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Toxicology Letters 150 (2004) 135–143
Toxicology Letters
www.elsevier.com/locate/toxlet

Review

Vanadium—an element of atypical biological significance

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Received 17 December 2003; received in revised form 18 December 2003; accepted 20 January 2004

Abstract

The biological image of the transition element vanadium ferments a great deal of contradiction—from toxicity to essentiality. Importance of this element as micro-nutrient is yet to be unequivocally accepted by biologists and biomedical scientists. In spite of toxicity, it seems interesting to analyze the different biological roles of the element. Vanadium compounds have been proven to be associated with various implications in the pathogenesis of some human diseases and also in maintaining normal body functions. Salts of vanadium interfere with an essential array of enzymatic systems such as different ATPases, protein kinases, ribonucleases and phosphatases. While vanadium deficiency accounts for several physiological malfunctionings including thyroid, glucose and lipid metabolism, etc., several genes are regulated by this element or by its compounds, which include genes for tumor necrosis factor-alpha (TNF-α), Interleukin-8 (IL-8), activator protein-1 (AP-1), ras, c-raf-1, mitogen activated protein kinase (MAPK), p53, nuclear factors—κB, etc. All these seem to be not far from its recognition as an element of pharmacological and nutritional significance, which is revealed through its increasing therapeutic uses in diabetes. Vanadium is also emerging as a potent anti-carcinogenic agent. This review summarizes the developments related to vanadium biology as a whole by analyzing the general biochemical functions of vanadium.

Keywords: Vanadium; Nutrition; Anti-diabetic; Anti-carcinogenic

1. Introduction

Vanadium is a member of group VB of the periodic table. This named after the Norse goddess Vanadis, the goddess of beauty and fertility (Morinville et al., 1998). Andres Manuel Del Rio was the first chemist to provide the idea of this new element in 1801. But it was discovered by Nils Sefstrom, a Swedish chemist in 1830. Pure vanadium is a bright sliver-white, soft and ductile metal and 22nd most abundant element in the earth's crust. Vanadium has become subject of interest amongst nutritionists since the discovery that various marine species have this metal as an essential element (Almedeida et al., 2001; Nriagu, 1998). Although most food contains low amount of vanadium (<1 ng/g), food is the major source of exposure to vanadium for general population (Barceloux, 1999). Many cereals,

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doi:10.1016/j.toxlet.2004.01.009

fishes, fresh fruits and vegetables contain this element more than 40 mg per gram of food. Foods rich in vanadium include mushrooms, shellfish, dill seed, parsley, black pepper, etc. (Barceloux, 1999; Badmaev et al., 1999). In most of these cases physiologically relevant forms of vanadium include vanadyl sulphate, sodium metavanadate, sodium orthovanadate and vanadium pentoxide.

During the last few decades, the facade of vanadium as a 'slightly' toxic and carcinogenic element eventually ratified to an essential trace element with anti−diabetic and anti-carcinogenic properties.

2. Absorption, distribution and excretion

Absorption, excretion and storage mechanisms of vanadium in living system are not thoroughly understood. Fig. 1 depicts a draft out-line of vanadium metabolism in higher animals. Several reports show that vanadium is poorly (only about 10%) absorbed from gastrointestinal tract (Nriagu, 1998; Poucheret et al., 1998). Report suggests that most of the ingested vanadium is transformed into the cationic vanadyl form in stomach before being absorbed in the duodenum through an unknown mechanism (Hirano and

