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REVIEW ARTICLE

Morphine: double-faced roles in the regulation of tumor development

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Abstract Morphine, a highly potent analgesic, is one of the most effective drugs for the treatment of severe pain associated with cancer. It directly acts on the central nervous system to relieve pain, but also cause secondary complications, such as addiction, respiratory depression and constipation due to its activities on peripheral tissues. Besides pain relief, morphine is of great importance on cancer management with its effect on tumor development being the subject of debate for many years with some contradictory findings. Morphine has shown both tumor growth-promoting and growth-inhibiting effects in many published research studies. And various signaling pathways have been suggested to be involved in these effects of morphine. Based on a thorough literature review, we summarized the double-faced effects of morphine in tumor development, including tumor cell growth and apoptosis, metastasis, angiogenesis, immunomodulation and inflammation. And we attempted to optimize morphine administration in cancer patients to attenuate its tumor growth-promoting effects.

Keywords Morphine · Tumor · Apoptosis · Metastasis · Angiogenesis · Immunosuppression

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Introduction

Morphine was separated in 1803 by Friedrich W. Sertürner for the first time [1]. Later, it was found to be a very good analgesic and sedative, far more effective than other opioids. It is not only used in pain management, but also routinely used for anesthetic procedures in cancer patients undergoing surgery. Morphine was reported to exert its effect by binding to the opioid receptor [2]. The mechanism to relieve pain is due to its direct effect on the central nervous system, but its effect on peripheral tissues is responsible for many of the secondary complications, including addiction, tolerance, respiratory depression, immunosuppression, and constipation. Although these side effects are well known, morphine is still inevitable in cancer treatment. For many years, there has been a debate about the effect of morphine on cancer growth and metastasis. Numerous studies employing different cancer cell lines and experimental animals have been performed to investigate the effects of morphine on tumor cells. However, the results are sometimes contradictory with several studies showing morphine promotes tumor development [3–9] and others showing morphine inhibits tumor development [10–13]. Morphine affects tumor growth through multiple mechanisms of actions, including apoptosis, angiogenesis, invasion, inflammation and the immune reaction. This article reviewed the double-faced effects of morphine on tumor development with the latest findings. Through the thorough literature review, we hope to build a comprehensive understanding of morphine's effects in tumor development and find the optimal approach for cancer pain treatment with morphine to limit its tumor growth-promoting effects.

Morphine inhibits tumor development

Morphine inhibits growth of tumor cell

Numerous studies have focused on the research of morphine's effects on tumor growth. Tegeder et al. reported that morphine inhibited tumor cell proliferation at concentrations of > 10 μM, and this high dose of morphine significantly reduced the growth of MCF-7 and MDA-MB-231 tumors in nude mice [10]. Similarly, studies by Yeager and Colacchio showed that tumor growth in the rat model of metastasizing colon cancer was reduced after intermittent injections of morphine [11]. And Sasamura et al. also found that the tumor growth inhibition occurs under the repeated administration of morphine (5 and 10 mg/kg daily for 6 days) [12].

