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REVIEW ARTICLE

The dual effect of morphine on tumor development

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Abstract
Morphine is a classic opioid drug used for reducing pain and is commonly prescribed as an effective drug to control cancer pain. Morphine has a direct role in the central nervous system to relieve pain, but because of its peripheral functions, morphine also has some side effects, such as nausea, constipation, and addiction (Gupta et al. in Sci World J 2015:10, 2015). In addition to its analgesic effect, the role of morphine in tumor development is an important question that has been investigated for many years with conflicting results. Numerous studies suggest that morphine has a role in both promoting and inhibiting tumor growth. In this extensive review, we attempt to comprehensively understand the effects of morphine and summarize both its positive and negative influences on various aspects of tumors, including tumor growth, angiogenesis, metastasis, inflammation, and immunomodulation.

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

Introduction

One of the most common symptoms of cancer is pain, with 50–80% of cancer patients experiencing some degree of pain. As tumors develop, they can cause severe pain by invading the surrounding nervous tissue, organs, and bones. This can cause a series of pathophysiological changes in the body, including changes in immune function.

Studies suggest [2] that pain can increase the release of corticotrophin-releasing hormone (CRH), resulting in immunosuppression. CRH acts on the neuroendocrine system, which leads to the redistribution of lymphocytes from circulating blood to lymphatic tissue. This causes lymphocytes to respond less to mitogens. Furthermore, immune cells synthesize and release β-endorphin, an endogenous opioid peptide that is an important immunomodulator and can rapidly decrease CD3 +, CD4 +, and CD4 +/CD8 + expression in peripheral blood, thereby leading to immunosuppression. Neuropeptides and other factors produced by the body as a result of cancer pain can inhibit the production and release of Il-2, which also leads to immune hypofunction.

Morphine is an analgesic for cancer pain which improves the quality of life of patients. Besides its analgesic effect, the clinical utility of morphine is limited by several adverse effects, including addiction, tolerance, immunosuppression, and constipation [3]. However, morphine is still regarded as the most effective medicine for patients with severe pain. How morphine influences tumor growth has been debated for years. Some studies indicate that morphine promotes tumor progression, while others suggest that morphine inhibits tumor progression.

This review attempts to clarify the dual function of morphine on tumor progression, including growth, angiogenesis, metastasis, inflammation, and immunomodulation (Fig. 1).

Effect of morphine on tumor cell growth

Many studies have investigated how morphine influences tumor cell growth. Some studies [4] reported that when morphine is administered at a concentration greater than 10 μM, tumor cell proliferation is inhibited. One study found that high concentrations of morphine reduced MCF-7 cell growth in nude mice [4]. A similar result was obtained when morphine treatment prevented neuroblastoma SH-SY5Y cells from differentiating [5]. Although many studies have shown that high concentrations of morphine can inhibit the proliferation of tumors, the mechanism remains unclear. The involvement of opioid receptors remains debatable. It was shown that opioids inhibit T47D cell growth, the mechanism

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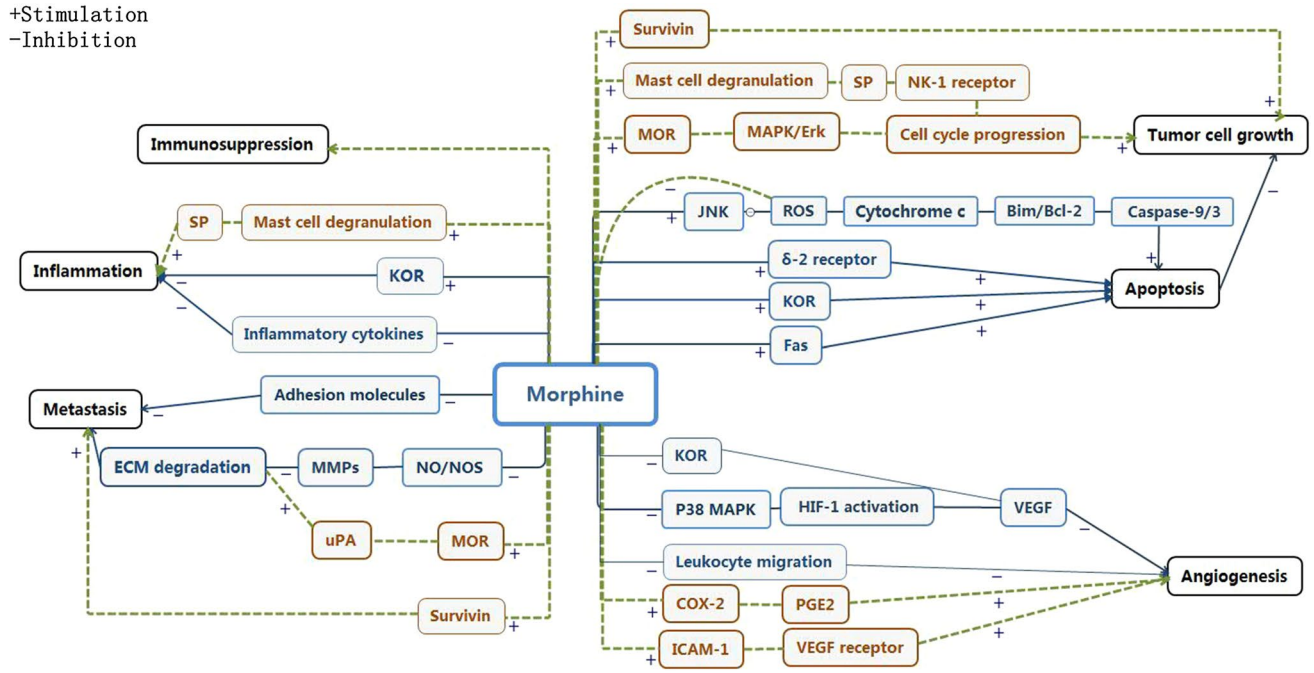

