Immunologic Effects of Opioids in the Presence or Absence of Pain

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Abstract
Opioids are acknowledged to suppress immune functions following both acute and chronic administration; however, there appear to be differences according to the schedule of administration as well as the state of the organism. For example, whereas a single dose of morphine in the absence of pain is well known to be immune suppressive, the biologic consequences of this suppression are largely unknown. Repeated and chronic opioid ingestion in the absence of pain appears to result in significant consequences including high infectious disease prevalence. On the other hand, in the presence of acute pain, there is evidence that opioid administration in analgesic doses is protective. Much less is known regarding the immune and disease implications related to chronic opioid treatment for chronic pain states.

Key Words
Natural killer cell, cancer, chronic, acute, infection

Introduction
Opioid administration is well known to affect immune function in many ways that are measurable; however, there remain several unknowns regarding this phenomenon. First, what is the biologic significance of such changes in immunity? Outcomes that can be assessed in humans are typically related to cell counts, changes from normal profiles of immune-to-immune cell communications (as in cytokine balance or the ability of cells to produce cytokines when stimulated in vitro), and functional assays such as natural killer cell activity and lymphocyte proliferation assays. The second major question relates to the organism receiving the opioid, whether or not it is experiencing pain and its related neuroendocrine and immune aberrations. The vast majority of studies exploring the impact of opioid administration on immune function employ the normal organism that is not experiencing pain or those undergoing chronic schedules of opioid administration; few have studied acute opioid administration in organisms experiencing pain states, and even fewer in chronic pain states. This article highlights these two issues in the context of opioid-induced changes in immune function.

Acute Opioid Administration and Immunity
It is a well-accepted adage that acute administration of opioid agonists is immune suppressive. Since the seminal reports by Shavit...
et al.," studies in animals have shown the prototypical opioid morphine to suppress natural killer cell activity (NKCA), inflammatory cytokine production, and mitogen-induced lymphocyte proliferation. The observed effects of systemically administered morphine also occur when the drug is injected intracerebroventricularly, suggesting that central opioid receptors are involved in these outcomes. The observed morphine-induced immunomodulatory effects are significantly attenuated or reversed by the pre- or co-administration of the opioid antagonist naltrexone.

An important consideration in the above-mentioned animal studies is the systemic morphine dose. Morphine doses have ranged from 5.0–10.0 mg/kg, considered to be within an analgesic range (up to 25–50 mg/kg). Morphine has been shown to exert immune suppression across this wide dosing range, and dose comparisons within study show a dose-response relationship such that increasing doses of morphine are associated with greater immune decrement.

Studies in animals also have shown that the acute administration of fentanyl is immune suppressive, but data are limited. Outcomes have included a decline in NKCA following doses of 0.3 mg/kg, which is within the anesthetic range; however, lower doses in the analgesic range of 0.04–0.06 mg/kg were not shown to suppress NKCA. On the other hand, analgesic doses of fentanyl have been shown to suppress lymphocyte proliferation.

The effects of acute opioid agonist administration on immunity have been much less studied in humans, but the results are consistent. Short-term exposure to morphine infusion at both low (0.015 mg/kg/hour) and high (0.03 mg/kg/hour) doses following respective loading doses of 0.025 or 0.05 mg/kg, resulted in significantly suppressed NKCA 2 hours after the initiation of the infusion. A single study of acute fentanyl infusion in humans tested a battery of immune measures at 1 and 24 hours after a 2 hour infusion of 1.2 µg/kg/hour following a 3 µg/kg initial dose. At one hour following the infusion initiation, no immune changes were observed; at 24 hours, NKCA was enhanced.

The above-mentioned studies show that there are statistical decrements in ex vivo (in vivo manipulations followed by in vitro assessment) immune functional measures in animals or humans given morphine. However, whether these statistical differences are predictive of changes in disease susceptibility or sensitization to a novel antigen has been shown in only a few animal studies. A single dose of morphine, 5 mg/kg, following the injection of Walker 256 carcinoma cells resulted in a naloxone-reversible increase in metastasis in rats. Lockwood et al. tested a range of morphine doses on in vivo antibody responses in an outbred versus an inbred rat strain, and showed dose-related differences in responses to the morphine within strain, as well as differing responses between strains, a complicated picture.

It was recently shown that whereas morphine exerted no effects on contact hypersensitivity responses when administered before the initial antigen exposure, when morphine was administered before antigen re-exposure, an enhanced inflammatory response was observed, likely via pro-inflammatory mediators interleukin (IL-6) and inducible nitric oxide synthase (iNOS).

Chronic Opioid Administration and Immunity

Studying the impact of chronic opioid administration has been motivated by observations that individuals addicted to opioid agonists suffer from immune suppression related illnesses. In animals, opioid administration is accomplished by either repeated injections over varying time periods or the implantation of a pellet, commonly used for studying the development of tolerance and dependence. It could be suggested that repeated injections model the experience of the individual addicted to opioids, with the oscillation of serum levels of the agonist.