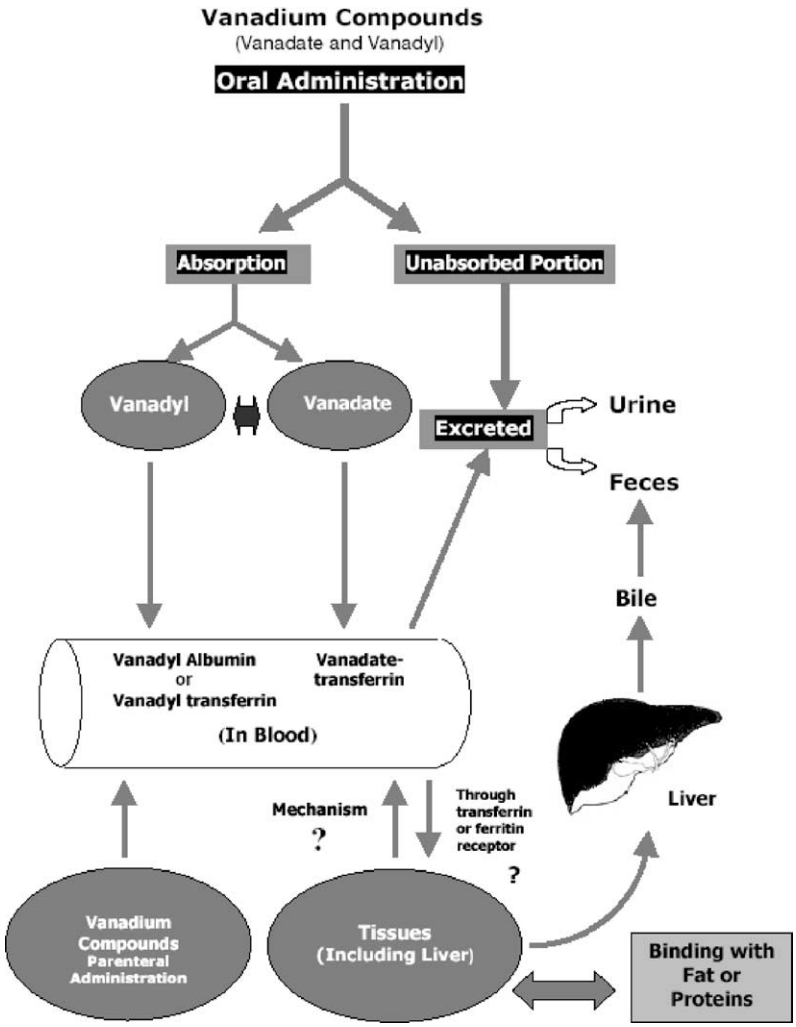

Fig. 1. Major routes of absorption, distribution and excretion of vanadium compounds.

Suzuki, 1996). Again, vanadium in its anionic vanadate form has been found to be absorbed at much higher quantities (about five times more than vanadyl form) through anionic transport system (Hirano and Suzuki, 1996). It has also been reported that vanadyl undergoes spontaneous oxidation to vanadate in vivo (Li et al., 1996). Multivalent existence of vanadium in nature and in living systems put forth the chemical complexity of this element. This multifaceted chemical character of vanadium in turn echoes in its biological and biochemical properties, especially in metabolism and in absorption. Again vanadate after reaching the blood stream is converted into 'vanadyl' ion, although the 'vanadate' form also exists. These vanadate (by transferrin) and vanadyl (by albumin and transferrin) forms are rapidly transported by blood proteins to various tissues (Fantus et al., 1995). Blood parameters showed little or no reflection of toxicity after a long-term supplementation of vanadium compounds (Fawcett et al., 1997; Guidotti et al., 1997), which might be due to the brisk transport of vanadium from blood to the tissues. Upon supplementation, vanadium has been reported to be incorporated in various organs and tissues including liver, kidney, brain, heart, muscles and bone. Kidney, spleen, bone and liver tissues of rat have been shown to accumulate distinctly high amounts of vanadium in chronically treated animals through oral administration (Hamel and Duckworth, 1995; Ramandham et al., 1991).

The effects of vanadium administration persist even after vanadium has been withdrawn for several days (Cam et al., 1997). Unabsorbed vanadium is excreted in feces. When vanadium was administrated through parenteral route, 10% of the vanadium was found in the feces of humans and rats (Barceloux, 1999; Sabbioni et al., 1981; Setyawati et al., 1998; Alimonti et al., 2000). Vanadium has been reported to be excreted through bile and through urine (Alimonti et al., 2000). It is, thus, the bile route through which a significant amount of vanadium may be ultimately excreted through feces. Moreover, it may be suggested that vanadium content in feces does not reflect the amounts of vanadium absorbed or unabsorbed.