Although many literatures suggest that high dose of morphine could inhibit tumor cell proliferation, but the mechanism is still indistinct. On one hand, the involvement of the opioid receptor in the inhibitory effect remains debatable. Morphine and other opioid receptor agonists were shown to inhibit the proliferation of breast cancer cell which had κ- and δ-opioid but not μ-opioid receptors [14]. Other researchers demonstrated μ-opioid receptor promotes tumor growth and metastasis [15]. On the other hand, the apoptosis of tumor cell is also involved. Apoptosis is a form of cell death which is a programmed sequence of events leading to the natural death of cells without releasing harmful substances into the surroundings. And apoptosis is deregulated in cancer cells, resulting in the obvious tumor proliferation and growth [16]. Researchers proposed that the protective role for morphine against tumor growth and metastasis may be through promoting apoptosis of tumor cells. This is based on the experiments quantifying apoptosis cells [17] or measuring the cleavage of proapoptotic caspase or the release of cytochrome c from mitochondria performed on human tumor cell lines in high concentration of morphine [18]. And they also found that there is a significant difference between different cell lines. For example, morphine produced a higher number of necrotic cells in the MCF-7 breast cancer cell line than in the A549 lung cancer cell line [19]. This probably mainly depends on different types of tumor respond differently to morphine. More attractively is how morphine generates the pro-apoptosis effect. Apoptosis is determined by two fundamental pathways: the intrinsic mitochondrial-mediated pathway [20] and extrinsic death receptor-mediated pathway [21]. Various signaling pathways have been suggested to be involved in the pro-apoptosis effect of morphine on tumor cells, including the activation of anti-apoptotic kinase Akt, activation of c-Jun N-terminal kinase (JNK), generation of reactive oxygen species (ROS), generation of nitric oxide (NO), increased expression of pro-apoptotic Bim, decreased expression of anti-apoptotic Bcl-2, and Fas associated death domain (FADD) or p53 and NF-κB mediated pathways [21–24] (Fig. 1). Besides, the sigma-2 receptor via a p53- and caspase-independent apoptosis pathway was found in MCF-7 cell line [25], and activation of the κ-opioid receptor via the phospholipase apoptosis pathway was found in CNE2 human epithelial tumor cell line [26]. And recent experiments showed new progress that low dose of morphine may inhibit cisplatin-induced apoptosis [27]. Nevertheless, numerous in vivo and in vitro experiments have been implied to reveal the mechanism of the pro-apoptosis effect of morphine, the comprehensive pathways remain not clear.

Morphine inhibits angiogenesis

The successful development of tumor requires new blood vessel growth. And as one of the most frequent agents used in cancer treatment, whether morphine can influence the angiogenesis of the tumor has drawn researchers' attention for a long time. Experiments were conducted to evaluate the effects of morphine on angiogenesis. In 1991, Pasi et al. showed angiogenesis was reduced in the chicken chorioallantoic membrane (CAM) assay under high concentrations of morphine (10 mg/mL of plasma) [5]. And a recent animal study reported concentrations of morphine in 10 and 1 μM showed obvious antiangiogenic effects [28]. Several in vivo and in vitro studies explored distinct pathways by which morphine can inhibit angiogenesis directly or indirectly. Among these pathways, the inhibition of hypoxia-induced vascular endothelial growth factor

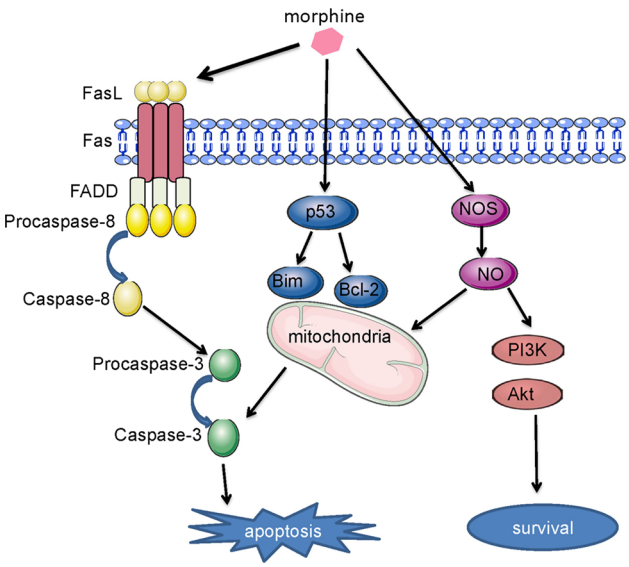

Fig. 1 Various signaling pathways involved in the pro-apoptosis effect of morphine on tumor cells