Daily injections of large doses of morphine, 30–50 mg/kg, for 4 days significantly suppressed splenic NKCA; however, if injections continued for 14 days, NKCA was no different than that exhibited by control animals. More recently, repeated injections of morphine were shown to result in a naloxone-sensitive promotion of macrophage apoptosis in both rats and mice, an effect mediated by morphine-induced increases in macrophage mRNA expression of iNOS. A subsequent study in both
rats and mice showed that as few as 3 subcutaneous morphine injections (40 mg/kg) over 24 hours resulted in macrophage injury, and 11 morphine doses over 3 days resulted in a Gram-negative bacteremia as well as bacterial growth in peritoneal fluid, liver, spleen, kidneys, heart, and lungs. Similarly, administration of naloxone before each morphine dose blocked these effects. Subcutaneous implantation of morphine pellets in mice was shown to result in marked reductions in splenic and thymus weights within 48 hours of implantation as well as significant reductions in lymphocyte proliferative responses, all of which were attenuated by twice daily administration of the glucocorticoid antagonist RU-486 or by adrenalectomy. NKCA was also shown to be suppressed at 48 hours after morphine pellet implantation, and similar to acute morphine injection studies, the magnitude of NKCA suppression was greater as morphine content in the pellet increased. RU-486 treatment also attenuated the NK-suppressive effects of the morphine pellet. Not unlike the acute morphine injection studies, after both 4 and 7 days of exposure to the pellet, NKCA was not different from placebo, suggesting the development of tolerance to the NK-suppressive effects of morphine.

The in vivo companion to the earliest ex vivo morphine studies in rats showed that 4 daily injections of a high dose of morphine reduced survival following ascites tumor challenge, whether the tumor was injected before or after the series of morphine injections. Survival was not affected if the 14 daily morphine injections were administered prior to tumor injection; however, if the same daily morphine regimen was administered after the tumor, survival was reduced. These differences likely relate to the stressful nature of the early course of this high dose morphine administration regimen. In particular, such high doses of morphine, 30–50 mg/kg, produce substantial behavioral changes and are likely very stressful for the naïve animal. On the other hand, when the tumor was injected after 14 days of morphine injections, the animals were likely tolerant to these effects. The implantation of morphine pellets was shown to compromise in vivo lymphocyte proliferation assessed as the development of a delayed type hypersensitivity response and a graft-versus-host reaction in mice; simultaneous implantation of naltrexone pellets reversed both outcomes.

Two more recent in vivo studies relate to possible effects on resistance against infection in rats. First, oral ingestion of morphine over 42 days resulted in a decreased resistance against the Trichinella spiralis parasite. Second, following 3 days of exposure to 75 mg morphine pellets, rats mounted a significantly less vigorous pulmonary inflammatory response to rat-adapted influenza virus. Taken together, these studies support the suggestion that chronic morphine, whether via continuous or intermittent exposure, renders the host more susceptible to some types of infectious or malignant disease.

A single human study reported that total doses of 90–150 mg of oral morphine over 36–60 hours resulted in significant suppression of antibody dependent cellular cytotoxicity in comparisons of baseline versus 12 hours after the final morphine dose. Similar comparisons of NKCA yielded no statistically significant change. Acute Opioid Administration for Pain and Immune Function

A prominent focus of studies in both animals and humans examining immune function in the context of acute pain employ surgery as the painful stimulus. It is important to note that in and of itself, pain has been shown to be immune suppressive, and immune-altering factors released from tissue injury likely substantially contribute to the immune consequences of undergoing and recovering from surgery. The impact of surgery on immune function is well studied in both animals and humans. Animals recovering from experimental abdominal surgery have been shown to exhibit decreased lymphocyte and splenocyte proliferative responses to mitogens and NKCA, and more invasive surgery has been shown to be associated with greater decrements in immune function. Similar to studies in
animals, more invasive surgery has been associated with larger decrements in immune function outcomes.\textsuperscript{45,46} Studies comparing postoperative analgesia regimens in humans have largely shown systemic opioid administration to be associated with greater NKCA suppression compared to epidural anesthesia.\textsuperscript{47,48} and animal studies have shown morphine to be similarly suppressive of NKCA in the context of surgery.\textsuperscript{37,49} Patients undergoing surgery for both malignant and non-malignant disease who received low dose fentanyl anesthesia, 1–5 $\mu$g/kg, exhibited a more rapid recovery of NKCA compared to those receiving high doses of fentanyl, 75–100 $\mu$g/kg.\textsuperscript{50} In animals, perioperative fentanyl administration did not contribute to surgery-induced NK-suppression, and did not improve ex vivo NKCA.\textsuperscript{14} On the other hand, tramadol improved NKCA in unoperated as well as operated animals\textsuperscript{37} and was also shown to improve NKCA and lymphocyte proliferation in cancer patients after surgery.\textsuperscript{38} An important issue in interpreting the results of ex vivo NKCA is that this assay takes place in a neutral environment, away from the hormonal milieu of the whole organism. Only the changes in NKCA that persevere through the preparation and transition into the in vitro environment are reflected in the outcomes.

