

Vanadium: Possible Use in Cancer Chemoprevention and Therapy

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Abstract: Vanadium belongs among the microelements and plays a role in human nutrition. However, it is not regarded as an essential micronutrient. Vanadium affects various biochemical processes and when present in the body, it is capable of interacting with a notable number of enzymes e.g. protein kinases, phosphatases, ATPases, peroxidases, ribonucleases, oxidoreductases and others. It is documented in scientific literature that vanadium takes part in biochemical processes in mammals. Vanadium is not carcinogenic but its presence in cancer cells and its interactions with many key enzymatic processes results in modified expression of p53 and Bax and in down regulation of Bcl2 proteins and in antiproliferative activity. Anti-carcinogenic and anticancer effects of vanadium in various forms have been demonstrated using *in vitro* and *in vivo* experiments. Presently, epidemiologic and clinical studies are necessary for developing a clinically useful, vanadium-based anticancer agent/drug for chemoprevention of cancer. This review summarizes recent scientific information on the role and potential use of vanadium in cancer chemoprevention and cancer therapy.

Keywords: Vanadium, vanadium-containing compounds, anti-cancer activity, chemoprevention, anti-carcinogenic effect, apoptosis, antiproliferative activity.

INTRODUCTION

The presence and role of vanadium in biological system is not considered as highly important and its role in human biology and diseases is not fully understood. In some species e.g. chicken and rats, it was shown that vanadium deficiency impairs reproduction [1] while pharmacological doses of vanadium may increase insulin sensitivity [2]. It was documented that vanadyl sulfate helps to control glucose levels in patients with type 2 diabetes [3-5] and various investigations have been carried out with the intention of using vanadium-containing compounds in diabetic patients.

Vanadium is present in nature as bivalent, trivalent, tetravalent or pentavalent. All types of vanadium substances are considered toxic in high quantities, however not all of them have been fully investigated for their various possible biological effects (including toxicity). It was shown that tetravalent vanadium in the form of VO_2SO_4 (vanadyl sulfate) was approximately 5 times more toxic compared to trivalent vanadium in the form of V_2O_3 (vanadium trioxide, vanadium(III) oxide) [6]. Despite this, no vanadium compound has been classified as carcinogenic and this is important for its potential use in cancer therapy [7].

Vanadium in peroxovanadium complexes irreversibly inhibits the majority of tyrosine phosphatases. It also affects many other enzyme systems, including phosphatases, ATPases,

peroxidases, ribonucleases, protein kinases, oxidoreductases and possibly other enzymes [8]. However, a direct relationship between interaction with these particular enzymatic systems and vanadium anti-cancer or anti-carcinogenic activities is not always obvious. Additionally, vanadium in the form of vanadate mimics phosphate in forming reversible bonds with thiol groups of enzymes [9, 10]. It is documented that vanadium in various forms damages DNA [11, 12]. One of the proposed mechanism of DNA damage involves generation of ROS (reactive oxygen species) by vanadium and vanadium-containing compounds [13].

The daily intake of vanadium was determined to vary between 10 μg and 2 mg [14]. The same authors [14] claim that it is essential for animals in concentrations of 1-10 μg but the fact that vanadium is essential for human is not yet established and there is no recommended daily intake by an established healthcare organization (such as Food and Drug Administration, USA). On the other hand, a therapeutic potential of vanadium in human disease is clear [15-17]. There is evidence [18] on the ability of vanadium (in the form of NaVO_3) to promote changes in gene expression even in the absence of vanadium for numerous cells divisions (*in vitro*).

The aim of this work is to review recent findings dealing with potential use of vanadium and vanadium-containing substances in cancer therapy.

VANADIUM IN VARIOUS OXIDATION STATES AND DNA DAMAGE

As mentioned above, vanadium is capable of damaging DNA in the form of inorganic ions or in the

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form of more complex vanadium-containing substances, such as peroxidovanadium (V) complexes [11]. As DNA of cancer cells is the primary target of anticancer therapy, it is important to assess the extent of vanadium's interaction with DNA. This can be done by measuring hyperchromicity in DNA spectra as a high vanadium or vanadium-containing compound interaction with DNA indicates possible antiproliferative activity of these substances [11].

