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REVIEW ARTICLE

Possible link between cyclooxygenase-inhibiting and antitumor properties of propofol

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Abstract The intravenous anesthetic propofol has a number of well-known nonanesthetic effects, including anti-oxidation and anti-emesis. Another interesting nonanesthetic effect of propofol may be its cyclooxygenase (COX)-inhibiting activity. This activity may have important clinical implications, as propofol could have antitumor properties through COX inhibition. Propofol could counteract the activity of COX, which elicits, via its major product prostaglandin E_2, (1) tumor growth stimulation, (2) increased tumor survival, (3) enhanced tumor invasiveness, (4) stimulation of new vessel formation, and (5) tumor evasion of host immune surveillance through suppression of immune cell functions. Indeed, accumulated evidence indicates that propofol suppresses the proliferation, motility, and invasiveness of tumors in vitro and in vivo. Therefore, propofol could be a particularly suitable anesthetic for use during the perioperative period for cancer surgery. However, whether the COX-inhibiting activity of propofol is related to the reported antitumor properties of propofol is not known. Definitive evidence remains to be provided.

Keywords Antitumor property · Cyclooxygenase · Immune cells · Metastasis · Propofol · Prostaglandin E_2

Introduction

Cyclooxygenase (COX) is an enzyme in the arachidonic acid (AA) cascade, in which AA is released from membranes by cytosolic phospholipase A_2 [1]. COX catalyzes the conversion of AA to prostaglandin H_2 (PGH_2), which is subsequently converted by specific prostanoid synthases to one of the five prostanoids (i.e., prostacyclin, thromboxane A_2, PGD_2, $PGF_{2\alpha}$, and PGE_2) [1]. COX is primarily classified as COX-1 or COX-2. COX-1 is constitutively expressed in almost all tissues; COX-2 is usually not expressed in the resting state but can be induced by various types of stimulation in certain cell types [2].

Besides use as an anesthetic, propofol is reported to have a number of nonanesthetic properties [3]. Among the off-target effects, the COX-inhibiting property of propofol may be particularly intriguing, as are the tumor suppressive properties of propofol. The antitumor effects may be caused by its direct suppression of tumor growth and invasiveness, or they may be mediated by immune reaction. Because COX is implicated in the progression of tumors, at least some of the propofol antitumor properties might be ascribed to COX inhibition. However, to what extent the COX-inhibiting property of propofol is associated with its antitumor properties is unknown.

In this review, we present experimental and clinical evidence supporting the idea that COX-2 plays a crucial role in tumor genesis, growth, and aggressiveness. Next, we present the COX-inhibiting property of propofol, followed by the antitumor properties of propofol currently known from laboratory studies. Finally, roles of propofol as a component of anesthesia for cancer surgery are mentioned in the context of surgery-induced immunosuppression.

COX-2 and tumors

COX-2 expression has been implicated in oncogenesis and tumor progression, which may be related to COX-2-

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induced disordered signal transduction and also to its ability to suppress the immune cells, mainly through production of prostaglandin E_2 (PGE_2).

Tumor growth and survival, tumor invasion and metastasis, and angiogenesis

Several human solid tumors are characterized by the presence of constitutive COX-2 expression, which is reported to contribute to the initiation, promotion, and metastasis of tumors [4]. COX-2 (a) stimulates growth, for example, through the activation of the extracellular signal-regulated kinase (ERK) [5]; (b) increases cell survival, which may result from the modulation of bcl-2, Bim, and survivin [6–8]; (c) enhances tumor cell invasiveness, involving increased tumor cell adhesion to the extracellular matrix, upregulation of matrix metalloproteinases (MMPs), and increased adhesion of tumor cells to the vascular bed [9]; and (d) stimulates neovascularization, which may involve increased production of vascular endothelial growth factor and the expression of urokinase plasminogen activator receptor [10]. The relevance of COX-2 expression in cancer is highlighted by clinical studies indicating that the presence of COX-2 correlates with a more aggressive phenotype and a worse overall clinical prognosis [11, 12]. By counteracting these COX-2 properties, the COX-2 inhibitor celecoxib suppressed human breast cancer cell invasion in vitro [13]. In humans, celecoxib was effective in mitigating cachexia in cancer patients in a Phase II nonrandomized study [14]. Celecoxib was also effective in preventing development of non-melanoma skin cancer in high-risk patients with precancerous skin lesions in a randomized, double-blind, placebo-controlled trial [15]. Daily treatment with aspirin, a nonsteroidal antiinflammatory drug (NSAID), for 5 years or more reduced the risk of developing colorectal cancer [16]. The effect of aspirin may be caused by its pro-apoptotic effects in the development of tumors, which may be mediated in part by inhibition of COX-2 [16].

