Chapter

Oxidative Stress and Vanadium

Marcela Rojas-Lemus, Patricia Bizarro-Nevares, Nelly López-Valdez, Adriana González-Villalva, Gabriela Guerrero-Palomo, María Eugenia Cervantes-Valencia, Otto Tavera-Cabrera, Norma Rivera-Fernández, Brenda Casarrubias-Tabarez, Martha Ustarroz-Cano, Armando Rodríguez-Zepeda, Francisco Pasos-Nájera and Teresa Fortoul-van der Goes

Abstract

Air pollution is a worldwide health problem, and metals are one of the various air pollutants to which living creatures are exposed. The pollution by metals such as: lead, cadmium, manganese, and vanadium have a common mechanism of action: the production of oxidative stress in the cell. Oxidative stress favors the production of free radicals, which damage biomolecules such as: DNA, proteins, lipids, and carbohydrates; these free radicals produce changes that are observed in different organs and systems. Vanadium is a transition element delivered into the atmosphere by the combustion of fossil fuels as oxides and adhered to the PM enters into the respiratory system, then crosses the alveolar wall and enters into the systemic circulation. In this chapter, we will review the oxidative stress induced by vanadium—as a common mechanism of metal pollutants—; in addition, we will review the protective effect of the antioxidants (carnosine and ascorbate).

Keywords: air pollution, metals, vanadium, oxidative stress damage, ascorbate, carnosine

1. Introduction

Air pollution is a worldwide concern because of the health problems associated with its uncontrolled emissions that affect all the biological systems. Within the wide range of pollutants, the suspended particles or particulate matter (PM) are of particular interest, which became more important since IARC listed them as carcinogens. The toxicity of PM is the consequence of the elements adhered to its surface [1]. An example of this are the particles generated by the combustion of fossil fuels and its derivatives, these particles usually consist of a carbon core on which complex mixtures of compounds are adhered, such as: polyaromatic hydrocarbons, toxins, sulfates, nitrates, and especially transition metals like vanadium, manganese, chromium, among others [2]. Metals are considered to play an important role in the induction of toxic effects reported in the literature [3].

Metals are the largest category of globally distributed pollutants with a tendency to accumulate in some human tissues and with a high toxic potential at relatively low concentrations. Constant exposure to certain metals has been linked to inflammation, cell damage, and cancer [4]. Each metal has its own mechanisms of action [5]. Some of them produce its adverse effects alone, while others interact with various factors resulting in greater damage in different organs and systems [4]. It is known that metals, including vanadium, have different toxic pathways, and oxidative stress is the most frequent mechanism [5].

Oxidative stress is the consequence of an imbalance between the production of free radicals and the antioxidant capacity of an organism [6]. It may result from the increase in exposure to oxidants, due to the decrease in the protection against oxidants, or because both events occur simultaneously [7].

A free radical represents any chemical species of independent existence that has one or more missing electrons spinning in its external atomic orbitals. This electrochemical configuration is unstable and gives them property of being a highly reactive and short-lived chemical species [8]. Most of the free radicals of biological interest are usually extremely reactive and have a very short life span (microsecond fractions). When a radical reacts with a non-radical compound, it results in other free radicals, thus generating chain reactions that produce biological effects [9], coupled with the fact that when they collide with a biomolecule and subtract an electron (oxidizing it), it loses its specific function in the cell [8].

Regardless of the origin, free radicals can interact with the biomolecules found in the cell such as nucleic acids [10], proteins, lipids, and carbohydrates [9], thereby causing potentially serious modifications and consequences in the cell [10].

Vanadium is an element that is find in various oxidation states and participates in reactions that lead to the production of free radicals such as superoxide, peroxovanadyl, and the highly reactive radical hydroxyl [8].

2. Oxidative stress, vanadium, and cellular and systemic damages

The increasing production of free radicals leads the cell to an imbalance in its redox state and thus generating oxidative stress; therefore, the cellular dysfunction will be reflected in the failure of organs and systems.

2.1 Oxidative stress and cellular damage

The cell is the basic functional unit of life and its dysfunction induced by oxidative stress might produce DNA damage and cell death.

2.2 Oxidative stress, vanadium, and DNA damage

The International Agency for Research on Cancer lists vanadium pentoxide (V_2O_5) as "a possible carcinogen for humans" in group 2B. The above was based on evidence of lung cancer generation in mice that was published by the National Toxicology Program [11]. However, evidence on the carcinogenicity of vanadium has been widely questioned by Duffus in 2007 [12] and Starr et al. [13]. Information related to the carcinogenic and genotoxic potential of vanadium pentoxide (V_2O_5) is limited [14]. In both animal and human models, the effects on the DNA caused by vanadium include single strand breaks, micronuclei, chromosomal aberrations (structural and numerical), and oxidation of nitrogenous bases [15, 16]. The spectrum of alterations that DNA might have as a consequence of free radicals interaction, in this case caused by vanadium, are: deoxyribose oxidation, modification of

nitrogen bases, chain cross-linking, and ruptures [6]. The double or single chain breaks that are generated by the interaction of free radicals with DNA are produced by the fragmentation of the sugar-phosphate skeleton or indirectly by the cleavage of oxidized bases [17].