(VEGF) plays a pivotal role in regulating tumor angiogenesis. When the solid tumor grows, newly proliferated tumor cells are settled far away from the vascular supply, and tumor cells would secrete pro-angiogenic factors stimulated by the low oxygen or hypoxia [29]. One of these pro-angiogenic factors is VEGF. VEGF stimulates blood vessel endothelial cell proliferation and migration, and promotes new blood vessel formation, thus supporting the growth of tumor [30]. Experiment conducted by Balasubramanian et al. showed that VEGF can promote the ability of hypoxia tumor cells to trigger angiogenesis. And this research also reported that morphine can inhibit hypoxia-induced VEGF secretion in rat cardiomyocytes and human umbilical vein endothelial cells in the ischemia environment [31]. Another pathway has been found is the suppression of the hypoxia-induced mitochondrial p38 mitogen-activated protein kinase (MAPK) pathway. Koodie et al. observed the effect of morphine on a murine Lewis lung carcinoma tumor model, and they found that both tumor cell-induced angiogenesis and tumor growth were significantly reduced when morphine was administered at the clinically relevant analgesic doses by continuous slow release implantation. The authors demonstrated that the morphine suppresses tumor angiogenesis through the hypoxia-induced mitochondrial p38 MAPK pathway [32]. Besides direct effect, morphine was also shown to inhibit angiogenesis indirectly in in vivo models through suppression of inflammation [33].

Morphine inhibits tumor invasion and metastasis

As we all know, invasion and metastasis are major features of tumor development. And most failure of tumor treatment is not due to the primary tumor itself, but on account of the secondary focus which is metastasis from primary one. One indispensable step in migration of tumor is degrading of the extracellular matrix (ECM). In this process, the activation of urokinase plasminogen activator system, including a serine proteinase, urokinase plasminogen activator (uPA), two inhibitors, PAI-1 and PAI-2, the membrane linked receptor (uPAR) and matrix metalloproteinases (MMPs), takes a significant place [34, 35]. Among these factors, the MMPs, one type of zinc-dependent endopeptidases, can remodel the components in the ECM [36]. In several tumor types especially breast and lung cancer, MMPs expression and activity were increased. And it was found that the level of MMPs is related with stage, invasion, and potential metastasis of tumor [37]. Attractively, in MCF-7 breast cell line, morphine decreased the level of MMP-2 and -9 in time- and concentration-dependent manner [38]. Therefore, morphine may inhibit tumor metastasis via regulating the expression of MMPs. Another significant step is adhesion, which is mediated by some adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM-1), and E-selectin. Min et al. conducted an experiment with the HCT 166 colon cancer cells to clarify morphine can reduce the expression of adhesion molecules, and also suggested that this effect may be through the attenuate of lipopolysaccharide (LPS) [39].

Morphine inhibits inflammation

It has reported accompanying with the existence of some cancer risk factors that inflammation can promote the tumor occurrence [40]. According to the same report, inflammation influences the development of tumor mainly through two direct pathways: regulate autoimmunity response to tumor and create a pro-tumorigenic microenvironment. Boettger et al. reported intrathecally applied morphine can attenuate induction and maintenance of the inflammatory response in a model of chronic antigen-induced arthritis (AIA) [41]. And further experiments showed that not only morphine can regulate the expression of some inflammatory cytokines and their receptors, but also found immune cells under the influence of cytokines can release endogenous opioids at sites of inflammation [42, 43]. On the other hand, indirect pathways through κ-opioid receptor and nitric oxide NO were found. It has been suggested that this pathway activation may induce an anti-inflammatory response [44]. And NO has the anti-inflammation effect which also can be unregulated by morphine [45]. Besides, one new research applied teleost fish model exposure to 1 mg/L morphine resulted in down regulation of several inflammation-related genes, including Myd88, Trif, Traf6, p38, NF-κb2, IL-1β, IL-8 and CCL34a [46].

