

## Biochemical and medical importance of vanadium compounds

Jan Korbecki<sup>1</sup>, Irena Baranowska-Bosiacka<sup>1</sup>, Izabela Gutowska<sup>2</sup> and Dariusz Chlubek<sup>1</sup>

<sup>1</sup>Department of Biochemistry and Medical Chemistry, Pomeranian Medical University, Szczecin, Poland; <sup>2</sup>Department of Biochemistry and Human Nutrition, Pomeranian Medical University, Szczecin, Poland

Vanadium belongs to the group of transition metals and is present in the air and soil contaminants in large urban agglomerations due to combustion of fossil fuels. It forms numerous inorganic compounds (vanadyl sulfate, sodium metavanadate, sodium orthovanadate, vanadium pentoxide) as well as complexes with organic compounds (BMOV, BEOV, METVAN). Depending on the research model, vanadium compounds exhibit antitumor or carcinogenic properties. Vanadium compounds generate ROS as a result of Fenton's reaction or of the reaction with atmospheric oxygen. They inactivate the Cdc25B<sub>2</sub> phosphatase and lead to degradation of Cdc25C, which induces G<sub>2</sub>/M phase arrest. In cells, vanadium compounds activate numerous signaling pathways and transcription factors, including PI3K-PKB/Akt-mTOR, NF-κB, MEK1/2-ERK, that cause cell survival or increased expression and release of VEGF. Vanadium compounds inhibit p53-dependent apoptosis and promote entry into the S phase of cells containing functional p53 protein. In addition, vanadium compounds, in particular organic derivatives, have insulin-mimetic and antidiabetic properties. Vanadium compounds lower blood glucose levels in animals and in clinical trials. They also inhibit the activity of protein tyrosine phosphatase 1B. By activating the PI3K-PKB/Akt pathway, vanadium compounds increase the cellular uptake of glucose by the GLUT4 transporter. The PKB/Akt pathway is also used to inactivate glycogen synthase kinase-3. The impact of vanadium compounds on inflammatory reactions has not been fully studied. Vanadium pentoxide causes expression of COX-2 and the release of proinflammatory cytokines in a human lung fibroblast model. Other vanadium compounds activate NF-κB in macrophages by activating IKKβ.

**Key words:** vanadium, pollution, cancer, diabetes, insulin-mimetic action, inflammation

**Received:** 12 February, 2012; **revised:** 19 April, 2012; **accepted:** 08 May, 2012; **available on-line:** 11 June, 2012

### NATURAL OCCURRENCE OF VANADIUM

Vanadium is a transition metal, owing its name to Vanadis – Norse goddess of beauty and fertility. It is estimated that more than 60 thousand tons of this element are emitted into the atmosphere each year as the result of human activities (mostly combustion of fossil fuels) (Aragón & Altamirano-Lozano, 2001). This is due to high vanadium concentrations in both crude oil (3–260 μg/g) and hard coal (14–56 μg/g). Atmospheric pollution with vanadium of natural origin is relatively low and estimated at several tons annually. The consequence of emission of large amounts of vanadium into the atmosphere is the relatively high concentration (20–

300 ng/m<sup>3</sup>) of this element in the air of big cities, with values reaching up to 10 mg/m<sup>3</sup> observed in the New York City and other large urban agglomerations (Aragón & Altamirano-Lozano, 2001; Lin *et al.*, 2004). Soils in areas not subject to anthropogenic changes contain small amounts of vanadium, originating mostly from volcanic rocks (Poledniok & Buhl, 2003; Nadal *et al.*, 2004). Industrial activities result in a significant increase in these levels, reaching 19.3 μg/g of soil in the vicinity of a crude oil refinery in Catalonia (Nadal *et al.*, 2004). Vanadium present in soil is accumulated in plants (Nadal *et al.*, 2004; Marcano *et al.*, 2006). Contamination with vanadium is also observed in water reservoirs: rivers, lakes and seas. Bottom sediments of the Persian Gulf contain vanadium at concentrations as high as 100 μg/g of dry sediment (Pourang *et al.*, 2005). About 10% of ground-water samples from California and some other states of the USA contain vanadium in amounts exceeding 25 μg/dm<sup>3</sup> (Wright & Belitz, 2010). This is due to vanadium being washed out of water-bearing rocks (Wright & Belitz, 2010).

As evidenced by studies of vanadium levels in the hair of residents of different countries, Poland's population as a whole is not significantly exposed to high levels of vanadium. The measured value is of the order of 0.055 μg/g, being three times lower than the value of 0.171 μg/g for residents of the U.S., Canada or India (Stefańska *et al.*, 2005). Hair vanadium content in students in Bialystok is even lower (0.038 μg/g) due to a non-polluted environment (Stefańska *et al.*, 2005). On the other hand, vanadium pollution is observed in the Upper Silesia region (Poledniok & Buhl, 2003). Industrial pollution of the Silesian regions combined with automobile exhaust fumes is transported by rivers into the sea and are deposited in bottom sediments of the rivers. Thus, the sediments in the Bay of Szczecin are highly polluted with vanadium and other elements originating

✉ e-mail: dclubek@sci.pum.edu.pl

**Abbreviations:** BEOV, bis(ethylmaltolato)oxovanadium(IV); BMOV, bis(kojato)oxovanadium(IV); BMOV, bis(maltolato)oxovanadium(IV); Cdc25B<sub>2</sub>, cell division control/cycle 25 homolog B<sub>2</sub>; Cdc25C, cell division control/cycle 25 homolog C; CksHs1, human cyclin dependent kinase subunit type 1; COX-2, cyclooxygenase 2; CXCL10, C-X-C motif chemokine 10; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; E2F, Transcription factor E2F; GLUT4, Glucose transporter type 4; GSK3, glycogen synthase kinase-3; HIF-1α, hypoxia inducible factor 1α; IC<sub>50</sub>, half maximal inhibitory concentration; IκBα, inhibitor of κB activity α; IKKβ, IκB kinase subunit β; IL-6 Interleukin-6; IL-8, Interleukin-8; MAPK, mitogen-activated protein kinase; MEK1/2, MAPK/ERK kinase 1 and 2; MIP-2, macrophage inflammatory protein-2; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; NF-AT, nuclear factor of activated T-cells; p38, protein 38; p53, protein 53; PI3K, phosphatidylinositol 3-kinase; PKB/Akt, protein kinase B; PTP-1B, protein tyrosine phosphatase 1B; pRb, retinoblastoma protein; ROS, reactive oxygen species; SSB, single-strand break; TNFα, Tumor necrosis factor α; VEGF, vascular endothelial growth factor.

from distant regions (Glasby *et al.*, 2004). Due to the river runoff, vanadium pollution of the Bay of Szczecin is comparable to the pollution of the Persian Gulf oilfields (Glasby *et al.*, 2004; Pourang *et al.*, 2005).