The ability of vanadium and vanadium-containing salts and complexes to interact with DNA is a cause of genotoxicity and other biological effects of vanadium. However, vanadium in different oxidation states (III, IV, V) induces such effects with different abilities as shown in a recent study using human blood leukocytes [11]. It was clearly demonstrated that vanadium produces genotoxic effect in any of these three oxidative states but only vanadium (IV) caused double-strand DNA breaks that were related to consequent chromosomal aberrations [11]. Another study [19] also demonstrated that various oxidation states of vanadium induced cytotoxicity but only vanadium in the oxidation state IV was capable of inducing clastogenic effects. In addition, low genotoxic activity of vanadium (V) was also demonstrated *in vivo* only after exposure to high doses of vanadium (V), possibly due to its low bioavailability [20]. The reasons for differences among various vanadium oxidative states in cytotoxicity is its ability to form double strand DNA breaks, clastogenic effects etc and these are not yet fully elucidated. Additionally, effects observed *in vitro* may not be observed *in vivo* and *vice versa*. Comparative bioavailability, transport and toxicity studies of vanadium in different oxidative states are necessary for getting more precise information on vanadium-DNA interactions.

VANADIUM AND DETOXIFICATION OF ROS (REACTIVE OXYGEN SPECIES)

Vanadium and vanadium-containing compounds modify ROS levels in biological systems [23-25]. It was shown that 5 days exposure of brain tissue to metavanadate (NaVO_3) led to formation of significant quantities of ROS and to changes in the oxidative defense system while catalase and Cu-Zn sodium dismutase activities were not affected [23]. The exposure to metavanadate led to a decrease in the GSH/GSSG ratio [23].

Other vanadium-containing molecules, VOSO_4 and bis (quercetinato) oxovanadium (IV) (BQOV), also

demonstrated increases in ROS formation in a time- and dose-dependent manner [23] and the exposure of rodents to VOSO_4 led to relatively significant necrosis of CHO cells *in vitro* and also to tubular necrosis *in vivo* [24]. The later finding was accompanied by changes in parameters indicating kidney dysfunction.

At the molecular level, vanadium in the form of vanadate is reduced by cysteine, glutathione and by other biological thiols. Vanadium reduction by NADPH (vanadium (V) to vanadium (IV)) [21], by L-cysteine methyl ester (CysME; vanadium(IV) to vanadium(III)) [21, 22] and an interaction between VO^{2+} cation and homocysteine [22] were also investigated in detail [21]. The above interactions are affected by steric parameters of molecules that contain thiol (-SH) functionalities. In polymeric molecules, the ability to form a complex with various molecules containing vanadium is more obvious as the reactivity of thiol groups is decreased due to steric conditions. In monomers of various biomolecules (e.g. actins), thiol groups are significantly more accessible to vanadium molecular species and are therefore oxidized easily with vanadium compounds while an increased reduction of vanadium ions (a reduction of vanadium (V) to vanadium (IV) takes place [25].

Detoxifying processes are important for protecting normal cells from the action of vanadium and vanadium-containing substance when toxic effects, especially formation of ROS may take place [23]. On the other hand, vanadium interactions with biological thiols may decrease its anticancer properties in cells that have undergone malignant transformation. In such cells, it is desirable to increase interactions of vanadium compounds with cellular macromolecules, especially with DNA, in order to induce apoptosis or necrosis of such malignant cells. These scientific findings [23] show the necessity of taking into account differences in chemical structure of vanadium-containing inorganic and organic substances when evaluating vanadium effects in various biological systems in order to maximize damaging effects to cancer cells while minimizing these effects in normal host cells. The limitations of the various models used for studying biological and side effects of vanadium should also be taken into consideration when interpreting experimental results.

VANADIUM IN RELATION TO APOPTOTIC PROCESSES

Apoptosis, including vanadium-induced apoptosis, is a very significant and complex cellular process

involving a high number of metabolic pathways. This is expressed through up- and down-regulation of various proteins. Vanadium compounds may exhibit various antitumor and carcinogenic properties that depend on the research model used. For example, it is documented that vanadium and vanadium-containing substances inhibit p53-dependent apoptosis while they also help cells with functional p53 to enter into S phase [26].