Morphine promotes tumor development

Morphine promotes tumor cell growth

Although lots of researchers found that morphine plays an inhibitor role in tumor cell proliferation, others have shown contradictory results. Several experimental studies reported that morphine promotes the growth of the tumor. Sergeeva documented in K562 leukemia cells morphine produced a pro-proliferation effect [47]. Similarly, Gupta et al., in orthotropic mouse model of MCF-7 breast cancer, demonstrated that morphine increased tumor growth in clinically relevant concentration [48]. And the result that morphine, in a dose of 50 nmol/L, 20, 40 μmol/L, was shown to trigger proliferation of human glioblastoma T98G cell also validates this hypothesis [49]. Some scholars conclude that tumor-promoting effects of morphine occur after administration of low daily doses or a single dose of morphine in vitro and in vivo [50]. However, the

mechanism of this concentration-dependent effect has not been well understood. But some researchers have pointed out that the μ-opioid receptor may be the key to the mechanism. Mathew et al. showed that in mice with knocked out μ-opioid receptor, no significant development of tumors was found when injected with Lewis lung cancer cells as compared to the wild-type controls. And after injection of methylnaltrexone, a μ-opioid receptor antagonist, tumor growth in wild-type mice treated with Lewis lung cancer cells significantly reduced by up to 90% [15]. As for the downstream transduction pathway, some scholars think after morphine binding to the μ-opioid receptor, it regulates cell cycle progression by stimulating MAPK or extracellular growth factor Erk pathways [51] (Fig. 2).

Another aspect morphine exerts its pro-growth effect is through inhibition of apoptosis. It was shown morphine inhibited the apoptosis of SH-SY5Y cells by antagonizing doxorubicin, a well-known anti-tumor drug [52]. And the mechanism was shown in supplementary studies, including the inhibition of ROS generation and mitochondrial cytochrome c release, blockade of NF-κB transcriptional activation [52]. Another pathway found in experiments is μ-opioid receptor. Also in SH-SY5Y neuroblastoma cells, morphine (10^{-7}–10^{-5} M) was shown to be able to inhibit serum deprivation-induced apoptosis, and this effect was fully reversed by naloxone, a medication designed to rapidly reverse opioid overdose [53]. And studies further demonstrated that μ-opioid agonists do not directly induce apoptosis in neuronal cells; it exerts its effect through the activation of the phosphatidylinositol 3-kinase/Akt (PI3K/Akt) signal transduction pathway, thus leading to cell survival [53] (Fig. 2). Recently, some researchers found morphine can increase the expression of survivin, a member of inhibitor of apoptosis (IAP) family [54]. Further study on the survivin may can provide a new understanding in the pro-growth effect of tumor.

Morphine promotes angiogenesis

Morphine was found not only to be able to inhibit angiogenesis, but also able to promote new vessels formation. This supports the hypothesis morphine promotes the tumor development. Early in 2002, Gupta's group have showed that at clinically relevant concentrations, morphine stimulated human microvascular endothelial cell proliferation and angiogenesis in vitro, and also enhanced tumor neovascularization in the MCF-7 breast cancer model in vivo [48]. Due to its central role in tumor angiogenesis, VEGF signaling pathway has been a major focus of basic research in this field. It was demonstrated that morphine promoted activation of VEGF receptor in the animal model of hormone-dependent breast cancer [55]. Similarly result was found when Singleton and Moss demonstrated that morphine can activate the VEGF receptor and promote angiogenesis in cultured human endothelial cells. And after