### VANADIUM IN LIVING ORGANISMS

After entering the circulatory system via the gastrointestinal or respiratory tract, vanadium compounds are transported by transferrin or, less commonly, by albumin or low-molecular components of plasma, such as citrates and, to a lesser extent, lactates or phosphates (Kiss *et al.*, 2000). Next, vanadium compounds are accumulated in kidneys and, to a smaller degree, in spleen, bones and liver (Hansen *et al.*, 1982). Human body contains ca. 100 µg of vanadium, with equilibrium between the amount of vanadium excreted from the body and the amount of vanadium absorbed from the outside environment (up to several dozen micrograms daily) (Byrne & Kosta, 1978; Kordowiak & Holko, 2009). For certain mammals, such as rats, vanadium is a necessary microelement; however, due to the omnipresence of this element at low concentrations, no necessity of nutritional intake of vanadium was determined in humans (Lin *et al.*, 2004; Kordowiak & Holko, 2009).

Aquatic organisms, such as ascidians, accumulate vanadium in circulatory system cells known as vanadocytes (Kawakami *et al.*, 2006; Kawakami *et al.*, 2009). Blood vanadium levels in these organisms exceed 10 mM, while the sea concentration of vanadium is about 35 nM (Kawakami *et al.*, 2009). Vanadium compounds are transported into the cytoplasm of vanadocytes, bound and reduced to the +4 oxidation state by the binding proteins – vanabins, and finally deposited in the acidic environment of vacuoles as vanadium compounds in the +3 oxidation state (Kawakami *et al.*, 2006).

In human body, vanadium has an oxidation state of +4 or +5 (Kordowiak & Holko, 2009). Vanadium compounds in the +5 oxidation state (metavanadates or orthovanadates, forming oligomers) enter cells via anionic channels, while vanadium compounds in the +4 oxidation state (vanadyl cations) permeate the cellular membrane by diffusion (Fig. 1) (Aureliano & Gándara, 2005; Kordowiak & Holko, 2009). Vanadium forms numerous derivatives with low-molecular organic compounds. Vanadium organic derivatives have been synthesized since 1990s (Thomson *et al.*, 2009). Examples of such compounds include maltol complexes such as BMOV or

BEOV – compounds of insulin-mimetic activity characterized by low toxicity compared to inorganic vanadium compounds; naglivan, a cystein derivative complex, or BKOV (Fig. 2) (Scior *et al.*, 2009; Thompson *et al.*, 2009; Kordowiak & Holko, 2009). As the result of reactions with intracellular antioxidants, vanadium within the cells has predominantly an oxidation state of +4 (Aureliano & Gándara, 2005; Kordowiak & Holko, 2009).

Vanadium compounds in the +4 oxidation state are oxidized by atmospheric oxygen to the +5 oxidation state with accompanying emission of a superoxide anion radical (Cuesta *et al.*, 2011). As a result of reduction with NADPH, the reaction may proceed with generation of hydrogen peroxide (Cuesta *et al.*, 2011). Moreover, vanadium in the +4 oxidation state can be oxidized to the +5 oxidation state with generation of a hydroxyl radical via a Fenton-like reaction (Cuesta *et al.*, 2011). In cells vanadium compounds oxidized to the +5 oxidation state by atmospheric oxygen or ROS are in equilibrium with vanadium compounds reduced to the +4 oxidation state by intracellular antioxidants. Thanks to their structural similarity to phosphate anions, orthovanadium anions may act as inhibitors of protein phosphatases or bind to such molecules as ADP or NAD to form ADPV and NADV, respectively (Crans *et al.*, 2004).

### VANADIUM COMPOUNDS AND DIABETES

Vanadium compounds have insulin-mimetic properties. First reports on therapeutic properties of vanadium compounds in diabetes appeared as early as in 1899 (Thompson & Orvig 2006). Many studies were conducted on inorganic and organic vanadium derivatives in induced-diabetes animal models, in which the studied compounds were found to impact the levels of glucose, cholesterol and triacylglycerols, with no harmful side effects upon prolonged administration (Yanardag *et al.*, 2003; Koyuturk *et al.*, 2005; Niu *et al.*, 2007; Wei *et al.*, 2007; Li *et al.*, 2009). The studied vanadium compounds normalize renal function and the indicator liver enzyme levels in diabetic model animals (Yanardag *et al.*, 2003; Koyuturk *et al.*, 2005). Many experiments were also performed in diabetic patients, confirming the therapeutic effect of the studied vanadium compounds on blood glucose levels with little side effects (Thompson *et al.*, 2009).

Vanadium compounds are characterized by multiple ways of action resulting in reduction of blood glucose