Tumor evasion of host immune response

COX inhibition also has immunological connotations because COX-2 (and its major product PGE_2) promotes the tumor evasion of the host immune system [17–21]. The mechanisms involved in the immunosuppressive effects of PGE_2 include suppression of T-cell and natural killer (NK) cell function [17], inhibition of dendritic cell (DC) activation [18], stimulation of T regulatory cell functions [19], and the polarization of activated macrophages, causing them to secrete M2-type molecules such as arginase I that inhibit T-cell activation [20]. Recent studies indicate that PGE_2 also stimulates the accumulation of myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment [20, 21]. MDSCs are potent inactivators of T-cell and NK-cell-mediated immune responses against tumor cells [20, 21]. Therefore, COX-2 inhibition could prevent the creation of a tumor-favorable microenvironment and break tumor immune tolerance. Additionally, COX-2 creates a proinflammatory environment that is conductive of tumor development, growth, and progression [22]. Thus, COX-2 inhibitors could potentially exert antitumor properties by modulating inflammation and immunity.

COX-2 inhibitors and postoperative cancer prevention

Although NSAIDs and COX-2 inhibitors for "cancer prophylaxis" are generally deemed to be successful in human studies [15, 16], whether COX-2 inhibitors are also effective in preventing postoperative metastasis in humans is of utmost interest. In one large-scale study investigating this possibility, patients were given the COX-2 inhibitor rofecoxib after curative colorectal cancer surgery [23] to assess direct inhibition of growth of residual micrometastases, prevention of angiogenesis, and reduction in tumoral expression of MMPs [4, 23]. Although there was a significant trend toward prevention of recurrence during the first year, rofecoxib did not improve overall survival or prevent recurrence [23]. Because rofecoxib was withdrawn from the market during the study period for reasons of its cardiovascular adverse event profile, and because there is still significant interest in the potential role of COX-2 inhibitors in secondary cancer prevention, a new Phase III trial to test the efficacy of celecoxib (also a COX-2 inhibitor with fewer cardiovascular adverse effects, similar to NSAIDs) to improve survival after colorectal cancer surgery is now open in the adjuvant setting with chemotherapy [23]. However, we assume that failure to obtain the expected favorable results in the earlier trial may be partly explained by initiation of rofecoxib or placebo treatment after patients had completed routine medical therapy (surgery ± radiotherapy ± chemotherapy) [23]. Thus, these patients were not treated with rofecoxib during the critical perioperative period when tumor micrometastasis may be more likely to occur. Maximal therapeutic benefit might have been realized if rofecoxib had been given during this time. At the time of randomization, patients had already experienced perioperative immunosuppression (see below), and residual micrometastasis might have already been established. Furthermore, after radiation and chemotherapy, it is expected that the surviving microtumors were selected for their growth advantages.

Propofol and its COX-inhibiting property

Propofol suppresses COX activity in vitro

Propofol appears to inhibit PGE_2 production from the human monocytic leukemia cell line THP-1 [24], human peripheral monocytes [25], and murine peritoneal macrophages [26]. Suppression occurred through direct inhibition of COX enzyme activity rather than downregulation of COX expression or inhibition of AA release from the plasma membrane [24–26]. Propofol also inhibits the activity of purified COX enzymes, inhibiting COX-2 significantly more than COX-1 [25]. Thus, propofol should also inhibit COX in tumors as well as in other tumor-infiltrating, COX-producing, immune and nonimmune cells.

