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REVIEW ARTICLE

Phosphodiesterase-5 inhibitors in the management of cancer

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ABSTRACT

Selective phosphodiesterase type-5 (PDE5) inhibitors such as sildenafil, vardenafil and tadalafil are commonly used first-line therapy for erectile dysfunction (ED). The safety and high tolerability of these drugs has garnered substantial interest among researchers to investigate further beneficial nonerectogenic uses for such drugs. PDE5 expression has shown to be increased in several human malignancies, suggesting that this enzyme may play a role in tumorigenesis. This is supported by the reported anticancer activity of PDE5 inhibitors such as exisulind and its analogs, as well as vardenafil. Further, PDE5 inhibitors have recently been reported to sensitize certain types of cancer to standard chemotherapeutic drugs. The aim of this review is to shed some light on the existing preclinical evidence supporting the use of PDE5 inhibitors as potential effective adjuncts in cancer chemotherapy and even as anticancer agents. I also showed our recent unpublished data with regard to the promising antitumor activity of vardenafil, a potent PDE5 inhibitor, against brain cancer.

Keywords: Phosphodiesterase type-5 inhibitors; sildenafil, tadalafil; vardenafil; cancer; leukemia; ABC transporters.

INTRODUCTION

The 3′,5′-cyclic nucleotide phosphodiesterases (PDEs) are intracellular enzymes that specifically hydrolyze the 3′-phosphoester bond of the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanylate monophosphate (cGMP) to their biologically inactive non-cyclic 5′–monophosphate derivatives AMP and GMP [1, 2]. By regulating the localization, duration and amplitude of signaling by such second messengers within subcellular domains, PDEs can play a critical role in intracellular signaling by controlling cAMP- and cGMP-regulated proteins and transcription factors [3, 4]. To date, there are at least 11 different families of mammalian PDEs, namely PDE1-PDE11, alternatively spliced in a tissue-specific manner, generating various mRNAs and proteins with altered regulatory properties. These cyclic nucleotide PDEs are usually homodimers, and there is a similarity in their structures [5]. They are classified based on sequence homology, sensitivity to inhibitors, regulatory properties, tissue distribution and enzymatic properties, including substrate specificity (cAMP versus cGMP) [3, 6]. PDEs have come into focus of biomedical research as interesting potential targets for PDE inhibitor-based therapies. This came from the fact that PDE inhibitors can prolong or augment the effects of physiological processes mediated by cAMP or cGMP by inhibiting their degradation [7, 8].

PDE5 AS AN INTERESTING THERAPEUTIC TARGET

Some of the several families of PDEs can hydrolyze cGMP, however only PDE5 exclusively catalyses the hydrolysis of cGMP, thereby lowering intracellular cGMP [7]. PDE5 is encoded by one gene PDE5A with the existence of three alternatively spliced PDE5 isoforms: PDE5A 1 (100 kDa), PDE5A2 (95 kDa) and PDE5A3 (95 kDa). These splice variants differ only in the 5′ ends of their corresponding mRNAs and N-terminals [3, 8]. PDE5, made from GTP in a reaction catalyzed by guanylyl cyclases, is highly expressed in smooth muscle cells of the corpus cavernosum. PDE5 is also expressed in various other tissues, including vascular smooth muscle, skeletal muscle and platelets [9]. In addition, PDE5 is expressed in various immune cells, including macrophages, dendritic cells (DCs) and T cells [10]. Moreover, PDE5 has been recently shown to be highly expressed in multiple human malignancies,

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including non–small cell lung cancer [11], urinary bladder cancer [12] and metastatic breast cancer [13]. Therefore, continuing advances in the understanding of the molecular pharmacology of PDE5 has led to the development of selective PDE5 inhibitors, including sildenafil and exisulind, as therapeutic agents for a broad array of conditions ranging from erectile dysfunction (ED) and heart failure to cancer [14, 15].

POTENTIAL ROLES FOR PDE5 INHIBITORS IN CANCER THERAPY

The increased expression of PDE5 in various human malignancies and the lack of such expression in normal cells, coupled with the great success of PDE5 inhibitors in the treatment of ED and their safety and high tolerability, have led to an increased interest in investigating their possible roles in the management of cancer. Thus, PDE5 inhibitors have been examined for: 1) direct anticancer effects on cancer cell lines; 2) sensitizing cancer cells to chemotherapeutic agents and 3) cancer chemoprevention.