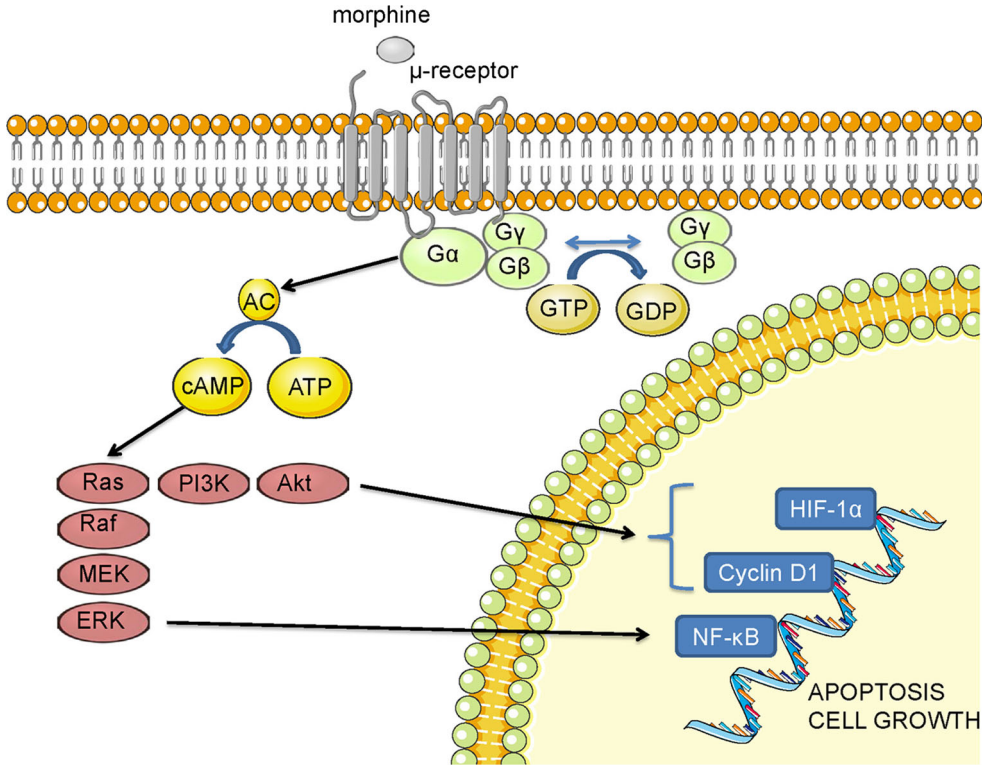

Fig. 2 The downstream transduction pathway after morphine binding to the μ-opioid receptor

applying methylnaltrexone, angiogenesis induced by opioid was blocked [56]. VEGF can increase endothelial cell migration by inducing adhesion molecules. It has been found that VEGF stimulated ICAM-1 expression, and ICAM-1-deficient endothelial cells showed reduced nitric oxide synthase activation (NOS) [57]. ICAM-1 can increase endothelial cell migration [58] and also can promote the recruitment of endothelial progenitor cells, which involved in angiogenesis [59]. Later, experiment showed the level of ICAM-1 was upregulated in endothelial cells exposed to μ-agonists [60]. These data indicate that the transactivation of VEGF receptor by morphine may be mediated by NOS and ICAM-1, thus promoting endothelial cell motility.

Another pathway included is the stimulation of MAPK signaling pathway via G protein-coupled receptors and NO. In a study of opioid-induced proliferation of vascular endothelial cells, morphine was found to stimulate vascular endothelial cell proliferation in vitro [61]. The author demonstrated this effect of morphine is transmitted by MAPK pathway as pre-treatment with PD98059, a highly inhibitor of MAPK pathway, inhibited this excessive proliferation. And they also found chronic morphine treatment increased the levels of NOS, NO, and cyclooxygenase-2 (COX-2) [61]. Similarly, 2 weeks of chronic morphine treatment in highly invasive SCK breast cancer mouse model stimulated COX-2, prostaglandin E2, and angiogenesis, accompanied with the increased tumor weight, increased metastasis, and reduced survival [55]. Combining the relationship between NOS, NO and COX-2, it can be concluded morphine can upregulate COX-2, thus promote angiogenesis of tumor.

Morphine promotes tumor invasion and metastasis

As previously mentioned, uPA, PAI-1 and uPAR play important roles in degrading of ECM. This is one indispensable step in migration of tumor. And in early 1996, Shapiro et al. have demonstrated that the level of uPA, PAI-1, and uPAR is unregulated in most types of cancers [62]. Later in 2008, it was found in HT-29 colon cancer cells, uPA secretion can be stimulated by morphine [63]. And some further experiments were conducted by researchers. Morphine can down-regulate the level of uPA significantly in MCF-7 breast cancer cells, in which uPA and uPAR mRNA levels were unregulated indeed. And this decline can be reversed by naloxone [64]. However, there are a very few studies addressing why morphine can upregulate uPA level, and inhibit MMPs expression. One recent experiment applied renal cell carcinoma (RRC) gives a new pathway that morphine enhances renal cell carcinoma aggressiveness by promoting survivin level [54]. Survivin, which we have mentioned, was found to increase genomic instability, thereby boosting malignant phenotypes, such as the local invasion and distant metastasis [65, 66]. But detailed mechanisms still need further exploration.