2.1. In vitro and systemic toxicity profiles

Cytotoxicity induced by vanadium compounds is well documented (Cortizo et al., 2000; Sabbioni et al., 1991, 1981; Shi et al., 1996). They have been shown to impede the activities of different ATPases (Sabbioni et al., 1991), protein kinases (Stankiewicz and Tracey, 1995; Bollen et al., 1990), ribonuclease (Lau et al., 1993) and phosphatases (Tracey, 2000). They have been shown to inhibit or stimulate the activity of many DNA or RNA enzymes inducing several genotoxic and mutagenic effects (Stemmler and Burrows, 2001). Altamirano-Lozano et al. (1996) showed single strand DNA breaks in individual testis cells of mice 24 h after a single i.p. injection of different doses (5.75, 11.5 and 23 mg/kg) of vanadium pentoxide. The lethal dose (LD50) of vanadium is highly dependent on species, their age and diet. In rats, the dose was reported to be 0.15 m mol/kg body weight (BW) and 0.8 m mol/kg body weight for sodium metavanadate by i.p. and by gavage, respectively, (Liobet and Domingo, 1984). LD50 levels of 0.2–0.3 m mol V/kg i.p. have been established in mice (Venugopal and Luckey, 1978). The toxicity of vanadium compounds increases as the valence increases (Barceloux, 1999). Vanadate has been found to inhibit expression of the gene for phosphorylpyruvate carboxylase (GTP) in rat hepatoma cells (Bosch et al., 1990). Again, vanadium salts (VS) have been shown to stimulate DNA synthesis using cultures of quiescent human fibroblasts and in Swiss mouse 3T3 and 3T6 cells (Smith, 1983). Shi et al. (1986) have shown vanadium mediated DNA damage. They claimed that vanadium(IV) mediated free radical generation causes 2′-deoxyguanosine hydroxylation, which leads to DNA strand breaks.

Researchers have shown that most of the toxic effects of vanadium compounds results in local irritation of eyes and respiratory tract rather than any systemic toxic manifestations (Barceloux, 1999; Guidotti et al., 1997) excluding some sporadic cases of ingestion. A group of researchers of the Temple University Schools of Medicine and Pharmacy, USA, demonstrated that administration of vanadyl sulfate at a dose of 50 mg twice daily for 4 weeks in eight patients (four men and four women) with non-insulin dependent diabetes mellitus, was well tolerated without any toxic manifestations. Vanadyl sulfate was associated with a 20% decrease in fasting glucose concentration and a decrease in hepatic glucose output during hyperinsulinemia (Boden et al., 1996). Supplementation of vanadyl sulfate at concentrations of 0.5–1.5 mg/ml for a year did not show any significant toxic manifestations in

streptozotocin induced diabetic rats and their normal counterparts (Dai et al., 1994). Vanadyl sulfate ($VOSO_4$) did not produce persistent changes in plasma aspartate aminotransferase, alanine aminotransferase and urea levels in those animals and no specific morphological abnormalities was detected in any organs in this study. Fawcett et al. (1997) studied the effects of oral vanadyl sulfate (0.5 mg/kg per day) for a period of 12 weeks in 31 weight training-athletes on their hematological parameters, including red and white cells, platelet counts, haemoglobin level, haematocrit, plasma viscosity, blood viscosity, lipids and indices of liver and kidney function. They reported that there was no effect of $VOSO_4$ treatment on hematological indices and biochemistry of the organs studied. The reason for almost no or very low long-term systemic toxicity of vanadium is really a subject of interest among vanadium scientists. Little or poor long-term systemic toxicity may be due to the fact that vanadium is absorbed poorly from gut (Hirano and Suzuki, 1996) and after reaching blood, it is rapidly transported by albumin and transferrin to organs and tissues (Fantus et al., 1995; Saponja and Vogel, 1996; Wilsky et al., 2001). Lower amounts of vanadium present in the cells may remain bound to fat molecules and may not be available to produce immediate toxicity as vanadium is known to be incorporated in adipose tissues upon supplementation (Nakai et al., 1995). This may well explain the phenomena of prolonged effects of vanadium, which is found even weeks after the cessation of vanadium administration (Cam et al., 1997). On the hierarchy of biochemical demand, organs and tissues may release vanadium. Further research on vanadium metabolism may only substantiate the truth of this hypothesis.