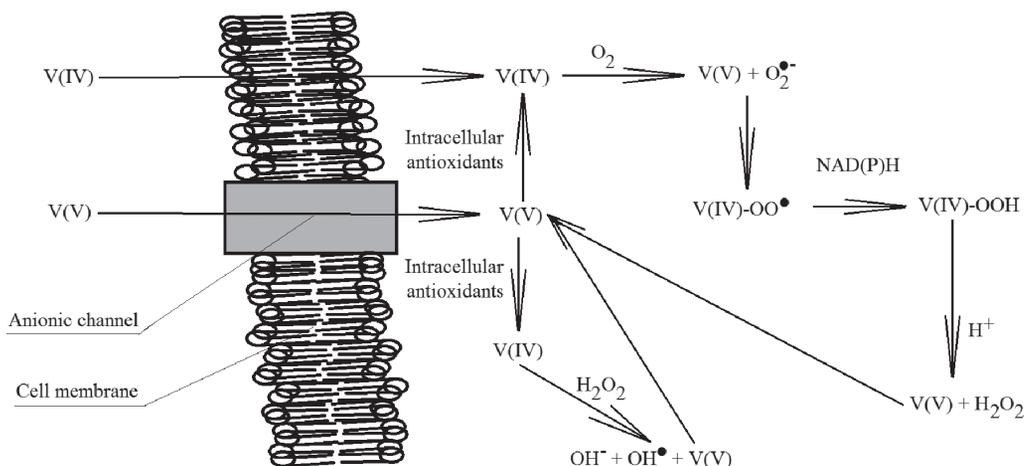
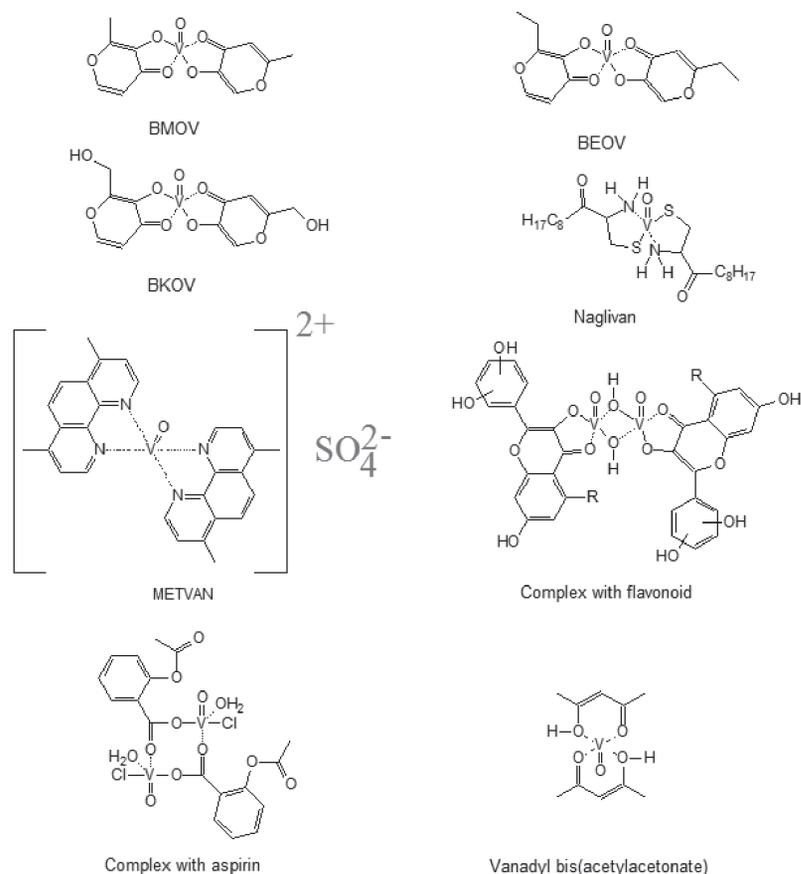


Figure 1. Biochemical pathways of inorganic vanadium compounds in the cytoplasm According to Aureliano & Gándara, 2005; Kordowiak & Holko, 2009; Cuesta *et al.*, 2010 (modified).



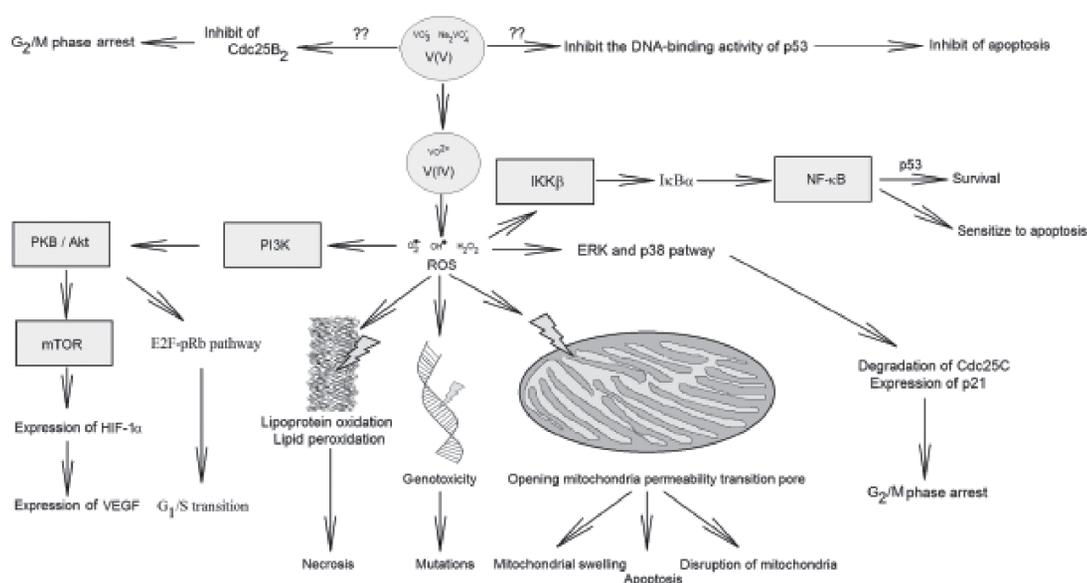
**Figure 2. Examples of organic vanadium derivatives of medical importance** According to Dong *et al.*, 2000; D'Cruz & Uckun, 2001; Scior *et al.*, 2008; Thompson *et al.*, 2009, (modified).

levels (Vardatsikos *et al.*, 2009). Thanks to their structural similarity to orthophosphate anions, the orthovanadate anion and vanadium organic derivatives are inhibitors of protein phosphotyrosine phosphatases (Fig. 4). (Crans *et al.*, 2004). They may inhibit the activity of PTP-1B,