For clinical use, propofol is dissolved as a lipid-emulsified formulation. The major vehicle ingredient, linoleic acid, could be a source of AA [27] and therefore may modify the effects of propofol on COX activity. In human monocytes, both propofol and diprivan suppressed the production of PGE_2; however, the degree of suppression was significantly less with diprivan than with propofol [25]. Thus, in the presence of the lipid vehicle, the COX-inhibiting property of propofol is somewhat attenuated.

An example of propofol COX-inhibiting activity altering immune reaction

Although definitive evidence of how propofol COX-inhibiting activity leads to antitumor immunity is lacking, one example of the effect of propofol on immune reactions may be relevant to its antitumor properties. Here, murine thioglycollate-elicited peritoneal macrophages were cocultured with NK cells in the presence of propofol [26]. In the coculture, propofol dramatically increased NK cell interferon (IFN)-γ production, which was instigated by interleukin (IL)-12/IL-18 [28], and the actions of propofol were mimicked by the selective COX-2 inhibitor, NS-398, as well as the selective EP4 receptor antagonist L-161,982 [26]. The results indicate that, in macrophage:NK cell coculture, propofol, via the suppression of macrophage PGE_2 production, upregulates NK cell IFN-γ production by alleviating the EP4 receptor-mediated suppression of IFN-γ production [26, 28] (Fig. 1). The net effect is the activation of NK cells by propofol.

In tumors in vivo, tumor-associated macrophages (TAMs) may be abundant [29]. The TAMs usually do not attack tumors; rather, via production of PGE_2, they may facilitate the growth of tumors and help the tumors evade immune attack by NK cells and cytotoxic T cells (CTLs) [29, 30]. In such circumstances, propofol, by inhibiting PGE_2 production from TAMs, may disrupt the tumor growth-facilitating microenvironment and promote tumor destruction by activated NK cells. This is one scenario in which the COX-inhibiting activity of propofol may lead to enhanced antitumor immunity.

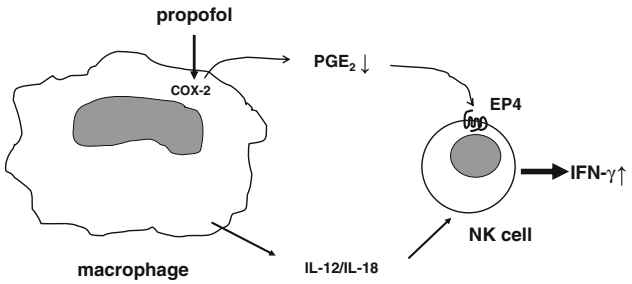

Fig. 1 Schematic depiction of propofol-induced increased interferon-γ (*IFN-*γ) production in macrophage:natural killer (*NK*) cell coculture. Activated macrophages secrete interleukin 12 (*IL-12*) and *IL-18*, which stimulate NK cells to produce IFN-γ. Macrophages also produce prostaglandin E_2 (PGE_2), which acts on *EP4* receptor on NK cells to downregulate IFN-γ production. Propofol, through inhibition of PGE_2 production, relieves EP4 receptor-mediated downregulation of IFN-γ production, leading to the net upregulation of IFN-γ production

Reported studies that indicate antitumor properties of propofol

There is evidence from both in vitro and in vivo laboratory studies that propofol has antitumor properties. However, whether the reported antitumor properties of propofol are related to the COX-inhibiting activity of propofol is not known.

In vitro studies

Propofol, in vitro, may directly suppress the viability, proliferation, and invasiveness of tumor cells, depending on the types of tumors examined. For example, in human promyelocytic leukemia HL-60 cells, propofol treatment resulted in apoptosis through activation of caspase-3, -6, -8, and -9, with consequent formation of the cleaved product of Bid (a pro-apoptotic Bcl-2 family member protein) and activation of the mitochondrial pathway, resulting in cytosolic release of cytochrome *c* [31]. In the human colon carcinoma cell line LOVO, propofol stimulation significantly decreased the expression of MMP-2 and -9, leading to decreased invasive activity of the cancer cells as measured using a Matrigel-coated transwell assay [32]. The decreased expression of MMPs was mediated mainly through the GABA-A receptor, followed by downregulation of ERK-1/2. In another study using a type IV collagen-coated transwell assay, propofol suppressed the migration of several human cell lines, including Hela cervical

carcinoma cells, HT1080 fibrosarcoma cells, HOS osteosarcoma cells, and RPMI-7951 melanoma cells [33]. When the Hela cells were treated with propofol, the formation of actin stress fibers as well as focal adhesions was inhibited through modulation of Rho A, which may account for the decreased migration [33].