Fig. 1 Morphine has dual effect on tumor development

of which was mediated through κ- and δ-opioid receptors [6]. Another aspect of morphine which may contribute to its antigrowth effect is via apoptosis promotion. Morphine activates c-JunN-terminal kinase, which generates reactive oxygen species (ROS), inducing the release of cytochrome c and caspase-9/3 by enhancing the pro-apoptotic protein Bim and reducing the anti-apoptotic protein Bcl-2 [7]. In addition to this mitochondrial pathway, morphine can also promote Fas-mediated apoptosis [8]. Apoptosis of MCF-7 cells was shown to be mediated by a novel δ-2 receptor, p53, and caspase-independent pathway [9]. Activation of the κ-opioid receptor (KOR) promotes apoptosis via a phospholipase C pathway in the CNE2 human epithelial tumor cell line [10]. There are obvious differences in the number of necrotic cells induced by morphine between different cell lines. For example, the number of necrotic cells in an MCF-7 cell line is higher than that in HL-60 and A549 cell lines [11]. This difference is largely dependent on how the cell lines react to morphine.

Despite this, there is also accumulating evidence for the growth-promoting effect of morphine. Sergeeva et al. [12] reported that morphine activates the proliferation of myeloid K562 and T-lymphoma Yurkat cells. Sabrina et al. [13] reported that clinically relevant concentrations of morphine can increase breast cancer progression. Recently, it was reported that morphine can inhibit cisplatin-induced apoptosis [14]. Some studies have confirmed that taking low doses of morphine can increase the growth of the tumor cell; however, the mechanism is still unclear. Some researchers have indicated that the μ-opioid receptor (MOR) may have a significant role in this mechanism. Mathew et al. [15] showed that compared to wild-type controls, μ-opioid receptor-knockout (MORKO) mice did not have significant tumor growth when injected with Lewis lung cancer cells. Further, after infusion of methylnaltrexone, a MOR antagonist, wild-type mice treated with Lewis lung cancer cells had a significant reduction, up to 90%, in tumor growth [15]. It has been pointed out that morphine can stimulate the mitogen-activated protein kinase (MAPK) or Erk pathways to regulate cell cycle progression by binding to the MOR [16]. Morphine can also stimulate the degranulation of mast cells to promote the release of neuropeptide substance P (SP) [17, 18], which has been shown to enhance the proliferation of tumor cells through the tachykinin 1 (NK-1) receptor [19]. The anti-apoptosis effect of morphine is involved. As naloxone cannot reverse this effect, a non-opioid receptor-mediated signaling pathway is implicated. Further reports suggest that morphine inhibits the generation of ROS and prevents the DOX-mediated activation of caspase-3, release of cytochrome c, and changes in Bax and Bcl-2 protein expression [20]. In addition, several researchers have focused their research efforts on Survivin, a member of the inhibitor of apoptosis family. It was shown that morphine can enhance renal cell carcinoma (RCC) growth by promoting the expression of Survivin [21].