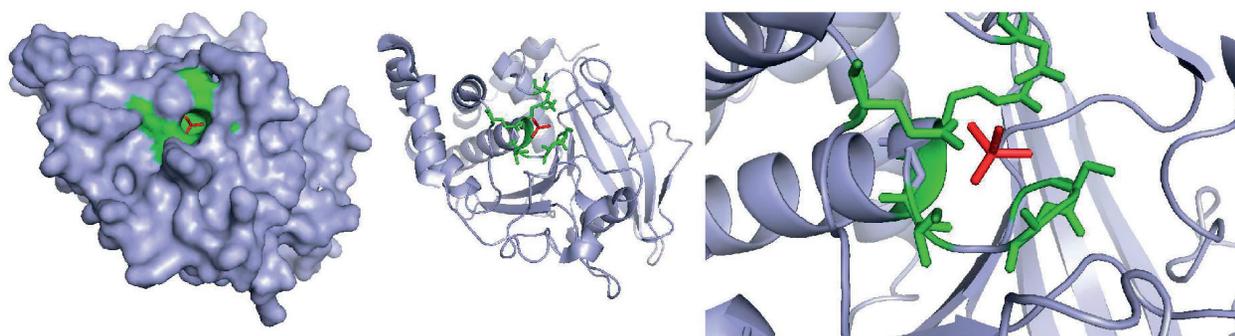
which is an enzyme responsible for dephosphorylation of insulin receptors, causing insulin resistance (Scior *et al.*, 2009; Scior *et al.*, 2010). However, the mechanism of phosphotyrosine phosphatase inactivation is not yet fully understood, as it appears that this process may also be caused by free radicals (Bartosz, 2003). One may assume that vanadium compounds cause PTP-1B inhibition via ROS (Kaltschmidt *et al.*, 2000). Another mechanism of reduction of blood glucose levels by vanadium compounds is the activation of PKB/Akt leading to increased uptake of glucose by the GLUT4 transporter (Vardatsikos *et al.*, 2009). Activation of PKB/Akt results also in phosphorylation and inactivation of GSK3, leading to stimulation of the synthesis of glycogen from glucose (Vardatsikos *et al.*, 2009).

## VANADIUM AND TUMOR CELLS

In chemically-induced tumor models in experimental animals, vanadium compounds show chemopreventive properties by means of optimization of phase I and phase II xenobiotic transformation enzymes (Bishayee *et al.*, 2000; Ray *et al.*, 2007; Chakraborty *et al.*, 2007). Inorganic and organic vanadium compounds were tested in human tumor cell line models. The results were promising with respect to introduction of va-



**Figure 3. Some antitumor and cancerogenic pathways of inorganic vanadium compounds** According to Chen *et al.*, 1999; Woo *et al.*, 1999; Gao *et al.*, 2002; Lapenna *et al.*, 2002; Zhang *et al.*, 2003; Zhang *et al.*, 2004; Wozniak & Blasiak, 2004; Soares *et al.*, 2008; Zhao *et al.*, 2010; Morita *et al.*, 2010; Parrondo, 2010 (modified).



**Figure 4. Phosphatase 1B with its inhibitor, the orthovanadate anion.**

From left to right: model of the spatial structure of the enzyme; tertiary structure of the enzyme with the orthovanadate anion and aminoacyl residues in its catalytic center; a close-up of the catalytic center of the enzyme with a model of the orthovanadate anion and aminoacyl residues interacting with the inhibitor according to Brandão *et al.*, 2010 (modified).

vanadium compounds into the therapy due to their low  $IC_{50}$  (several micromoles depending on cell line and vanadium compound), antiproliferative and proapoptotic effects (Kordowiak *et al.*, 2007; Holko *et al.*, 2008; Fu *et al.*, 2008; Klein *et al.*, 2008; Molinuevo *et al.*, 2008). Vanadium compounds are genotoxic and cause selective oxidation of pyrimidine bases and SSB-type DNA damages in tumor cells, which are characterized by less efficient DNA repair processes (Fig. 3) (Wozniak & Blasiak, 2004; Rodríguez-Mercado *et al.*, 2011). Another mechanism of action of vanadium compounds on tumor cells is the opening of mitochondrial permeability transition pores, leading to the release of cytochrome c and induction of apoptosis (Soares *et al.*, 2008; Zhao *et al.*, 2010). Vanadium compounds inhibit the activity of phosphatase Cdc25B<sub>2</sub>, responsible for dephosphorylation and activation of Cdk2 in cyclin-A and -B complexes (Woo *et al.*, 1999). Inhibition of Cdc25B<sub>2</sub> induces G<sub>2</sub>/M phase arrest. Another mechanism of action of vanadium compounds on the G<sub>2</sub>/M phase arrest is the degradation of Cdc25C *via* MAPK cascades: ERK and p38 (Zhang *et al.*, 2003; Liu *et al.*, 2012). Another target for the vanadium compounds is CksHs1 (Arvai *et al.*, 1995). Experiments on embryonic p53-knockout fibroblasts led to conclusion that vanadium compounds promote S phase entry of cells with wild-type p53 and induce G<sub>2</sub>/M phase arrest of p53-knockout cells (Zhang *et al.*, 2002). In addition, vanadium compounds activate NF- $\kappa$ B by the action of ROS in various cell types (Chen *et al.*, 1999; Jaspers *et al.*, 2000). The role of NF- $\kappa$ B in tumor cells is subject to discussion, as activation or overexpression of this transcription factor in non-tumor cells as well as in certain tumor cell lines leads to cell survival and inhibition of apoptosis (Parrondo, 2010). However, in prostate cancer cell lines treated with anticancer drugs, chemical activation of NF- $\kappa$ B increases the percentage of apoptotic cells (Parrondo, 2010). Inactivation of NF- $\kappa$ B in cells treated with vanadium compounds, such as pervanadate, decreases apoptotic cell death (Kaltschmidt *et al.*, 2000).

One group of organic vanadium compounds tested as antitumor drugs includes complexes of the vanadyl cation with phenanthroline derivatives, such as METVAN [bis(4,7-dimethyl-1,10-phenanthroline)sulfatoxovanadium(IV); VO(SO<sub>4</sub>)(Me<sub>2</sub>-Phen)<sub>2</sub>] (Narla *et al.*, 2000; Narla *et al.*, 2001). These vanadium compounds are characterized by antiproliferation  $IC_{50}$  values of the order of several micromoles in many tumor cell lines and, when present at low concentrations, induce apoptosis and inhibit the cell cycle (Narla *et al.*, 2000; Dong *et al.*, 2000). METVAN is cytotoxic against many tumor

cell lines ( $IC_{50}$  of less than 1  $\mu$ M), reduces the invasiveness of leukemia by inhibiting the activity of metalloproteinases and damages mitochondria by generating ROS, thus causing apoptosis (Dong *et al.*, 2000; Narla *et al.*, 2001). One of side effects of the treatment is inhibition of spermatogenesis and apoptosis of male germ cells (D'Cruz & Uckun, 2001).

