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# Opioid therapy and tumor progression

**Abstract**

It is well established that opioids help the organism to cope with environmental stress, tissue injury, pathogen invasion, inflammation, and tumor growth. Opioids elicit immunosupressive effects which may become benefitial in the context of chronic inflammation, however, it may be detremental in the context of tissue repair. These direct immunosuppressive effects of opioids would possibly facilitate tumor growth, however, in the context of pain and distress, which is known to promote tumor progression by a reduction in NK cell cytotoxicity, opioids clearly show a beneficial effect in reducing local tumor growth as well as dissemination of metastases. Recently, growing evidence accumulates that tumor cells express both opioid receptors and their ligands, the opioid peptides, suggesting that opioids may also directly affect tumor progression. Met-enkephalin seems to play a most prominent role possibly acting via a different receptor than the classical opioid receptor. However, there is still great need for further studies to corroborate these interesting findings.

**Key words:** cancer pain, morphine, tumor proliferation, natural killer cells, opioids

Adv. Pall. Med. 2009; 8, 2: 53–56

## Introduction

Cancer patients are often treated with high doses of opioids such as morphine for pain relief. Opioid analgesics act on their corresponding receptors, mainly $\mu$-opioid receptors, along the neuraxis of pain transmission, i.e. peripheral sensory neurons, spinal cord, and brain [1]. They inhibit the release of excitatory neurotransmitters and reduce the excitability of sensory neurons which results in subsequent pain relief. The opioid system consisting of opioid receptors and endogenous opioid ligands exists in vertebrates since more than 400–500 million years [2, 3]. Therefore, it is conceivable that opioids do not only modulate pain, but also affect many other physiological functions. Indeed opioid receptors also exist outside the nervous system [4], and previous studies have emphasized the role of opioids to cope with environmental stress (i.e. mechanical, thermal, chemical), tissue injury, pathogen invasion, inflammation, and tumor growth [1]. This review will focus on the immunemodulatory effects of opioids and in particular their impact on tumor growth and dissemination of metastases.

## Opioid effects on the immune system

The discussion about the influence of opioids on the immune system is not new. Already in the 1980s many *in vitro* studies were published with controversial results [for review see 5]. However, more recent results from opioid receptor knock-out mice strongly support an immunosuppressive effect. Consistently, chronic use of opioids has been associated with an increased incidence of infectious diseases such as HIV or tuberculosis [6–8]. Early reports by Liebeskind and colleagues demonstrated immunosupressive effects of morphine that were depen-

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Advances in Palliative Medicine 2009, 8, 53–56

dent on activation of central opioid receptors and of the hypothalamo-pituitary stress axis [9]. The periaqueductal grey area has been identified as a brain region with a high density of opioid receptors that reliably respond with immunosuppression following injections of opioids [10]. However, opioids also exert their immunosuppressive effects via opioid receptors on various immune cells such as granulocytes, monocytes/macrophages and lymphocytes. All opioid receptors ($\mu$-, $\delta$-, $\kappa$) are present on immune cells, they couple to $G_{\alpha i/o}$ proteins and they influence immune cell function [11, 12]. In addition, all opioid peptides — $\beta$-endorphin, enkephalin and dynorphin — their precursors, and necessary processing enzymes were identified in activated granulocytes, monocytes and lymphocytes suggesting an autoregulatory role [13]. Immunosuppressive effects are more overt following chronic opioid administration resulting in atrophy of thymus and spleen and inhibition of NK cell activity [14]. Consistently, $\mu$-receptor knock-out compared to wild type mice lacked lymphoid organ (thymus, spleen) atrophy as well as inhibition of NK cell activity [15]. In a very impressive example of the immunosuppressive effects of opioids it was demonstrated that $\mu$- and $\delta$-opioid agonists resulted in a dramatic reduction of macroscopic and microscopic inflammatory signs, an almost complete reversal of immune cell infiltration, and more importantly a significant reduction in mortality [16]. These effects are in part due to local opioid effects on immune cells as it has been shown with the use of peripherally selective opioids that profoundly diminish macroscopic and microscopic signs of arthritis [17, 18]. Whether immunosuppressive effects of opioids are to the advantage or disadvantage of the organism, is very much dependent on the situation under which opioids and the immune system interact [19]. For example in arthritis and autoimmune disease an immunosuppressive effect of opioids is advantageous, whereas in conditions such as HIV and drug addiction immunosuppressive effects of opioids might lead to further complications such as infections and disturbed wound healing [20].