2.2. Impacts of vanadium deficiency in higher animals

Vanadium-deprived goats exhibited abortion rates and depressed milk production (Badmaev et al., 1999). Other biochemical alterations in vanadium deficient goats included decreased levels of isocitrate dehydrogenase, lactate dehydrogenase, serum creatinine and betalipoproteins and elevated serum glucose. Physical abnormalities included swollen forefoot tarsal joints and skeletal deformations in forelegs. Vanadium deficiency affects thyroid metabolism, decreased thyroid weight and thyroid weight-body weight ratio (Badmaev et al., 1999). Vanadium compounds were reported to modulate thyroid hormone levels in blood. Plasma triiodothyronine was higher in vanadium supplemented rats (Badmaev et al., 1999). Vanadium compounds are also known to affect glucose and lipid metabolism (Nakai et al., 1995). It is found to be essential for a number of species such as chicken and rats, deficiency symptoms in such species include retarded growth, impairment of reproduction, disturbance of lipid metabolism and inhibition of Na^+/K^+ ATPase activity in the kidney, brain and in heart (Nriagu, 1998).

3. Vanadium and genetic modulation

Modulation of different genes by vanadium compounds has brought interest amongst biological scientists about this conspicuous element. Several genes are known to be activated by vanadium compounds. Levels of macrophage inflammatory protein (MIP)-2 mRNA have been reported to be elevated accompanied by increased NF-κB binding activity in bronchoalveolar lavage (BAL) cells (Chong et al., 2000a). Induction of tumor necrosis factor-alpha (TNF-α), Interleukin-8 (IL-8), activator protein-1 (AP-1) gene expressions due to vanadate exposure are already known (Ding et al., 1999; Jaspers et al., 1999; Ye et al., 1999). Sodium metavanadate was found to induce macrophage inflammatory protein-2 gene expression (Chong et al., 2000b) and the increase in this gene expression was claimed to be involved in post transcriptional control via increased mRNA stability. Transient transfection study showed that the TNF-α gene promoter was activated by vanadate which was mediated through nuclear factors−κB (Jaspers et al., 2000; Ouellet et al., 1999). Vanadium compounds were shown to increase levels of ras, c-raf-1, MAPK, $p70^{s6k}$ in insulin receptor over-expressing cells (Pandey et al., 1999). After parenteral administration, vanadium induces p53 activation and it is claimed that this activation is required for vanadate induced apoptosis (Huang et al., 2000). Most of these gene expressions were claimed to be due to reactive oxygen species attributed in vanadate activity. These expressions may be better explained by the customary changes in REDOX potentials of the

environment due to the presence of this multivalent element.

3.1. Pharmacological and therapeutic importance of vanadium

Pharmacological uses of vanadium include lowering of cholesterol, triglycerides and glucose levels, diuretic and natriuretic effects, anti-carcinogenic effect, contraction of blood vessels, enhancement of oxygen-affinity of hemoglobin and myoglobin. (Poucheret et al., 1998; Rehder, 1992; Thompson et al., 1993).

Vanadyl sulfate in the doses of 0.4–0.6 mmol/kg caused significant and sustained decrease in blood pressure in spontaneously hypertensive rats (Bhanot and McNeill, 1994). Bis (maltolato) oxovanadium(IV) was found to decrease appetite and body weight by decreasing hypothalamic neuropeptide mRNA expression and the compound was claimed to be a possible therapeutic agent in obesity (Wilsky et al., 2001; Wang et al., 2001).

