of encephalomyocarditis virus-induced death (78). The diminished resistance to the viral infection closely paralleled the suppression in viral-induced interferon production as well. Using Friend murine leukemia virus, another study showed that a single bolus of morphine (300 mg/kg, ip) given to the virally infected mice substantially increased the mortality (100%) whereas a chronic dosing regimen (10–100 mg/kg, ip) for 10 days (including a state of tolerance) prior to virus infection had no effect on the mortality incidence (79). In another study with this virus, it was found that the increased incidence of mortality mediated by a single bolus of morphine (200 mg/kg, ip) was antagonized by the administration with naloxone (20 or 100 mg/kg, ip) at the time of or 5 min prior to morphine exposure (80). In this same study, it was also noted that chronic administration of morphine (50 mg/kg day over 9–21 days) had no effect on the mortality of mice infected with Friend virus even though there was a marked decline in spleen weight and a decrease in splenic viral titers. Although measurements on cell-mediated immune parameters (e.g., interferon production and NK and CTL levels) were not measured in this system, it would seem that these functions may not have been affected by the chronic administration of morphine. However, in another study assessing the effects of chronic morphine (50 mg/kg/day for 21 days, sc) administration on viral-induced death and modification of cell-mediated immunity, it was found that morphine exacerbated the encephalitic incidence of herpes simplex virus type 1 (HSV-1)–infected C3H/HeN mice (81). Likewise, chronic morphine exposure significantly suppressed the generation of CTLs in alloimmunized C3H/HeN mice. This effect was blocked by the μ-selective antagonist β-funaltrexamine (82) but not the δ-selective antagonist naltrindole (83), indicating the μ-opioid receptor involvement in the suppression. Although there is a discrepancy as to the number of lymphocytes responding to alloantigen versus viral antigen, the effects of morphine on CTL generation may in part contribute to the deleterious effect of morphine on the immune response to HSV-1 infection.

In perhaps a more complete evaluation of immunocompetence under the duress of morphine tolerance, pigs immunized with bacterial and viral antigens were found to mount a humoral immune response to these antigens (84). However, the cell-mediated immune response as measured by delayed type hypersensitivity to 2,4 dinitrofluorbenozene was found to be diminished in the morphine-tolerant pigs. As a follow-up to this study, morphine tolerant pigs infected with swine herpes virus–1 and subsequently infected with *Pasteurella multocida* were found to display fewer neurologic signs and mortality associated with the encephalitis induced by the virus yet exhibit significantly greater viral-induced and secondary bacterial pneumonia (85). The protective effect against viral-induced encephalitis elicited by morphine is attributed to the anti-inflammatory action of the opioid on cell-mediated immunity, which would explain the reduction in neuropathology typically associated with encephalitis (85).

The relationship between opioid use and viral infection/pathogenesis is portrayed most effectively with the primary causative agent of acquired immune deficiency syndrome (AIDS), human immunodeficiency

virus type 1 (HIV-1). Given the high prevalence of HIV-1 infection among iv drug users and the ability of morphine to alter T lymphocyte and monocyte function, Peterson and colleagues investigated the *in vitro* effects of morphine of HIV-1 replication. Morphine was found to increase HIV-1 replication in human peripheral blood mononuclear cell (PBMC) HIV-1_{AT} PBMC co-cultures as measured by p24 supernatant levels in a dose-dependent and β-funaltrexamine (μ-opioid–selective antagonist)–sensitive fashion (86). Other investigators have made similar observations using heroin and measuring HIV-1 replication *via* syncytia formation in phytohemagglutinin-stimulated human PBMCs (87) and the monkey equivalent simian immunodeficiency virus (SIV) and measuring morphine modification of the cytopathic effects and RT activity in SIV-infected CEM × 174 cells (86).