An important aspect of vanadium biological activity is that removal of damaged precancerous cells by apoptosis can prevent establishing of malignant cells in an organism and further development of cancer. A significant positive correlation between p53 immun-expression and intensity of apoptotic processes is linked to vanadium-mediated apoptotic induction [27]. Complexes of vanadium with various quinolone or pyridinone ligands possess antiproliferative caspase-independent activity (*in vitro*) depending mainly on lipophilicity of these compounds [28]. Additionally, chronic daily intake of vanadium (more than 15 mg/kg) causes lymphocyte apoptosis because of mitochondrial injury accompanied by changes in concentrations of apoptogenic proteins (Bcl-2, Bax and caspase-3) [29].

Some other published work found conflicting data. Orthovanadate was capable of inducing a pro-proliferative response in low doses but its inhibitory concentrations activated PI3K/Akt signaling pathway and induced DNA fragmentation and other processes typical of apoptosis [30]. It was also shown that vanadium, in complexes with organic substances, may act as a sensitizer enhancing cell arrest in a specific cell-cycle phase and also enhancing apoptosis [31]. Elucidation of the mechanisms involved in these processes, induced by taxol, showed that this results in a decrease in the ratio of Bcl-2 and Bax concentrations. This change is thought to be responsible for decreasing the apoptotic threshold of treated cells [31]. Additionally, it was shown that vanadium compounds initiate apoptosis through induction of oxidative stress in mitochondria resulting in mitochondria permeability transition pore (PTP) opening that consequently leads to collapse of Deltapsi (m) and Cyt c release as the initiation of cell apoptosis [32]. Also, sensitizing of HaCaT keratinocytes *in vitro* to apoptotic processes by their exposure to vanadyl (IV) sulfate $VOSO_4$ demonstrated that this exposure resulted in the antiproliferative effects. Apoptosis mediated by $VOSO_4$ was stimulated by the oncoprotein c-fos and this, consequently, led to changes in clustering (CLU)

isoform processing and to the pro-death protein, nCLU (nuclear CLU) induction [33].

VANADIUM IN CANCER CHEMOPREVENTION

Anticancer properties of vanadium were studied not only on developed cancers but also in situations where cancer development was prevented or stopped. The reported data deal mainly with mammary and hepatocellular cancers. In one of the early reports, Thompson *et al.* [34] reported on the ability of vanadium in the form of vanadyl (IV) sulfate to block mammary carcinogenesis in rodents when given as a part of their diet. This diet was evaluated as non-toxic for experimental animals. These findings were confirmed by later results [35]. It was established that vanadium in diet improves concentration of antioxidants in various tissues and modulates activities of drug metabolizing enzymes (phase I and II). Consequently, it protects against mammary carcinogenesis induced by dimethylbenz (a) anthracene (DMBA) in experimental rodents. This conclusion was supported by histological findings indicating that no sign of hyperplasia or other abnormality was present in mammary tissue after vanadium supplementation. Also, parameters of incidence, total number, multiplicity and size of palpable mammary tumors were significantly improved [35]. Moreover, vanadium supplementation was shown to reduce genomic instability in mammary carcinoma in rats [36] as the mammary cells were protected against generation of single-strand breaks in their DNA. Protection against chromosomal aberrations *in vitro* was also documented [36]. Some studies support the idea of beneficial effects by administration of vanadium together with fish oil for preventing mammary carcinogenesis [37]. It seems that the vanadium-fish oil combination reduces DNA strand breaks, incidence of palpable mammary tumors and cell proliferation. Additionally, it activates apoptotic processes in malignant cells [37]. Although, the mechanism of this interaction is not clear, it was shown that women with higher concentrations of vanadium in their body (measured as vanadium concentration in urine) had significantly decreased risk of breast cancer [38]. This finding shows the importance of optimal concentrations of vanadium in the diet for prevention of breast cancer and possibly other cancers.