PDE5 inhibitors as promising anticancer agents

Following clinical improvement of one previously untreated chronic lymphocytic leukemia (CLL) patient with sildenafil therapy (50 mg once a week) in the absence of any other treatment, Sarfati et al. [16] were prompted to examine four PDE5/6 inhibitors, namely sildenafil, vardenafil, zaprinast and methoxyquinazoline (MQZ), for the in vitro induction of apoptosis in CLL cells. Vardenafil induced caspase-dependent apoptosis and was 3 and 30 times more potent an inducer of apoptosis than sildenafil and MQZ, respectively. Zaprinast exerted no killing effect. Normal B lymphocytes isolated from control donors were completely resistant to the PDE5 inhibitor-induced apoptosis. These results reveal that both vardenafil and sildenafil exert a preferential pro-apoptotic activity against cancer cells. Sildenafil has also shown promising anticancer activity against Waldenstrom's Macroglobulinemia (WM), an incurable B-cell malignancy [17]. In this study, Treon et al noticed an unusual response activity in five patients with WM apparently related to their use of sildenafil, with one patient exhibited a remarkable complete remission and four other patients demonstrated less dramatic, but also unexpected responses. The results of the above mentioned studies substantiate previous findings showing that the PDE5 inhibitor exisulind (Sulindac sulfone), a derivative of the oral anti-inflammatory drug sulindac induced apoptosis and inhibited cell proliferation in several human tumor cell lines [18, 19]. The drug appeared to exert its pro-apoptotic effects by inhibiting PDE5, causing a persistent increase in cellular cGMP, and inducing cGMP-dependent protein kinase (protein kinase G; PKG) [18]. It has also been shown to directly inhibit growth of human prostate cancer [20] and lung tumors [11] in murine models by enhancing apoptosis. Another study by Zhu et al. [21] confirmed the importance of PDE5 as a therapeutic target for treatment of cancer through a genetic approach. They reported that transfection of human colonic carcinoma (HT29) cells with PDE5 anti-sense constructs results in suppression of PDE5 gene expression, sustained increase in intracellular cGMP concentrations, growth inhibition and apoptosis.

PDE5 inhibitors sensitize cancer cells to chemotherapeutic agents

One of the major obstacles in the successful treatment of cancer is MDR. One of the most important causes of MDR, both *in vitro* and *in vivo*, is over-expression of the adenosine-triphosphate-binding cassette (ABC) transporters, such as ABC sub-family B member 1 ABCB1 (P-glycoprotein/MDR1), the most important mediator of MDR, multidrug resistance proteins (ABCCs/MRPs) and breast cancer resistant protein (ABCG2/BCRP). When such transporters are overexpressed in cancer cells, they actively pump out a variety of structurally and mechanistically unrelated chemotherapeutic drugs out of cancer cells, thereby lowering the intracellular drug accumulation. This mechanism was shown to be responsible for chemotherapeutic drug resistance to various anticancer agents, including anthracyclines, vinca alkaloids, epipodophyllotoxins and taxanes [22, 23]. In addition, a considerable body of evidence also points to the importance of ABC transporters in tumorigenesis [24]. Interestingly, Jedlitschky et al. [25] discovered a link between cGMP elimination and ABC transporters. They showed that the multidrug resistance protein isoform MRP5 (ABCC5) mediates cellular export of cGMP and that sildenafil, the classic PDE5 inhibitor, enhances intracellular cGMP concentrations by a dual action involving inhibition of both its degradation by PDE5 and its export by ABCC5. In this regard, Shi et al. [22] recently reported that sildenafil significantly decreased the efflux activity of the ABC transporters ABCB1 and ABCG2, but had no significant effects on ABCC1. They also assessed the effect of another PDE5 inhibitor, vardenafil, on ABC transporter-mediated MDR in cancer cells and reported that vardenafil significantly sensitized ABCB1 over-expressing cells to the ABCB1 substrates vinblastine and paclitaxel. Further, Chen et al. [26] recently showed that sildenafil and vardenafil enhanced the sensitivity of multidrug resistance protein 7 (MRP7; ATP-binding cassette C10)-transfected HEK293 cells to paclitaxel, docetaxel and vinblastine, and reversed MRP7-mediated MDR through inhibition of the drug efflux function of MRP7.