Vanadium compounds have carcinogenic properties and stimulate tumor development. Vanadyl cations and V<sub>2</sub>O<sub>5</sub>, a vanadium compound found in air pollution, generate ROS that cause DNA damage which may lead to mutations and, as a consequence, development of tumor cells (Ehrlich *et al.*, 2008). Vanadium compounds have also antiapoptotic properties (Morita *et al.*, 2010). Activation of NF- $\kappa$ B by ROS generated by vanadium compounds leads to cell survival and inhibition of apoptosis (Chen *et al.*, 1999; Jaspers *et al.*, 2000). In addition, by means of altered p53 phosphorylation, vanadates cause disturbances in the course of apoptosis (Suzuki *et al.*, 2007; Morita *et al.*, 2010). Another mechanism of carcinogenic action of vanadium compounds is activation of PI3K by generation of hydrogen peroxide (Gao *et al.*, 2002). PI3K activates PKB/Akt, which promotes S phase entry *via* the E2F-pRb pathway (Zhang *et al.*, 2004). In addition, activation of the PI3K-PKB/Akt-mTOR pathway results in increased expression of HIF-1 $\alpha$  and, as a consequence, expression and release of VEGF (Gao *et al.*, 2002). Expression of VEGF stimulated by vanadium compounds is controlled not only by the PI3K-PKB/Akt pathway, but also by two other pathways: MEK1/2-ERK or increase in intracellular calcium levels (Li *et al.*, 2005). Release of VEGF causes angiogenesis and thus contributes to the development of tumor.

The effects of vanadium compounds depend on many factors, mainly on the type of cells, the type of vanadium compound and its dose. It appears that the proapoptotic or antiapoptotic effect of vanadium compounds depends largely on the cell type. The key protein, defects of which diametrically change the effects of vanadium compounds, is p53 (a large number of tumor cell types have defects in the gene encoding this protein). In p53-defective cells (tumor cells or non-tumor p53-knock out cells), vanadium compounds inhibit the cell cycle and thus induce apoptosis (Zhang *et al.*, 2002). Activation of NF- $\kappa$ B by ROS generated by vanadium compounds enhances the apoptotic effect (Parrondo, 2010). In contrast, in p53-functional cells, disturbed phosphorylation of p53 leads to inhibition of apoptosis (Morita *et al.*, 2010). In addition, vanadium compounds stimulate the

cell cycle, thus inhibiting apoptosis, as both processes are mutually connected (Zhang *et al.*, 2002). Moreover, NF- $\kappa$ B activation inhibits apoptosis of tumor cells. Another important fact is that vanadium compounds cause much more DNA damage in tumor cells compared to non-tumor cells when present at the same levels (Wozniak & Blasiak, 2004). Extensive DNA damage leads to apoptosis of tumor cells while a less intensive damage evoked by vanadium compounds in non-tumor cells may stimulate synthesis and activation of repair enzymes, thus protecting those cells from apoptosis. The above processes promote tumor cell growth at early stages of the disease and have an antitumor effect in the advanced stages of cancer. Studies in animals treated with carcinogens suggest that vanadium compounds used at low levels have selective effects on the tumor cells (Ray *et al.*, 2007; Chakraborty *et al.*, 2007).

### VANADIUM COMPOUNDS AND INFLAMMATORY REACTIONS

The impact of vanadium compounds on inflammatory reactions has not been fully studied. Experiments conducted to date suggest that vanadates activate NF- $\kappa$ B, a transcription factor of key importance in inflammatory reactions (Chen *et al.*, 1999; Ye *et al.*, 1999). Studies conducted on RAW 264.7 macrophages showed that this was due to activation of IKK $\beta$  and degradation of I $\kappa$ B $\alpha$  (Chen *et al.*, 1999; Ye *et al.*, 1999). Activation of NF- $\kappa$ B leads to changes in expression of numerous genes, including TNF $\alpha$  and MIP-2, which belong to the CXC chemokine family (Ye *et al.*, 1999; Chong *et al.*, 2000). Another vanadium compound prevalent in air pollution and causing inflammatory reactions is vanadium pentoxide. Exposure to vanadium pentoxide-containing dust causes inflammatory reactions in lungs, leading to expression of, among others, COX-2, IL-6, IL-8 and CXCL10 (Ingram *et al.*, 2007; Rondini *et al.*, 2010). Vanadium pentoxide causes COX-2 expression in epithelial bronchial Beas-2B cells *via* the NF-AT pathway (Tang *et al.*, 2007). Another pathway for the increase in COX-2 expression, encompassing EGFR and the p38 cascade, was observed in A249 lung cancer cells (Chen *et al.*, 2006).

### CONCLUSIONS AND FUTURE DIRECTIONS

Due to the ability to generate ROS, which exert non-specific effects on different cell structures, vanadium compounds have many routes of action, sometimes diametrically opposite. They may have both antitumor and carcinogenic properties. The mechanisms of action of the vanadium compounds can be understood thanks to rapid advances in the knowledge of free radicals and the signaling pathways involving them. However, still little is known regarding the effect of vanadium compounds on the immune system and inflammatory reactions. New findings in this area may shed new light on the biochemical processes taking place in organisms treated with vanadium compounds. Currently, promising clinical trials of organic vanadium derivatives in the treatment of diabetes are under way. Soon they should be of common use. However, the effects of a long-term administration of low doses of vanadium as a potential carcinogen and correlation between the use of vanadium compounds and disorders of a free-radical background have not been fully studied yet. One of such diseases having a free-radical background is Parkinson's disease. Vanadium compounds induce ROS generation in the brain,

which may contribute to degeneration of dopaminergic neuronal cells of the *substantia nigra*, which in turn leads to Parkinson's disease (Afeseh Ngwa *et al.*, 2009; Cuesta *et al.*, 2011).