In vivo studies

To examine the antitumor property of propofol in vivo, lung metastasis was studied after murine osteosarcoma inoculation in the backs of mice. Continuous infusion of propofol into the peritoneal cavity with an osmotic pump significantly decreased the number of pulmonary nodules without affecting the growth of the tumor at the inoculation site [33]. Other studies focused mainly on immune reaction-mediated tumor suppression by propofol rather than direct tumor suppression. Among immune cells that may provide surveillance against tumors are NK cells and CTLs [34]. In animal studies, propofol may modulate the immune reaction to suppress tumors. For example, the activity of circulating NK cells was not affected by propofol, whereas it was significantly reduced with ketamine, thiopental, and halothane [35]. Consistent with this, lung tumor retention and metastasis of MADB106 mammary adenocarcinomas were not affected by propofol, whereas they were significant with ketamine, thiopental, and halothane [35]. Therefore, in contrast to other anesthetics tested, the NK cell-suppressing effect of propofol may be minimal. In a clinical study, NK cell activities were compared in patients undergoing ophthalmic surgery under enflurane/nitrous oxide/oxygen anesthesia, droperidol/fentanyl/nitrous oxide/oxygen anesthesia, or droperidol/ketamine/fentanyl/oxygen anesthesia. On the first postoperative day, the enflurane anesthesia group, but not other groups, was associated with decreased NK cell activity, indicating that, compared to intravenous anesthetics, volatile anesthetics might be particularly immunosuppressive for NK cells [36].

Intraperitoneal injection of propofol significantly upregulated the activity of CTL against EL4 tumor cells, which may contribute to the delayed EL4 tumor growth in mice [37].

Dendritic cells (DCs) are another type of cell that may have a critical role in antitumor immunity by presenting tumor-specific antigens to effector cells in the immune system [34]. In one study, bone marrow-derived DCs produced in the presence of propofol were used as a DC vaccine to examine its efficacy against inoculated B16 melanoma cell growth in mice [38]. The propofol-treated DC vaccine was more effective in delaying tumor growth than vehicle-treated DC vaccine. In this experiment, CTL activity was equally upregulated with both propofol-treated and vehicle-treated DCs, but the NK cell activity against both B16 melanoma cells and YAC-1 cells (a cell line highly sensitive to NK cell killing) was stronger with the propofol-treated DC vaccine. Therefore, in this mouse model, propofol seems able to upregulate NK cell activity by differentiating DCs to be efficient in DC-NK crosstalk.

Effects of propofol lipid vehicle on antitumor immunity

In clinical settings, propofol is dissolved in a lipid emulsion, of which one example is diprivan. The main ingredient of the diprivan vehicle is soybean oil, which contains a high percentage of linoleic acid [27]. Previous studies indicated that the diprivan vehicle itself delayed EL4 tumor growth in mice [37, 39]. Thus, the lipid vehicle has a weak antitumor property. That lipids may have an antitumor property is not new, as evidenced epidemiologically by the strong link of consumption of fish oil [which is rich in docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)] to low incidences of several types of cancer [40, 41]. In this respect, it is interesting that Siddiqui et al. [42] reported anticancer properties of propofol–DHA and propofol–EPA conjugates against breast cancer cells.