The role of vanadium was investigated relatively extensively in hepatocarcinogenesis using rats as hosts and diethylnitrosamine (DEN, 200 mg/kg body weight) as a carcinogen [39, 40]. In a long-term experiment, vanadium limited metallothionein (MT)

expression and led to a restoration of hepatic levels of essential trace elements, decreased incidence of nodules by almost 60% and also of their multiplicity in experimental animals [39, 41]. These results suggest a potential usefulness of vanadium for chemoprevention of liver cancer. Further elucidation of the molecular mechanism of vanadium action in preventing carcinogenesis [41] indicates that supplementation of vanadium (0.5 ppm) abated the formation of 8-hydroxy-2'-deoxyguanosines (8-OHdGs) by 81%, formation of DNA single-strand breaks (ss-DNA), DNA-protein cross links (DPC) by 59% and chromosomal aberrations (CAs) by 72% in preneoplastic rat liver [41]. All of these findings point to vanadium, an easily available substance, being suitable for exploitation as a chemopreventive agent which can be supplemented as part of a daily diet.

As discussed earlier, chemoprevention of cancer based on vanadium and vanadium-containing compounds has to be based on proper investigation of dosing of a specific type of a vanadium substance used in chemoprevention because of the potential for failure and toxicity. Also, the type of tissue where vanadium acts has to be taken into consideration [23]. It is likely that vanadium in oxidative tissue may be easily oxidized by ROS (thus detoxifying them) and may gain or lose its beneficial effect for chemoprevention of cancer due to its role in the cellular and molecular oxidative mechanisms..

VANADIUM IN CANCER THERAPY

There is limited data regarding the use of vanadium in therapy of cancer. The only information available in this regard is from experimental cancer therapy using various cancer cell lines and occasionally animal models. As much as vanadium and vanadium-containing substances seem to be suitable for development into clinically useful anticancer agents or cancer chemopreventive drugs due to their low toxicity and potential effect, no compound or vanadium-containing substances actually have made it to clinic and hence no clinical data on the use of vanadium or vanadium-containing substances to treat cancer patients is available at the moment.

The most interesting and relevant data were obtained with vanadium used in a rat mammary carcinogenesis model [42]. Histological results indicated repair of lesions with hyperplasia and immunohistochemical data indicated increase in apoptotic cells strongly expressing p53 and Bax and down regulating Bcl2 family of proteins with vanadium

[42]. These findings explained the decreased incidence, multiplicity and size of tumors. Other works confirmed these strong dose-dependent pro-apoptotic effects in mammalian cancer cells that resulted in a significant chromatin condensation and cell cycle arrest [43]. Promising results were also obtained with retinoic acid combined with various vanadium-containing inhibitors in neuroblastoma cells [44]. However, all these results are still far from clinical application.

Some studies have also examined the effects of vanadium compounds for potential use in cancer chemotherapy. However, many of these interesting compounds, even when cytotoxic to leukemia cells, possess other toxic effects or do not up-regulate anti-oncogenes. One such study investigated vanadocene dichloride effects [45] on human acute lymphoblastic leukemia cell line MOLT-4 and human peripheral blood mononuclear cells. Vanadocene demonstrated cytotoxicity in both types of cells (but stronger in peripheral blood mononuclear cells) but, in contrast to cisplatin, did not induce up-regulation of p53.

Other recently published data deal with the complex of the oxovanadium (IV) cation with the flavonoid silibinin [46]. Complexation with vanadium improved antioxidant properties of silibinin. The important aspect of the action of this flavonoid-vanadium complex was that it was more cytotoxic in cancer cells [46], and this is different when compared to vanadocene [45].

CONCLUSIONS

In general, it is clear that our knowledge on the potential of vanadium (in its various forms) use as a chemopreventive agent or as anticancer drug is not sufficient and that many preclinical, clinical and epidemiological studies are needed. These future studies need to investigate vanadium effects in various cancers and on various organs. This would very likely lead to synthesis and further development of new compounds with improved vanadium pharmacokinetics and pharmacodynamics and with limited toxicity. On the other hand, it is clear that exploiting vanadium and its potential for cancer prevention and therapy may bring significant benefit to the areas of human cancer detection, prevention and therapy, needs that are currently not optimally met.

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