However, these results need to be corroborated by additional studies, particularly when it comes to *in vivo* studies. Very recently, Lin et al. [27] have reported that sildenafil, at a supraclinical dose (50mg/kg) did not improve the brain penetration of docetaxel and

topotecan, even though it increased the plasma concentrations of the two drugs, but not via inhibition of ABCB1 or ABCG2. They also have showed that sildenafil did not improve the efficacy of doxorubicin against subcutaneous CT26 colon tumors in mice. Nonetheless, Black et al. [28] reported that sildenafil and vardenafil increased the transport of doxorubicin across blood-brain tumor barrier in 9L gliosarcoma. Vardenafil also potentiated the efficacy of doxorubicin in the 9L gliosarcoma-bearing rats. These effects appeared to be mediated by a selective increase in tumor cGMP levels and increased vesicular transport through tumor capillaries, although the involvement of ABC transporters in such effects was not reported in this study. Moreover, it has been recently reported that co-treatment with sildenafil enhanced the antitumor efficacy of doxorubicin in both prostate cancer cells, *in vitro*, and in mice bearing prostate tumor xenografts, while simultaneously ameliorating doxorubicin-induced cardiac dysfunction [29]. The increased apoptosis by sildenafil and DOX was associated with enhanced expression of proapoptotic proteins caspase-3, caspase-9, Bad and Bax and suppression of the anti-apoptotic protein Bcl-xL. Furthermore, in a clinical study, sildenafil (50 mg) has aided radiotherapy for the treatment of Kaposi's sarcoma of the penis. In this study, sildenafil, combined with manual sexual stimulation, aided in achieving an appropriate focusing of the electron beam therapy on the lesions, resulting in complete resolution of such lesions [30].

Another PDE5 inhibitor, exisulind, has been utilized in several pre-clinical, as well as clinical studies to augment the chemotherapeutic efficacy of well-known anticancer agents. Exisulind in combination with docetaxel has been shown to prolong survival, inhibit tumor growth and metastases and increase apoptosis in athymic nude rats with orthotopic lung tumors [31]. These results have been corroborated by Whitehead et al. [11] who have shown that exisulind-induced apoptosis significantly enhanced docetaxel anticancer effects in non-small cell lung cancer orthotopic lung tumor, and that the mechanism of exisulind-induced apoptosis involves inhibition of PDE5. Unfortunately, exisulind does not appear to enhance antitumor activity of many anticancer agents, including docetaxel [32, 33], gemcitabine [34], docetaxel/carboplatin [35], carboplatin/etoposide [36] and estramustine/docetaxel [37].

PDE5 inhibitors as cancer chemopreventive agents

The high expression of PDE5 in cancerous cells, coupled with the high safety profile of PDE5 inhibitors, has encouraged researchers to investigate cancer chemopreventive activity of such drugs. One of the earliest studies in this regard was that reported by Thomson and colleagues [38]. They showed that sulindac sulfone (exisulind) dose-dependently inhibited 1-methyl-1-nitrosourea (MNU)-induced mammary carcinogenesis in rats, and at concentrations that were well tolerated by the animals. In addition, Piazza et al. [39] have reported that sulindac sulfone dose-dependently suppressed azoxymethane-induced colon carcinogenesis in rats without reducing prostaglandin levels. Moreover, exisulind has been shown to inhibit N-butyl-N-(4-hydroxybutyl) nitrosamine-induced rat urinary bladder tumorigenesis, at least in part by cGMP-mediated apoptosis induction [12]. Furthermore, nitric oxide donor exisulind inhibited UVB-induced skin tumor development in a murine model [40] by blocking proliferation, inducing apoptosis and reducing epithelial-mesenchymal transition (EMT) markers in tumor keratinocytes. Clinically, exisulind has shown modest chemopreventive activity in patients with familial adenomatous polyposis (FAP), as suggested by regression of small polyps and stimulation of mucus differentiation and apoptosis in glandular epithelium [41, 42]. In addition, exisulind has been shown to significantly prevent the increase in prostate specific antigen (PSA) and prolonged PSA doubling time in men with increasing PSA after radical prostatectomy compared with placebo [43].

ONGOING RESEARCH IN OUR LABORATORY

PDE5 is highly expressed in many brain tumor cell lines, brain capillary endothelial cells and human brain tumor samples [28]. Therefore, we recently examined the anticancer activity of the highly potent PDE5 inhibitor vardenafil against two brain cancer cell lines, namely the human medulloblastoma Daoy cell line and rat C6 glioma cells in vitro. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide) results showed that vardenafil suppressed the proliferation of both cell lines in a dose dependent manner (Ashour et al., unpublished data). In addition, Annexin V propidium iodide assay results revealed that the inhibition of Daoy and C6 cell growth is mediated, at least in part, by inducing Daoy and C6 cell apoptosis. Wound healing and soft agar colony formation assays showed that VAR inhibited the migration and anchorage-independent growth of both cell lines, respectively. Taking all these results in consideration, we recently investigated the antitumor efficacy of vardenafil in an orthotopic murine glioma model. Vardenafil significantly inhibited tumor growth and prolonged survival of glioma bearing rats, as compared to control treated animals. These results suggest that vardenafil is a promising anticancer agent against brain cancer (Ashour et al., unpublished data).

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