## Opioids, natural killer cells and tumor progression

Studies showing direct effects of exogenous opioids on tumor growth and dissemination are still contradictory, because experiments were mainly done in cell cultures under *in vitro* conditions. While it is reported that morphine stimulates microvascular endothelial-cell proliferation and angiogenesis in breast cancer cells [21], it is also described that morphine inhibits the adhesion, invasion and metastases of colon cancer cells [22]. However, to look exclusively at direct effects of opioids on tumor cells may not comply with the much more complex scenario of tumor progression in cancer patients.

Tumor progression is — particularly through its initial stage — under immune surveillance. Transformed surface antigen presenting cancer cells may become a target for cytotoxic natural killer (NK) cells. This initiates an "evolutionary" process of selection pressure by the immune system upon malignant cells [23]. Some tumors seem to be more susceptible to cytotoxic NK cell activity, e.g. melanomas and breast cancer, whereas others are less, e.g. colon cancer. Pain and subsequent stress, e.g. following surgery, have been shown to signicantly impair NK cell activity which led to enhanced lung tumor retention of mammary adenocarcinoma cells in animals [24]. In NK cell depleted animals, however, this enhanced lung tumor retention could not be observed underlining the important involvement of cytotoxic NK cells. Consistently, NK cell number and activity of patients undergoing major surgery were significantly reduced [25]. In patients with hepatocellular or gastric carcinoma, impaired NK cell activity following surgery was demonstrated to be a prognostic predictor for increased tumor progression and dissemination [26, 27]. Although several studies in healthy animals have shown that opioids suppress NK cell activity [28], in the context of surgery, pain, and distress opioids rescued impaired NK cell activity [24, 29]. This resulted in significantly reduced tumor dissemination and increased survival [24, 30]. In a very elegant animal study of melanoma cells inoculated in the paw of mice, time-dependent local tumor growth and dissemination of lung metastases were dose-dependently reduced by increasing doses of morphine which was naloxone reversible [31]. Therefore, similar to the immunosuppressive effects of opioids which may be advantageous in the context of chronic arthritis and disadvantageous in the context of wound healing, opioids in the absence or presence of pain may impair or rescue NK cell activity and limit tumor progression, respectively.

## Expression of opioid receptors and peptides in tumor tissue

Recently evidence is accumulating that different tumor cells express opioid receptors and their en-

dogenous ligands, the opioid peptides. In a human colon cancer cell line as well as in tumor tissue of human colon cancer patients mu-opioid receptors were identified by immunohistochemistry suggesting that opioids may affect tumor progression [32]. In addition, opioid peptides (mainly $\beta$-endorphin and Met-enkephalin) and their precursors have been demonstrated in breast cancer cell lines and in tumor tissue of the majority of human breast cancer patients [33, 34]. Evidence for $\beta$-endorphin and opioid receptor binding sites have also been demonstrated in human lung cancer cell lines [35, 36]. In a systematic screening of different opioid peptides for their inhibitory effects on the proliferation of a murine neuroblastoma cell line Met-enkephalin was identified to be the most potent opioid peptide [37]. Interestingly in this screening assay, prodynorphin- and proopiomelanocortin-derived peptides did not have a significant influence on cultured cells. Therefore, it was postulated that not the traditional opioid receptors but a new, yet unidentified receptor was responsible for the antiproliferative properties [37]. This receptor has been cloned and sequenced in human, rat, and mouse and presumably has no resemblance to the classical opioid receptors or other known receptors [37]. Because of Met-enkephalin's newly discovered properties different from its analgesic effects, it was named "opioid growth factor" (OGF) and its receptor "opioid growth factor receptor". Recently, OGF receptor has been identified in several human cancer tissues [38, 39] and patients with advanced unresectable pancreatic cancer have been treated with OGF without major complications in a first phase I clinical trial [40]. Although these results look very promising, they have to be confirmed by other groups. Taken together, cancer cells seem to express both opioid receptors and their endogenous ligands to regulate tumor proliferation most likely by an autocrine mechanism.

## Summary

Consistent with its existence in vertebrates since more than 500 million years, opioids help the organism to cope with environmental stress, tissue injury, pathogen invasion, inflammation, and tumor growth. There is clear evidence for an immunosupressive effect of opioids which may be benefitial in chronic inflammatory conditions, however, it may be detremental in conditions such as tissue repair. This immunosuppressive effect of opioids would possibly facilitate tumor growth, however, in the context of pain and distress, which promote tumor progression by a reduction in NK cell cytotoxicity, opioids clearly show a beneficial effect in reducing local tumor growth as well as dissemination of metastases. Recently, evidence is accumulating that tumor cells express both opioid receptors and opioid peptides, their endogenous ligands, suggesting that opioids may affect tumor progression. Met-enkephalin seems to play an important role possibly acting via a different receptor than the classical opioid receptor. However, future studies have to corroborate these promising findings.

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