Interest in vanadium pharmacology becomes greatly advanced with the discovery of vanadium containing enzymes (Almedeida et al., 2001; Badmaev et al., 1999). These enzymes are capable to exercise the activities of nitrogenase, haloperoxidase and bromoperoxidase. Vanadium sulfate is now-a-days used as muscle mass builder (Clarkson and Rawson, 1999) and used to improve performance in weight training athletes (Fawcett et al., 1997). Vanadium compounds have been reported to induce calcium signaling and Ca^{2+} release-activated Ca^{2+} channel activation in Jurkat T-lymphocytes and rat basophilic leukemia-2H3 mast cells (Ehring et al., 2000). Peroxovanadium compounds have been found to induce NO synthase in livers of mice and enhance circulating nitrate level in blood. Control of progression of leismaniasis by vanadium compounds is believed to be an NO dependent process (Matte et al., 2000). Vanadyl treatment significantly reduced the incidences of the occurrence of urinary stones in non-diabetic rats and overall; it significantly reduced the mortality rate and did not show the development of renal and testicular tumors (Alimonti et al., 2000; Shi et al., 1996).

The blood glucose concentration in insulin-dependant diabetic rats and humans was reported to be almost normalized after administration of vanadium compounds (Cam et al., 2000). Various mechanisms have been proposed in search of blood glucose lowering effect of vanadium. One predominant hypothesis was associated with modulation of several enzymes including 6-phosphofructokinase, glucokinase and fructose 2,6-biphosphatase. Administration of vanadate to non-diabetic rats did not significantly affect the glycaemic condition (Bollen et al., 1990). Again, it has been proposed that impaired glucogenic response of the diabetic liver to glucose results from the decreased activity of glycogen synthase phospatase. Vanadium increased the activity of this enzyme to improve the diabetic condition (Bollen et al., 1990). By activation and auto-phosphorylation of solublized insulin receptor, stimulating the tyrosine kinase activity of the insulin receptor β subunit (Li et al., 1996) and by inhibition of phospo-protein tyrosine phosphatase (Fantus et al., 1995) vanadate was reported to stimulate glucose metabolism (Barceloux, 1999). Latest research indicates that molecular basis of insulin mimetic effects of vanadium or vanadium salts do not involve the insulin receptor tyrosine kinase activity and the subsequent phosphorylation of insulin receptor substrate-I (D'Onofrio et al., 1994), rather vanadium salts activate mitogen-activated protein kinase and phosphatidylinositol 3-kinase activities (PI3-K) activities via a pathway which includes the stimulation of the ras-ERK cascade by VS is dependent on PI3-K activation and requires a protein farnesylation step. It is suggested that stimulation of the PI3-K/ras/ERK pathway plays a key role in mediating the insulinomimetic effects of inorganic vanadium salt (Pandey et al., 1999). Treatment of insulin receptor over-expressing cells with vanadyl sulfate showed increased levels of ras, c-raf-1, MAPK, $p70^{s6k}$ (Pandey et al., 1999). Based on these observations it may be stated that vanadium provide insulin mimetic effect choosing a complicated pathway which is not yet clearly understood. Again it shows that vanadium-biology is equally complex like-vanadium chemistry.

Kingsmorth et al. (1986) studied the effect of ammonium vanadate (10–20 mg/l) supplemented drinking water to the tumor size and tumor incidence and types in CD-1 mice injected weekly for 20 weeks 1,2-dimethyl hydrazine. They claimed increased thymidine incorporation and reduced RNA content, but no effect of types and incidence of tumor (Kingsmorth et al., 1986). Feeding a purified

diet supplemented with vanadyl sulfate prevented the induction by *N*-methyl-*N*-nitroso-urea induced mammary cancers, when given during the post inhibition stages of neoplastic process (Thompson et al., 1986). Djordjevic and Wampler (1985) reported a significant antitumor activity of vanadium complexes against L-1210 murine leukemia. Vanadium compounds have been shown to possess pronounced antineoplastic activity against rat liver tumors (Bishayee and Chatterjee, 1995a), fluid and solid Ehrlich ascites tumor (Harding and Mokdsi, 2000) and TA3Ha murine mammary adenocarcinoma (Murthy et al., 2000). Vanadium compounds have also been shown to inhibit markedly the growth of human tumor colony formation (Hanauske et al., 1987), HEP-2 epidermoid carcinoma cells (Murthy et al., 2000). Sakurai et al. (1995) have also found strong antitumor activities of vanadyl complexes of 1,10-phenanthroline and related derivatives. Bishayee and Chatterjee (1995b) reported the antitumor activities of a number of vanadium compounds in animal model systems.