The employment of animal models of metastasis offers one avenue to further study the immune effects of opioid agonists in the organism experiencing pain. The advantages of such a model include the reflection of the rich hormonal milieu of the whole organism in the outcome; a suggestion of biologic relevance of the outcome; and strong evidence of the immune-mediated control of metastatic development, particularly NKCA. Briefly, evidence that NK cells control metastatic development includes studies showing that an absence of NKCA results in a many-fold increase in metastasis;\textsuperscript{51–54} reconstitution of NK cells restores metastatic resistance;\textsuperscript{54} and boosting NKCA above normal improves metastatic resistance.\textsuperscript{53}

Possible benefits of opioid agonist administration on surgery-induced decreases in metastatic resistance have been studied only in the past 12 years. Yeager and Colacchio first showed that morphine administration in the context of the intra-abdominal portal vein injection of a syngeneic colon tumor significantly reduced hepatic tumor load compared to animals not receiving perioperative morphine.\textsuperscript{55} In three separate studies, pre- and postoperative systemic morphine administration was shown to significantly attenuate abdominal surgery-induced decreases in resistance against the pulmonary metastasis of a syngeneic NK-sensitive mammary adenocarcinoma (MADB106) in Fisher 344 rats, including: 1) the development of tumor colonies on the lungs assessed 3 weeks after intravenous injection at 5 hours postoperative;\textsuperscript{56} 2) the lung retention of radiolabeled tumor cells assessed at 20 hours after intravenous injection at 4 hours postoperative;\textsuperscript{49} and 3) the lung retention of radiolabeled tumor cells related to pre- versus postoperative schedules of morphine administration.\textsuperscript{37} It is important to note that Gaspani et al. were unable to show morphine’s benefits using the same surgery and tumor injection schedule; however, there was a slight difference in the morphine regimen.\textsuperscript{37} Notably, in our efforts to establish an effective morphine regimen, we found that too little morphine exerted virtually no beneficial effects and too much resulted in tumor cell retention levels exceeding those observed in untreated surgery animals.\textsuperscript{57} Other opioids shown to provide protection against the metastatic-enhancing effects of surgery using the MADB106 tumor model include tramadol\textsuperscript{37} and fentanyl.\textsuperscript{14}

\textbf{Chronic Opioid Administration for Pain and Immunity}

A single human study described immune function in individuals experiencing pain of both nonmalignant and malignant origin both before and during 12 weeks of treatment using sustained release morphine tablets. At baseline and throughout morphine treatment, pain patients exhibited similar lymphocyte proliferation profiles compared to a healthy age- and sex-matched comparison group. Additionally, whereas stimulated blood production of IL-2 increased up to 5-fold in pain patients 4 weeks after treatment began; no such changes in IL-2 production were observed in the comparison group. Despite exhibiting normal circulating levels of immunoglobulins throughout, pain patients exhibited reduced in vitro production of
immunoglobulins both before therapy initiation and throughout.8

An intriguing in vivo study used a model of cancer-related pain producing significant hyperalgesia associated with melanoma tumor development following hind paw tumor injection in mice. Daily injections of morphine, 5 or 10 mg/kg, from day 16–21 post tumor inoculation inhibited primary tumor growth through post inoculation day 25, the day of tumor excision. Further, pre-excision morphine treatment significantly reduced the number of lung metastases evident at 14 days post tumor excision.59

Given the demonstrated role of the immune system, particularly that of NKCA,51,52,54 in the control of metastatic disease, this study is encouraging when considering opioid treatment for malignant pain.

Conclusions

The evidence seems to indicate that a single dose of morphine in the absence of a pain state can be immune suppressive; however, the consequences of this suppression are largely unknown, and likely relate to concurrent circumstances such as antigen exposure. On the other hand, the consequences of repeated, chronic ingestion of opioids in the absence of a pain state appear to be quite significant, including a high prevalence of infectious disease.

The immune effects of opioid administration in an organism experiencing pain are in need of more study; however, some suggestions are warranted in light of our current understanding of the issue. First, until rather recently, the assays employed to assess immune function in animals necessitated the removal of blood or organs for ex vivo measurement, in the absence of the rich in vivo hormonal milieu, such that only alterations that survived the processing emerged. The meaningfulness of changes from normal is not established. Second, despite the ability to document the NK sensitivity of the tumor models showing the benefits of providing opioid analgesia in pain states, only a portion of the metastatic process is modeled, for example, the MADB106 tumor is injected intravenously, reflecting a later aspect of the metastatic process when cells have already been released into the vascular beds. Third, and important theoretically, pain is a stressor well known to be immune suppressive and tumor-enhancing. If opioid administration reduces pain, and its associated allostatic load, then perhaps there can be some relief of the immune consequences of pain. Current in vivo evidence supports this hypothesis, with the caveat that the dosing and timing of the opioid may be key.

References


41. Pollock RE, Lotzova E, Stanford SD. Mechanism of surgical stress impairment of human perioperative