Effect of morphine on angiogenesis

The formation of new blood vessels is an essential part of tumor development. Because morphine is one of the most commonly used drugs for treating cancer pain, its effect on angiogenesis has attracted great attention from researchers. When a solid tumor grows, newly proliferating tumor cells are localized far away from their vascular supply. This low oxygen or hypoxic environmental stimulates tumor cells to secrete vascular endothelial growth factor (VEGF) [22], which promotes the formation of new blood vessels to sustain the tumor growth [23]. Balasubramanian et al. [24] reported that in rat cardiomyocytes and human umbilical vein endothelial cells, morphine inhibits the secretion of VEGF induced by hypoxia. Koodie et al. [25] observed that when morphine is administered at clinically relevant analgesic doses by continuous slow release implantation, tumor cell-induced angiogenesis is reduced. They also confirmed that this inhibitory effect was mediated by hypoxia-induced mitochondrial p38 MAPK pathway inhibition [25]. Others [26] have argued that morphine also inhibits angiogenesis by suppressing VEGF signaling via the KOR, as KOR knockout mice grafted with Lewis lung carcinoma or B16 melanoma had more proliferation and enhanced angiogenesis compared to wild type mice [26]. In addition to its direct effect, morphine can also suppress the migration of leukocytes and reduce angiogenesis [27].

Morphine not only inhibits angiogenesis, but also promotes the formation of new blood vessels. It was shown by Bimonte [13] that clinically relevant concentrations of morphine stimulates tumor angiogenesis. Singleton and Moss [28] found that morphine can transactivate the VEGF receptor and stimulate angiogenesis and further, angiogenesis was blocked after the application of a MOR antagonist [28]. The transactivation of the VEGF receptor by morphine may be mediated by adhesion molecules, such as ICAM-1 [29]. Another implicated pathway is the stimulation of the MAPK signaling pathway through G protein-coupled receptors and nitric oxide (NO). Chronic morphine therapy can increase the levels of nitric oxide synthase (NOS), NO, and cyclooxygenase-2 (COX-2) in mouse kidneys [30]. Similarly, 2 weeks of chronic morphine therapy stimulated COX-2, prostaglandin E2, and angiogenesis, which was accompanied by increased tumor weight and metastasis and reduced survival [31]. It could thus be postulated that morphine can upregulate COX-2, increase prostaglandin E2, and promote angiogenesis.

Effect of morphine on tumor invasion and metastasis

The most common reason why a patient fails to respond to cancer treatment is not because of the original tumor itself, but instead, because of metastasis from the primary one. The activation of urokinase plasminogen activator (uPA) and matrix metalloproteinases (MMPs) play an important role in the degradation of the extracellular matrix (ECM), which is regarded as an indispensable step in tumor migration [32, 33]. MMP is a type of endopeptidase which can remodel the constituents of the ECM [32]. It was reported that morphine reduces the migration and invasion of breast cancer cells by inhibiting MMPs [34]. The findings from Katarzyna et al. [35] indicate that morphine exerts its inhibitory effect on MMP-2 and MMP-9 by inhibiting the NO/NOS system. Adhesion is also important for metastasis. Min et al. [36] clarified that morphine can weaken endothelial cell adhesion molecules induced by LPS-stimulated colon cancer cells and reduce metastasis.

However, conflicting data on the effects of morphine on tumor metastasis were simultaneously published. As mentioned before, uPA plays a crucial role in the degradation of the ECM [33]. Gach et al. [37] reported that in MCF-7 breast cancer cells, morphine significantly increases the secretion of uPA. Similarly, Nylund et al. [38] showed that in HT-29 colon cancer cells, morphine induces the secretion of uPA. Naloxone can reverse this morphine-induced upregulation, proving that opioid receptors were involved in the process. Recently, it has been found that over-expressing Survivin can promote tumors to metastasize and increase genomic instability, thereby promoting tumor invasion and metastasis [39, 40]. It was also shown that morphine can enhance RCC growth by promoting Survivin expression [39, 40].

Effect of morphine on inflammation

The inflammatory response plays a crucial role in the different stages of tumor development and mainly affects the tumor through two direct pathways: (1) adjusting the antitumor immunity of the host and (2) creating a pro-tumorigenic microenvironment. Boettger et al. [41] reported that morphine can reduce the inflammatory response in the chronic antigen-induced arthritis model. Further research showed that morphine can modulate inflammatory cytokines to inhibit inflammation [42]. In addition, morphine can induce the activation of KOR to exert its anti-inflammatory response [43]. As such, morphine can prevent inflammation, inhibit tumor growth, and ameliorate addiction.

In contrast to its inhibiting effects on inflammation, morphine can also stimulate the degranulation of mast cells to promote the release of the neuropeptide SP [17, 18]. This then aggravates the inflammatory response, helps the tumor escape from the immune surveillance, induces addiction, and increases the infection rate.

Effect of morphine on the immune system

A number of mechanisms for the effects of morphine on immunity have been described. Morphine regulates immune function by directly acting on immune cells and via indirect actions, which include interacting with the central nervous system (CNS) and promoting its release of immune mediators (Table 1).

Direct effects

Morphine induces immune suppression by directly regulating adaptive and innate cells, including macrophages, natural killer (NK) cells, B cells, and T cells.

For morphine to exert its direct effects on an immune cell, either the immune cell must express opioid receptors or morphine must be capable of working through non-opioid receptors [44].