Likewise selenium, vanadium came as a cancer producing agent. Eventually it is becoming popular as an anticancer agent. In various carcinogenic models, vanadium was found to reduce tumor sizes and tumor incidences (Basak and Chatterjee, 2000; Bishayee et al., 1999) along with the modulation of preneoplastic and neoplastic focal lesions. Vanadium was found to modulate phases I and II hepatic metabolizing enzymes and improve antioxidant status during the development of carcinogenesis (Bishayee et al., 2000; Chakraborty and Sevaraj, 2000). But the mechanisms are yet unclear. In a previous study conducted in our laboratory showed for the first time that dietary micro-nutrient vanadium supplemented at the concentration of 0.5 ppm in drinking water offers a considerable protection against DMBA induced mammary carcinogenesis in female Sprague–Dawley rats (Bishayee et al., 2000). The study depicts a possible role of representative hepatic phase I and II xenobiotic metabolizing enzymes in this protection (Bishayee et al., 2000). Decrease in lipid peroxidation was noted while an increase in hepatic glutathione (GSH) level was observed in vanadium treated groups. Vanadium-treated animals showed a significant ($P < 0.05$) reduction in hepatic superoxide dismutase (SOD) activity when compared against corresponding carcinogen controls. Vanadium treatment augmented hepatic cytochrome P450 levels by 52% as compare to DMBA control group. Vanadium along with 1α, 25-dihydroxyvitamin D_3 supplementation showed to improve diethylnitrosamine induced chromosomal aberrations and DNA-strand breaks in rat liver (Basak et al., 2000). The predominant sequence of cellular changes during the development of hepatocarcinogenesis starts with glycogenotic-acidophilic hepatocytes and progresses through intermediate phenotypes in mixed cell populations to glycogen-poor basophilic hepatocytes prevailing in undifferentiated hepatocellular carcinoma (Bannasch et al., 1997a). The similar sequence of changes of acidophilic to basophilic cell populations was also reported during other carcinogenesis (Bannasch et al., 1997b). Modulation of carbohydrate metabolism seems to have some definite implications in the pathogenesis of neoplasm (Bannasch et al., 1997c). Vanadium, like insulin, can restore the glyconeogenitic response (Goldwaser et al., 2000) by a mechanism yet to be elucidated. It may be little tempting here to speculate that anti-carcinogenic effect of vanadium is produced by following the same pathway through which it provides anti-diabetic action.

4. Conclusion

The dose differentiates a remedy or poison. The same is true for vanadium. There has been no definite evidence that vanadium deficiency reproducibly impairs biological function in humans. Though it has been pointed out that the element is a toxic agent and caution is to be taken during the supplementation. Still, vanadium showed some positive roles, especially in controlling the development of diseases like cancer and diabetes. The pool of scientific data favors the supplementation with a very low dose of this element in fatal diseases like cancer. The paramount medicinal use of vanadium in diabetes is an established therapy now. A ‘toxic element’ of yesteryears is gradually turning to be an effective therapeutic and essential element as in case of selenium (Vernie, 1982). More clear understanding of the relevant biological and biochemical basis of this element is needed to bring the element into a new chemotherapeutic program. Scientific exploration must continue to elucidate the mechanism of action of this trace element in a varied assortment

of biological phenomena; which in turn will define the contribution of this potential element in human benefit.

Acknowledgements

Research of this laboratory is funded by grants from the Department of Science & Technology (DST), Govternment of India, University Grants Commission (UGC), Govternment of India and Indian Council of Medical Research (ICMR). P.B. is a recipient of Senior Research Fellowship awarded by Council of Scientific and Industrial Research (CSIR), Govternment of India.

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