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Review Article

Morphine as a suspect of aiding the propagation of cancer cells

Yusom Shin

Department of Anesthesiology and Pain Medicine, College of Medicine, Kosin University, Busan, Korea

Controlling pain in cancer patients is important for several reasons including patient quality of life (QOL). In moderate-to-severe cancer-pain management, opioid analgesics are indispensable. Among these, morphine is the most representative. Unfortunately, many studies have shown that morphine is potentially associated with cancer growth, recurrence, and metastasis. Specifically, in animal as well as in vivo and in vitro studies, morphine has been demonstrated to have possibly positive effects on cancer progression. However, those effects have not yet been confirmed as entirely harmful, for several reasons: the results of animal and laboratory research have not been subjected to clinical trials; there are as yet no well-designed clinical studies, and indeed, some studies have shown that morphine can have negative, suppression effects on tumor growth. This review paper will present some of the data on the potentially positive relationships between morphine and cancer. It should not be forgotten, though, that such relationships remain controversial, and that pain itself promotes cancer progression.

Key Words: Metastasis, Morphine, Opioid

Approximately 64% of patients experience pain as cancer progresses.[1] In fact, there has been no significant change in the prevalence of cancer pain, despite its impact on the quality of life (QOL) of patients. Although the need for adjuvant analgesics or interventional pain management techniques is emphasized in cancer-pain protocols,[2,3] the World Health Organization (WHO) analgesic ladder remains the most basic guideline. According to the WHO three-step ladder, opioids such as morphine have been used for nearly 30 years to effect adequate cancer-pain relief for 70 to 80% of patients.[4] However, there is a growing body of evidence from animal- and cell studies that morphine has positive effects on tumor growth, progression and metastasis.[5-9] Then again, there is controversy as to whether morphine can really be favorable to cancer, particularly as there are several studies showing the opposite outcomes,[10-12] and the results of animal or laboratory experiments, moreover, have not been subjected to clinical trials. This review paper discusses the possible role of morphine in promoting cancer propagation.

Corresponding Author: Yusom Shin, Department of Anesthesiology and Pain Medicine, College of Medicine, Kosin University,262, Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel:+82-51-990-6283 Fax:+82-51-254-2504 E-mail: yusom2015@gmail.com

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The μ-opioid receptor

There are three types of opioid receptors: mu, delta, and kappa. Among these, the μ-opioid receptor (MOR) is recognized as the major target of morphine, owing to its higher binding affinity.[13,14] Activation of MOR results in a variety of physiologic changes such as analgesia and altered immunity and inflammatory response.[15-18] In cancer progression, μ-opioids have not only indirect effects, such as immune suppression and pro-inflammatory response,[14,19] but also direct effects such as in MOR over-expression in relation to lung cancer growth and metastasis. This could be a basis for diagnostic and treatment studies using MOR antagonists.[20] Morphine binding to MOR activates the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and inhibits apoptisis. Further, it stimulates urokinase plasminogen activator (uPA) and promotes metastasis, activates the mitogen-activated protein kinase/extracelluar-regulated kinase (MAPK/ErK) pathway, resulting in cell-cycle progression via epidermal growth factor (EGF) receptors, and influences angiogenesis by transactivation of vascular endothelial growth factor (VEGF) receptors.[21] Moreover, polymorphisms in the MOR gene have been shown to negatively influence breast cancer survival.[22]

Immunosuppression

An intact immune system's cancer immunosurveillance is known to be influential to tumor cell growth.[18,23] Morphine induces immunosuppression by immunomodulation. Immunomodulation is caused by the interaction between opioids and opioid receptors.[24] MOR is expressed in immune cells such as lymphocytes and macrophages, and MOR gene expression is influenced by cytokines secreted from immune cells. In this way, morphine inhibits immune system function.[21] Anti-inflammation due to reduced immunosurveillance can stimulate cancer development.[25] Morphine acts directly through binding to opioid receptors on immune cells, or, when opioids bind to the classical opioid receptors in the central nervous system, causes catecholamine and/or steroid release, thus indirectly affecting immune cell functions.[15,16] Especially, morphine can play an important role in cancer recurrence by participating in regulatory T cells via VEGF receptor 2 or modulating the function of immune cells or cytokines.[26] Furthermore, morphine-induced expression of Fas (CD95 or APO-1, a receptor on the cell surface) binding to its ligand promotes cell death by apoptosis in the immune system.[27] Cytotoxicity, a function of morphine concentration, is activated at supratherapeutic doses.[28,29]

Pro-inflammatory response

It has been reported that chronic inflammation increases cancer risk. Inflammation itself is a risk factor for tumor occurrence, but it affects the overall process of tumor development. When re-

active oxygen species (ROS) and reactive nitrogen intermediates (RNI) are secreted from inflammatory cells, they cause mutations in epithelial cells. Cytokines from inflammatory cells increase intracellular ROS and RNI in premalignant cells, thus creating an environment favorable for tumorigenesis. Cytokines secreted from tumor-infiltrating immune cells activate key transcription factors regulating pro-tumorigenic processes, which processes include chemokine secretion that attracts additional immune and inflammatory cells that sustain tumor-associated inflammation. Cytokines also can cause inflammatory sites to release endogenous opioids from leukocytes.[15,18] MOR is related to pro-inflammation, but the K-opioid receptor (KOR) is associated with anti-inflammation.[19,30,31]

Pro-angiogenesis

When opiates such as morphine bind to MOR, non-receptor tyrosine kinase (Src)-mediated VEGF receptors are transactivated by morphine concentration and Akt and ras homolog gene family, member A (RhoA) signaling are activated, leading to opioid-induced angiogenesis of endothelial cell proliferation and migration. Also, morphine affects angiogenesis, as it is involved in stimulating mast-cell degranulation that induces secretion of substance P. Both mast cells and substance P have been shown to aid cancer progression in animal and in vivo models, respectively.[14] On the other hand, it has been reported that morphine can reduce tumor-associated angiogenesis in mice.[11] Peripheral MOR antagonist methylnaltrexone inhibits angiogenesis through direct inhibition of MOR and MOR-independent activation of tyrosine phosphatase activity.[14,32] KOR agonists have an anti-angiogenetic effect via suppression of VEGF expression.[25] In addition to angiogenesis, morphine destroys endothelial-barrier integrity, which potentially is important in circulating tumor cells, and directly promotes human bronchioloalveolar carcinoma cell proliferation and migration.[14,15,21,25]

CONCLUSION

According to a number of studies on the relationship between morphine and cancer, morphine seems to be related to tumor growth and metastasis, whether tumor growth promotion or suppression. The studies indicating positive results on tumor development (i.e., growth promotion) outnumber those indicating negative ones (i.e., growth suppression). However, there is as yet no consensus on how to interpret these results. Because opioids are widely used for cancer patients' pain relief, not only animal or laboratory studies but also well-designed clinical studies are desperately needed to clarify the inter-relationships between tumor progression and opioids in terms of dose and duration of use.

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Peer Reviewer's Commentary

In moderate-to-severe cancer-pain management, opioid analgesics, such as morphine are commonly used. Evidences exists that morphine effects cancer progression invitro and in vivo animal studies. This review discusses molecular evidences of the possible role of morphine in promoting cancer propagation.

(Editorial Board)