Thirty to fifty percent of the HIV-1–infected patients will develop neurological impairments including multinucleated giant cell encephalitis and vacuolar myelopathy. Within the central nervous system, HIV-1 appears localized within the macrophages and microglia (for review, see Ref. 87). The entrance of HIV-1–infected monocytes into the brain has been predicted to be facilitated by secondary infections (e.g., bacterial or viral) that activate these monocytes into over expressing cytokines (TNF-α and IL-1β) and thus, allowing the cells to marginate and subsequently diapedis through the endothelial lining into the brain parenchyma and perivascular regions of the brain (87). Similar to in PBMCs, morphine has been found to amplify HIV-1 replication in chronically infected promonocytes (U1) co-cultured with human fetal brain cells (88). The mechanism of enhancement may involve TNF-α, since other studies by this group have shown that TNF-α production by microglia can enhance HIV-1 expression in the promonocytic clone U1 (89) and morphine can potentiate the production of TNF-α by LPS-stimulated microglial cells in a dose-dependent and naloxone/β-funaltrexamine–sensitive fashion (90). These results are consistent with earlier reports showing that TNF-α induces the expression of HIV-1 in chronically infected T-cell clones (91) and membrane bound TNF-α stimulates HIV-1 gene expression (92). The observations showing the promotion/reactivation of HIV-1 replication by morphine calls into question the potential role of the endogenous opioids including dynorphin, [met]-enkephalin, and endorphins. Recently, β-endorphin has been shown to augment the replication and enhance the transactivation of the promoter of a neurotropic strain of HIV-1 (HIV_{JR-FL}) in fetal perivascular microglia through a naloxone-sensitive manner (93). Since the pro-opiomelanocortin derived peptide is typically secreted by the corticotrophs of the anterior pituitary following stress-induced corticotropin releasing hormone secretion of the hypothalamus, these results have important implications into the health and stress-related management of HIV-1–infected patients. Moreover, the reports of endorphin production by macrophages (94) might also play a crucial role in the neuropathogenesis of HIV-1 infection in the brain.

Although the relationship between opioids and infectious pathogens is most clearly demonstrated using viruses, morphine has been shown to modify the host response to parasitic infections including *Toxoplasma gondii* (95) and *Plasmodium berghei* (96). Moreover, a recent communication suggested that morphine pellet implantation facilitated the dissemination of indigenous microbial flora (specifically *Proteus mirabilis*) into the peritoneal fluid, spleen, and liver 24–48 hr post implantation in a naltrexone reversible manner (97). In addition, morphine was also found to sensitize mice to LPS-induced endotoxic shock suggesting that morphine may act as a co-factor in gram-negative sepsis (97).

Summary

Our understanding of the impact of opioid compounds on the function of the immune system has expanded greatly over the past 5 years. It is now clear that several cell populations serve as targets for the effects of the opioids, and this includes T cells, macrophages, and NK cells. The mechanism(s) of immunomodulation are now being described in greater detail on both a cellular and biochemical level. Indeed, the finding that the production of lymphokines and cytokines may be altered following opioid treatment may be particularly important since all immune responses are dependent to some degree on the synthesis of these protein mediators.

The opioid receptors have now been successfully cloned from cells of the immune system. There is no longer serious doubt about the presence of opioid receptors expressed by these cell populations. Extremely valuable information regarding the role of the opioid receptors in the function of the cells of the immune system should be obtained using molecular methods. Clearly, the molecular basis for the effect of the opioid compounds on the immune response represents a critical area of research in the immediate years ahead.

It is not surprising that opioid compounds have been found to alter resistance to infectious agents, since a great deal of evidence shows that these compounds modulate the immune response. The significance of the drugs of abuse in the host-parasite interaction for a number of microorganisms, including HIV, remains a critical area for additional research. In addition, because of the importance of opportunistic infections in the AIDS patients, the impact of opioids on the resistance to these infectious agents is also a

matter of great concern. It is possible that combinations of certain drugs of abuse may serve to alter resistance to some, but not all, of these infectious diseases. In any case, answers to these questions will most certainly come only once a greater understanding of the basic mechanisms of immunomodulation is achieved.

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