Morphine exerts immunosuppression

The immune system disorder is related to many inflammatory diseases and cancer. Traditional wisdom holds that intact immune responses, such as immune surveillance or immunoediting, are required for preventing and inhibiting tumor development [67]. And numerous reports have indicated morphine and some other opioids can exert the immunosuppression effect. In the study of immune and tumor, professors concluded that tumor cellscan express non-self-antigens, to attract and be killed by activated T lymphocytes, NK cells and the cytotoxic cytokines such as interferon γ [40]. And study verified the susceptibility to tumor of mice model which are lacking in various components of the immunosurveillance system is increased [68]. As for how morphine can act on the immune system, there are different opinions. On one hand, the mediation of μ-opioid receptor is involved. The expression of the μ-opioid receptor gene in neuronal cells is regulated by cytokines, which is released by the immune cells [69]. And opioid receptors have been expressed in cells of the immune system including polymorphonuclear leukocytes, macrophages, T lymphocytes, splenocytes, macrophage-like and T cell-like cell lines [70]. It have been debated opioid-induced immunosuppression is centrally or peripherally mediated. The result people recognized is both regulated [71]. On the other hand, morphine exerts immunosuppression through inhibiting components of the immune system including production of antibody, activity of NK cell, the expression of cytokine, proliferation of blood lymphocyte, and activity of phagocytic [72]. To support this hypothesis, one recent experimental study confirmed morphine indeed can reduce both the proliferation of T cell and the levels of T-cell subtypes [73].

Discussion and perspectives

Existing studies have shown that morphine have double-faced effects on the regulation of tumor development. The mechanisms involved in the effects of morphine on growth and metastasis, angiogenesis, immunosuppression and inflammation related to tumor remains not clear. M-opioid receptor expression may be the key to the mechanism. The role of morphine in tumor growth and metastasis may be through promoting or suppressing apoptosis of tumor cells and VEGF signaling.

The factors that induced the double-faced effects of morphine on the progress of tumor are mainly concentrations of morphine and different tumor types. In general, under high concentrations, morphine inhibits tumor cell growth, angiogenesis and tumor invasion and metastasis. While at a low daily dose or clinically relevant concentrations, morphine stimulated tumor cell proliferation, angiogenesis and immunosuppression. The mechanism of this concentration-dependent effect has not been well understood. In addition, different types of tumor have different responses to morphine which may be related to different opioid receptors between different cell lines.

For patients suffering from cancer pain, we still could not decide to use the right concentration of morphine for the right cancer patient. How to take advantage of the beneficial effects of morphine without the harmful ones demands more studies. Up until now, there has not been any clear clinical evidence to support that morphine promotes tumor development. It is very important to use enough morphine for cancer patients to relieve pain and improve their quality of life until study reveals clear evidence.

Conclusion

The effect of morphine on tumor development has been debated for more than 20 years; though the result remains not clear, the study has progressed greatly. Numerous studies have showed both growth-promoting and growth-inhibiting effects. On one hand, morphine was shown to inhibit tumor growth, promote apoptosis, inhibit angiogenesis and migration of tumor cells, but on the other hand, anti-apoptotic and pro-angiogenic properties of morphine were also demonstrated. And this article describes the double-faced effect of morphine through a comprehensive review of latest literature about morphine on tumor development. These include direct influence on growth of tumor cells, and indirect influence on the angiogenesis, invasion and metastasis, anti-inflammation, immunosuppression, mediated by various pathways. And the effects may vary when the experiments were performed on different kinds of cells or when the different doses of morphine were applied. Therefore, the dose of administration of morphine and these diverse pathways might be critical factors that need to be taken into consideration in clinical settings. How to take advantage of the beneficial effects of morphine without the harmful ones demands more studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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