It is possible that an antitumor therapy using vanadium compounds will be developed in the near future. However, due to the carcinogenic effect of vanadium, such treatment should be combined with numerous other drugs (such as anti-VEGF antibodies) to enhance the therapeutic effect of vanadium.

### REFERENCES

- Afeseh Ngwa H, Kanthasamy A, Anantharam V, Song C, Witte T, Houk R, Kanthasamy AG (2009) Vanadium induces dopaminergic neurotoxicity via protein kinase Cdelta dependent oxidative signaling mechanisms: relevance to etiopathogenesis of Parkinson's disease. *Toxicol Appl Pharmacol* **240**: 273–285.
- Aragón AM, Altamirano-Lozano M (2001) Sperm and testicular modifications induced by subchronic treatments with vanadium (IV) in CD-1 mice. *Reprod Toxicol* **15**: 145–151.
- Arvai AS, Bourne Y, Hickey MJ, Tainer JA (1995) Crystal structure of the human cell cycle protein CksHs1: single domain fold with similarity to kinase N-lobe domain. *J Mol Biol* **249**: 835–842.
- Aureliano M, Gândara RM (2005) Decavanadate effects in biological systems. *J Inorg Biochem* **99**: 979–985.
- Bartosz G (2003) Obrazki z pola bitwy. In *Druga twarz tlenu*. pp 324–325. PWN, Warszawa (in Polish).
- Bishayee A, Oinam S, Basu M, Chatterjee M (2000) Vanadium chemoprevention of 7,12-dimethylbenz(a)anthracene-induced rat mammary carcinogenesis: probable involvement of representative hepatic phase I and II xenobiotic metabolizing enzymes. *Breast Cancer Res Treat* **63**: 133–145.
- Brandão TA, Hengge AC, Johnson SJ (2010) Insights into the reaction of protein-tyrosine phosphatase 1B: crystal structures for transition state analogs of both catalytic steps. *J Biol Chem* **285**: 15874–15883.
- Byrne AR, Kosta L (1978) Vanadium in foods and in human body fluids and tissues. *Sci Total Environ* **10**: 17–30.
- Chakraborty T, Swamy AH, Chatterjee A, Rana B, Shyamsundar A, Chatterjee M (2007) Molecular basis of vanadium-mediated inhibition of hepatocellular preneoplasia during experimental hepatocarcinogenesis in rats. *J Cell Biochem* **101**: 244–258.
- Chen F, Demers LM, Vallyathan V, Ding M, Lu Y, Castranova V, Shi X (1999) Vanadate induction of NF-kappaB involves IkappaB kinase beta and SAPK/ERK kinase 1 in macrophages. *J Biol Chem* **274**: 20307–20312.
- Chien PS, Mak OT, Huang HJ (2006) Induction of COX-2 protein expression by vanadate in A549 human lung carcinoma cell line through EGF receptor and p38 MAPK-mediated pathway. *Biochem Biophys Res Commun* **339**: 562–568.
- Chong IW, Lin SR, Hwang JJ, Huang MS, Wang TH, Tsai MS, Hou JJ, Paulauskis JD (2000) Expression and regulation of macrophage inflammatory protein-2 gene by vanadium in mouse macrophages. *Inflammation* **24**: 127–139.
- Crans DC, Smeets JJ, Gaidamauskas E, Yang L (2004) The chemistry and biochemistry of vanadium and the biological activities exerted by vanadium compounds. *Chem Rev* **104**: 849–902.
- Cuesta S, Francés D, García GB (2011) ROS formation and antioxidant status in brain areas of rats exposed to sodium metavanadate. *Neurotoxicol Teratol* **3**: 1–6.
- D'Cruz OJ, Uckun FM (2001) Bis(4,7-dimethyl and 5-dinitro-1,10-phenanthroline) sulfato-oxovanadium(IV)-mediated *in vivo* male germ cell apoptosis. *J Appl Toxicol* **21**: 331–339.
- Dong Y, Narla RK, Sudbeck E, Uckun FM (2000) Synthesis, X-ray structure, and anti-leukemic activity of oxovanadium(IV) complexes. *J Inorg Biochem* **78**: 321–330.
- Ehrlich VA, Nersesyan AK, Atefi K, Hoelzl C, Ferik F, Bichler J, Valic E, Schaffer A, Schulte-Hermann R, Fenech M, Wagner KH, Knasmüller S (2008) Inhalative exposure to vanadium pentoxide causes DNA damage in workers: results of a multiple end point study. *Environ Health Perspect* **116**: 1689–1693.
- Fu Y, Wang Q, Yang XG, Yang XD, Wang K (2008) Vanadyl bisacetylacetonate induced G1/S cell cycle arrest *via* high-intensity ERK phosphorylation in HepG2 cells. *J Biol Inorg Chem* **13**: 1001–1009.
- Gao N, Ding M, Zheng JZ, Zhang Z, Leonard SS, Liu KJ, Shi X, Jiang BH (2002) Vanadate-induced expression of hypoxia-inducible factor 1 alpha and vascular endothelial growth factor through phosphatidylinositol 3-kinase/Akt pathway and reactive oxygen species. *J Biol Chem* **277**: 31963–31971.
- Glasby GP, Szefer P, Geldon J, Warzocha J (2004) Heavy-metal pollution of sediments from Szczecin Lagoon and the Gdansk Basin, Poland. *Sci Total Environ* **330**: 249–69.