Tumor dissemination during surgery and COX inhibition

By the time an established solid tumor in a primary site is detected, host immune surveillance against the tumor is probably ineffective because the tumor has created its niche by modifying the tumor microenvironment in such a way that malignant cells can further flourish and progress and be protected from the surrounding harsh environment [34, 43]. Therefore, the most effective way to eradicate such solid tumors is surgery. During surgery, microdissemination of tumor cells from their primary site may occur, as demonstrated by the polymerase chain reaction (PCR) detection of tumor DNA in blood obtained at the time of surgery [44]. After seemingly “curative” surgical tumor resection, “minimum residual disease” remains, which might be “minimum” enough to be managed by the host immune surveillance [34]. Host surveillance against metastasis is critically important, because an estimated 90% of cancer-related deaths is attributed to the metastatic spread of cancer [45].

Among cells involved in host immune surveillance, NK cells may be one of the most crucial to eradicate minimum residual disease [34, 46]. Eradication may be more efficacious when tumor invasiveness is attenuated by the use of COX inhibitors. Higher COX-2 expression in a tumor is reported to make the tumor more prone to metastasis [4]; inhibition of COX-2 with propofol may discourage primary tumors from disseminating to distant sites. COX-2

inhibition of tumors may also preclude the new establishment of tumors at distant sites of metastasis by preventing the formation of a tumor-favorable microenvironment [4].

Surgery, immunosuppression, and COX inhibition

Surgery induces immunosuppression

Surgery suppresses the immune system [47, 48] through the following sequence of events. Catecholamines are released in response to surgical stimulation as a result of activation of the sympathetic nervous system [49]; upon surgical stimulation, the hypothalamic–pituitary–adrenal (HPA) axis is activated and glucocorticoids are released [49]. Surgery also inevitably damages tissues, resulting in the release of proinflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor-α, which stimulate the HPA axis, leading to the release of glucocorticoids [50]. Such released catecholamines and glucocorticoids, through β2-adrenergic and glucocorticoid receptor stimulation, respectively, inhibit proinflammatory cytokine production and promote antiinflammatory cytokine production, leading to immunosuppression after surgery [51–53]. Because surgery induces immunosuppression, especially suppression of NK cell activity, it could leave patients susceptible to metastasis from primary tumors after cancer surgery [54, 55].

COX-2 inhibition and surgical stress alleviation

COX-2 inhibition in combination with alleviation of surgical stress is especially advantageous for preventing metastasis, as evidenced by two laboratory studies. In one study, Benish et al. [56] employed β-blockers and COX-2 inhibitors in a rat model of laparotomy to simulate postoperative tumor metastasis. Blocking catecholamine responses with a β-blocker (proporanolol) and PGE_2 production with a COX-2 inhibitor (etodolac) successfully attenuated the suppression of NK cell activity and reduced metastasis to the lungs. In a similar study, the same treatment combination improved NK cell activity and reduced the death rate caused by metastasis after amputation of the B16 melanoma-bearing paw [57]. Thus, surgical stress alleviation plus COX-2 inhibition could be a very efficacious strategy for mitigating postoperative metastasis.

Use of propofol as a component of anesthesia

Current studies implied that anesthetic technique alters the serum molecular milieu in ways that may affect cancer cell function, possibly by altering anesthetic and opioid drug administration and resultant pain scores [58, 59]. The COX-2-inhibiting property of propofol may be exploited during the perioperative period. Further evidence may favor the use of propofol as a component of anesthesia. In surgical patients, propofol-based total intravenous anesthesia attenuated the stress (assessed by measuring the serum cortisol concentrations) [60, 61] and stress-induced adverse response (assessed by measuring the lymphocyte Th1/Th2 ratios) [62] more efficiently than isoflurane/opioid anesthesia. Thus, besides its COX-inhibiting property, propofol might be a better choice than isoflurane for cancer surgery with respect to the suppression of surgical stress, stress that might make patients susceptible to tumor metastasis.

Conclusion

Propofol displays antitumor properties in laboratory settings. Propofol also inhibits COX in vitro. Thus, it may be plausible that part of the antitumor properties of propofol can be ascribed to its COX-inhibiting activity. However, in clinical settings, the questions of whether propofol also possesses antitumor properties and whether this is the result of its COX-inhibiting property remain to be answered.

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