Macrophages/phagocytic cells, together with NK cells, constitute the major part of innate immunity. Morphine reduces the number of macrophages that can be used to respond to infection by reducing the proliferation of macrophage progenitor cells [45] and inhibiting the recruitment of these cells [46]. In addition, macrophage phagocytosis can be inhibited [47] and macrophage bactericidal activity can be disrupted by reducing the release of NO [48]. Further studies have shown that deletion of the MOR gene completely eliminates the inhibitory effect of morphine on phagocytosis and bactericidal activity. Morphine substantially decreases the activity of NK cells. It is thought that morphine suppresses the activity of NK cells as a result of the activation of opioid receptors in the CNS [49].

Similar to its effect on the innate immune system, prolonged morphine treatment attenuates the adaptive immune response. T lymphocytes are the main cells involved in cellular immunity. They also regulate the activity of other cells through neuroendocrine mechanisms or cytokines. Chronic morphine treatment results in a decrease in cell viability, proliferative responses, T-helper cell function, and CD4/CD8 cell populations [50]. In addition, morphine has been shown to significantly reduce the production of IL-2, TNF-α, and IFN-γ in mouse spleen cell cultures [51]. Mechanistically, morphine can impair the proliferation of lymphocytes by interfering with the transcriptional activation of the *IL-2* gene [52], as well as interfering with the activity of the IFN-γ promoter through two distinct cAMP-dependent pathways [50]. These effects are absent in MORKO mice, further demonstrating that the activation of MOR can lead to immunosuppressive effects. Contrary to T cell research, the effect of morphine on B-cell function is limited. B lymphocytes are involved in humoral immunity mainly by producing antibodies and memory cells. Morphine inhibits the function of macrophages and polymorphonuclear leukocytes via the neural immune circuit, thereby indirectly regulating B cell function [53].

Table 1 Morphine modules immune function by direct and indirect actions

	The effects of morphine
Immune cells	
Innate cells	
Macrophages	Reduce the proliferation of macrophage progenitor cells
	Reduce recruitment
	Reduce Fcg R mediated phagocytosis
	Reduce the release of NO
NK cells	Suppress the activity of NK cells
Adaptive cells	
B cells	Inhibit the function of macrophages and polymorphonuclear leukocytes
T cells	Interfere with transcriptional activation of the IL-2 gene
	Inhibit IFN-γ
CNS	
Acute administration	
PAG	Suppress NK cell cytotoxicity and lymphocyte proliferaiton
NAS	Inhibit NK cell cytotoxicity
Chronic administration	
HPA axis	Decrease NK cell cytotoxicity

Indirect effects

The indirect action of morphine on the immune system via the CNS is also supported by conflicting evidence [54]. Acute morphine administration releases biological amines into the periaqueductal gray to suppress NK cell cytotoxicity and lymphocyte proliferation [54–56]. Additionally, morphine releases neuropeptide γ via D1 receptors into the nucleus accumbens shell to inhibit splenic NK cell cytotoxicity [57]. Chronic morphine administration increases the activity of the hypothalamic–pituitary–adrenal axis and the release of immunosuppressive glucocorticoids, both of which decrease the cytotoxicity of NK cells [58, 59].

Conclusions and perspectives

Current research shows that morphine plays a dual role in the regulation of tumors, including its effect on tumor growth, angiogenesis, metastasis, inflammation, and immunity. However, the mechanisms remain unclear. The expression of MOR in tumors may be the key to these mechanisms. Morphine has a role in tumor growth and metastasis by modulating apoptosis and VEGF signaling. Thus, opioid antagonists might become novel therapeutic options for tumor treatment.

The major factors responsible for the dual role of morphine in tumors is the dose of morphine and type of tumor. Generally speaking, at high concentrations, morphine inhibits tumor cell growth, angiogenesis, invasion, and metastasis. However, low daily doses of morphine stimulates tumor cell proliferation, angiogenesis, and immunosuppression. The mechanism of the concentration-dependent effect of morphine is not clear. In addition, the effect of morphine is dependent on the type of cancer, since different cancer cells overexpress different opioid receptors.

In vitro and animal studies are principally used to explore these mechanisms, because the environment can be carefully controlled. However, the findings from these studies cannot be completely extrapolated to humans, as the internal environment of the human body is complex. As a result, further research is necessary to fully understand the effects of morphine on the development of tumors in a human physiological environment. A small number of studies have found that greater morphine requirement are associated with shorter progression-free and shorter survival rate [60, 61]. Thus, further studies are needed to determine how to utilize the advantages of morphine and minimize the negative effects. Until there is more reliable evidence, it is currently necessary to use the adequate dose of morphine needed to relieve pain in cancer patients.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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

Informed consent No informed consent is required.

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