- Hansen TV, Aaseth J, Alexander J (1982) The effect of chelating agents on vanadium distribution in the rat body and on uptake by human erythrocytes. *Arch Toxicol* **50**: 195–202.
- Holko P, Ligeza J, Kisielewska J, Kordowiak AM, Klein A (2008) The effect of vanadyl sulphate (VOSO<sub>4</sub>) on autocrine growth of human epithelial cancer cell lines. *Pol J Pathol* **59**: 3–8.
- Ingram JL, Antao-Menezes A, Turpin EA, Wallace DG, Mangum JB, Pluta LJ, Thomas RS, Bonner JC (2007) Genomic analysis of human lung fibroblasts exposed to vanadium pentoxide to identify candidate genes for occupational bronchitis. *Respir Res* **8**: 34.
- Jaspers I, Samet JM, Erzurum S, Reed W (2000) Vanadium-induced kappaB-dependent transcription depends upon peroxide-induced activation of the p38 mitogen-activated protein kinase. *Am J Respir Cell Mol Biol* **23**: 95–102.
- Kaltschmidt B, Kaltschmidt C, Hofmann TG, Hehner SP, Dröge W, Schmitz ML (2000) The pro- or anti-apoptotic function of NF-kappaB is determined by the nature of the apoptotic stimulus. *Eur J Biochem* **267**: 3828–3835.
- Kawakami N, Ueki T, Amata Y, Kanamori K, Matsuo K, Gekko K, Michibata H (2009) A novel vanadium reductase, Vanabin2, forms a possible cascade involved in electron transfer. *Biochim Biophys Acta* **1794**: 674–679.
- Kawakami N, Ueki T, Matsuo K, Gekko K, Michibata H (2006) Selective metal binding by Vanabin2 from the vanadium-rich ascidian, *Ascidia sydneiensis samea*. *Biochim Biophys Acta* **1760**: 1096–1101.
- Kiss T, Kiss E, Garribba E, Sakurai H (2000) Speciation of insulin-mimetic VO(IV)-containing drugs in blood serum. *J Inorg Biochem* **80**: 65–73.
- Klein A, Holko P, Ligeza J, Kordowiak AM (2008) Sodium orthovanadate affects growth of some human epithelial cancer cells (A549, HTB44, DU145). *Folia Biol (Krakow)* **56**: 115–121.
- Kordowiak AM, Holko P (2009) Pochodne wanadu jako związki o istotnym znaczeniu biologicznym. Część I. Działanie przeciwcukrzycowe. *Post Biol Kom* **36**: 361–376 (in Polish).
- Kordowiak AM, Klein A, Goc A, Dabros W (2007) Comparison of the effect of VOSO<sub>4</sub>, Na<sub>2</sub>VO<sub>4</sub> and NaVO<sub>3</sub> on proliferation, viability and morphology of H35-19 rat hepatoma cell line. *Pol J Pathol* **58**: 51–57.
- Koyuturk M, Tunali S, Bolkent S, Yanardag R (2005) Effects of vanadyl sulfate on liver of streptozotocin-induced diabetic rats. *Biol Trace Elem Res* **104**: 233–247.
- Lapenna D, Ciofani G, Bruno C, Pierdomenico SD, Giuliani L, Giamberardino MA, Cuccurullo F (2002) Vanadyl as a catalyst of human lipoprotein oxidation. *Biochem Pharmacol* **63**: 375–380.
- Li J, Tong Q, Shi X, Costa M, Huang C (2005) ERKs activation and calcium signaling are both required for VEGF induction by vanadium in mouse epidermal Cl41 cells. *Mol Cell Biochem* **279**: 25–33.
- Li M, Smece JJ, Ding W, Crans DC (2009) Anti-diabetic effects of sodium 4-amino-2,6-dipicolinatodioxovanadium(V) dihydrate in streptozotocin-induced diabetic rats. *J Inorg Biochem* **103**: 585–589.
- Lin TS, Chang CL, Shen FM (2004) Whole blood vanadium in Taiwanese college students. *Bull Environ Contam Toxicol* **73**: 781–786.
- Liu TT, Liu YJ, Wang Q, Yang XG, Wang K (2012) Reactive-oxygen-species-mediated Cdc25C degradation results in differential anti-proliferative activities of vanadate, tungstate, and molybdate in the PC-3 human prostate cancer cell line. *J Biol Inorg Chem* **17**: 311–320.
- Marcano L, Carruyo I, Fernández Y, Montiel X, Torrealba Z (2006) Determination of vanadium accumulation in onion root cells (*Allium cepa* L.) and its correlation with toxicity. *Biocell* **30**: 259–267.
- Molinuevo MS, Cortizo AM, Etcheverry SB (2008) Vanadium(IV) complexes inhibit adhesion, migration and colony formation of UMR106 osteosarcoma cells. *Cancer Chemother Pharmacol* **61**: 767–773.
- Morita A, Yamamoto S, Wang B, Tanaka K, Suzuki N, Aoki S, Ito A, Nanao T, Ohya S, Yoshino M, Zhu J, Enomoto A, Matsumoto Y, Funatsu O, Hosoi Y, Ikekita M (2010) Sodium orthovanadate inhibits p53-mediated apoptosis. *Cancer Res* **70**: 257–265.
- Nadal M, Schuhmacher M, Domingo JL (2004) Metal pollution of soils and vegetation in an area with petrochemical industry. *Sci Total Environ* **321**: 59–69.
- Narla RK, Chen CL, Dong Y, Uckun FM (2001) *In vivo* antitumor activity of bis(4,7-dimethyl-1,10-phenanthroline) sulfatooxovanadium(IV) (METVAN [VO(SO<sub>4</sub>)(Me<sub>2</sub>-Phen)<sub>2</sub>]). *Clin Cancer Res* **7**: 2124–2133.
- Narla RK, Dong Y, D'Cruz OJ, Navara C, Uckun FM (2000) Bis(4,7-dimethyl-1,10-phenanthroline) sulfatooxovanadium(IV) as a novel apoptosis-inducing anticancer agent. *Clin Cancer Res* **6**: 1546–1556.
- Narla RK, Dong Y, Klis D, Uckun FM (2001) Bis(4,7-dimethyl-1,10-phenanthroline) sulfatooxovanadium(IV) as a novel antileukemic agent with matrix metalloproteinase inhibitory activity. *Clin Cancer Res* **7**: 1094–1101.
- Narla RK, Dong Y, Uckun FM (2001) Apoptosis inducing novel anti-leukemic agent, bis(4,7-dimethyl-1,10 phenanthroline) sulfatooxovanadium(IV) [VO(SO<sub>4</sub>)(Me<sub>2</sub>-Phen)<sub>2</sub>] depolarizes mitochondrial membranes. *Leuk Lymphoma* **41**: 625–634.
- Niu Y, Liu W, Tian C, Xie M, Gao L, Chen Z, Chen X, Li L (2007) Effects of bis(alpha-furancarboxylato)oxovanadium(IV) on glucose metabolism in fat-fed/streptozotocin-diabetic rats. *Eur J Pharmacol* **572**: 213–219.
- Parrondo R, de las Pozas A, Reiner T, Rai P, Perez-Stable C (2010) NF-kappaB activation enhances cell death by antimetabolic drugs in human prostate cancer cells. *Mol Cancer* **9**: 182–195.
- Poledniok J, Buhl F (2003) Speciation of vanadium in soil. *Talanta* **59**: 1–8.
- Pourang N, Nikouyan A, Dennis JH (2005) Trace element concentrations in fish, surficial sediments and water from northern part of the Persian Gulf. *Environ Monit Assess* **109**: 293–316.
- Ray RS, Ghosh B, Rana A, Chatterjee M (2007) Suppression of cell proliferation, induction of apoptosis and cell cycle arrest: chemopreventive activity of vanadium *in vivo* and *in vitro*. *Int J Cancer* **120**: 13–23.
- Rodríguez-Mercado JJ, Mateos-Nava RA, Altamirano-Lozano MA (2011) DNA damage induction in human cells exposed to vanadium oxides *in vitro*. *Toxicol In Vitro* **25**: 1996–2002.
- Rondini EA, Walters DM, Bauer AK (2010) Vanadium pentoxide induces pulmonary inflammation and tumor promotion in a strain-dependent manner. *Part Fibre Toxicol* **7**: 9.
- Scior T, Guevara-García JA, Melendez FJ, Abdallah HH, Do QT, Bernard P (2010) Chimeric design, synthesis, and biological assays of a new nonpeptide insulin-mimetic vanadium compound to inhibit protein tyrosine phosphatase 1B. *Drug Des Devel Ther* **4**: 231–242.
- Scior T, Mack HG, García JA, Koch W (2009) Antidiabetic Bis-Maltolato-OxoVanadium(IV): conversion of inactive trans- to bioactive cis-BMOV for possible binding to target PTP-1B. *Drug Des Devel Ther* **2**: 221–231.
- Soares SS, Henao F, Aureliano M, Gutiérrez-Merino C (2008) Vanadate induces necrotic death in neonatal rat cardiomyocytes through mitochondrial membrane depolarization. *Chem Res Toxicol* **21**: 607–618.
- Stefańska E, Ostrowska L, Czapska D, Karczewski J, Borawska M (2005) Hair vanadium content and nutritional status of students of the Medical University of Białystok. *Roczn Panstw Zakl Hig* **56**: 157–163.
- Suzuki K, Inageda K, Nishitai G, Matsuoka M (2007) Phosphorylation of p53 at serine 15 in A549 pulmonary epithelial cells exposed to vanadate: involvement of ATM pathway. *Toxicol Appl Pharmacol* **220**: 83–91.
- Tang H, Sun Y, Xiu Q, Lu H, Han H (2007) Cyclooxygenase-2 induction requires activation of nuclear factor of activated T-cells in Beas-2B cells after vanadium exposure and plays an anti-apoptotic role. *Arch Biochem Biophys* **468**: 92–99.
- Thompson KH, Lichter J, LeBel C, Scaife MC, McNeill JH, Orvig C (2009) Vanadium treatment of type 2 diabetes: a view to the future. *J Inorg Biochem* **103**: 554–558.
- Thompson KH, Orvig C (2006) Vanadium in diabetes: 100 years from Phase 0 to Phase I. *J Inorg Biochem* **100**: 1925–1935.
- Vardatsikos G, Mehdi MZ, Srivastava AK (2009) Bis(maltolato)-oxovanadium(IV)-induced phosphorylation of PKB, GSK-3 and FOXO1 contributes to its glucoregulatory responses (review). *Int J Mol Med* **24**: 303–309.
- Wei D, Li M, Ding W (2007) Effect of vanadate on gene expression of the insulin signaling pathway in skeletal muscle of streptozotocin-induced diabetic rats. *J Biol Inorg Chem* **12**: 1265–1273.
- Woo ES, Rice RL, Lazo JS (1999) Cell cycle dependent subcellular distribution of Cdc25B subtypes. *Oncogene* **18**: 2770–2776.
- Wozniak K, Blasiak J (2004) Vanadyl sulfate can differentially damage DNA in human lymphocytes and HeLa cells. *Arch Toxicol* **78**: 7–15.
- Wright MT, Belitz K (2010) Factors controlling the regional distribution of vanadium in groundwater. *Ground Water* **48**: 515–525.
- Yanardag R, Bolkent S, Karabulut-Bulan O, Tunali S (2003) Effects of vanadyl sulfate on kidney in experimental diabetes. *Biol Trace Elem Res* **95**: 73–85.
- Ye J, Ding M, Zhang X, Rojanasakul Y, Nedospasov S, Vallyathan V, Castranova V, Shi X (1999) Induction of TNFalpha in macrophages by vanadate is dependent on activation of transcription factor NF-kappaB and free radical reactions. *Mol Cell Biochem* **198**: 193–200.
- Zhang Z, Chen F, Huang C, Shi X (2002) Vanadate induces G<sub>2</sub>/M phase arrest in p53-deficient mouse embryo fibroblasts. *J Environ Pathol Toxicol Oncol* **21**: 223–231.
- Zhang Z, Gao N, He H, Huang C, Luo J, Shi X (2004) Vanadate activated Akt and promoted S phase entry. *Mol Cell Biochem* **255**: 227–237.
- Zhang Z, Leonard SS, Huang C, Vallyathan V, Castranova V, Shi X (2003) Role of reactive oxygen species and MAPKs in vanadate-induced G<sub>2</sub>/M phase arrest. *Free Radic Biol Med* **34**: 1333–1342.
- Zhao Y, Ye L, Liu H, Xia Q, Zhang Y, Yang X, Wang K (2010) Vanadium compounds induced mitochondria permeability transition pore (PTP) opening related to oxidative stress. *J Inorg Biochem* **104**: 371–378.