The above indicates that vanadium is an element with mutagenic potential, because its genotoxic, aneugenic, and clastogenic effects, although there are not strongly data supporting that vanadium is carcinogenic, this possibility should not be eliminated, because the DNA damage caused by the exposure and therefore genetic instability, processes closely related to the generation of malignancy [18].

2.3 Oxidative stress, vanadium, and cellular death

Cell death is central to physiological homeostasis; the balance between cellular differentiation, proliferation, and death support aspects of biology, including embryogenesis, organ function, tissue remodeling, immune regulation, and carcinogenesis. Cell death was once believed to be the result of one of three different processes: apoptosis, autophagy or necrosis; however, in the last decade about 15 different types have been reported, highlighting that a cell can die via different pathways which depends on the intensity of the stimuli [19]. Reactive oxygen species (ROS) activates cell death and plays different roles in the biological systems which can be either injurious or beneficial. Generation of ROS might be caused by metals such as: arsenic, cadmium, chromium, cobalt, copper, gold, iron, nickel, rhodium titanium or vanadium [8]. Vanadium compounds can interconvert into different species (vanadyl and vanadate) event which is constantly occurring inside the cell in the presence of ROS [20].

Studies *in vivo* and *in vitro* showed that vanadium compounds induce cell death in leukemia [21], lung cancer [22] cervical and breast carcinoma [23], neuroblastoma [24], liver carcinoma [25], osteosarcoma [26], and pancreatic ductal adenocarcinoma [27]. *In vitro* studies demonstrated that the cell lines stimulated with vanadium compounds produce H_2O_2 and O_2 and induce autophagy, necroptosis, and mitotic catastrophe [27]. Apoptosis is the main type of cell death associated with vanadium compounds, reporting the release of cytochrome c from mitochondria [21] and the disruption of the mitochondrial membrane potential [25]. This type of cell death is mediated through the activation of p53 and p21 [27], which modulate the activation or inactivation of phosphorylation of some proteins such as MEK, ERK 1/2, PI3K, p38, JNK, TNF-alpha, and NFkB [28].

2.4 Oxidative stress and vanadium in different systems

The systemic vanadium effects observed *in vivo* and *in vitro* are briefly described below.

2.4.1 Reproductive system

The reprotoxic effects of vanadium in male reproductive system in laboratory animals include interruption of spermatogenesis [29], morphological and biochemical changes in spermatogenic cells [30], abnormalities in the shape and movement of sperm, as well as decrease in the weight of the testis, epididymis, and prostate [31].

One of the mechanisms of vanadium toxicity includes imbalance in the cellular redox state [30]; testicular cells are highly susceptible to free radical actions because its membranes are rich in polyunsaturated fatty acids, which limits the fluidity of the membrane and alters the functioning of integral membrane proteins [32].

In rat's testis, after given sodium metavanadate ($NaVO_3$), an increase in malondialdehyde (MDA) was found, which is a product of lipid peroxidation, as well as a decrease in the activity of superoxide dismutase (SOD) and catalase [33]. Intraperitoneal administration of $NaVO_3$ caused in the testis a decrease in the number of germ cells, the presence of degenerated cells, and necrosis of the seminiferous tubules, associated to the increase in testicular lipid peroxidation and inhibition of the activity of antioxidant enzymes (SOD and catalase) [34]; alteration in spermatogenesis, decrease in serum testosterone, LH and FSH levels, inhibition of steroidogenic enzyme activity, increase in testicular vanadium concentration, inhibition of antioxidant enzymes (SOD, catalase and GPx), increased levels of lipid peroxidation [29], and abnormalities in the form of sperm have also been reported [35].

During female reproductive processes, such as ovarian follicle development, ovarian steroid synthesis, ovulation, fertilization, and implantation, require certain amounts of ROS [36]; however, due to the oxidizing effects of vanadium, the delicate balance between ROS generation and the cellular antioxidant system can be altered.

In the case of the female reproductive system of rats, it has been observed that the administration of vanadium sulfate ($VOSO_3$) causes oxidative stress and biochemical alterations in uterine cells, such as the decrease in the activity of alkaline phosphatase and adenosine triphosphatase; while in the ovary, the damage of the oocyte and ovarian follicles was observed, as well as stromal fibrosis [37]. In an inhalation model of vanadium in non-pregnant females, histological alterations were found in the ovary and uterus and lipid peroxidation, indicated by the increase in the levels of 4-hydroxynonenal (4-HNE) a marker of oxidative stress [30].

Vanadium crosses the placental barrier and exerts its toxic effects on embryos and fetuses; in rats, it has been observed that fetal weight decreases and the number of implants and fetuses, while the number of resorptions, malformations, and dead fetus increases [31]. The fetotoxic and embryotoxic effects of vanadium have also been associated with oxidative stress since both in fetuses and in mothers exposed to vanadyl sulfate ($VOSO_4$), and lipid peroxidation was observed in the liver [37].

2.4.2 Urinary system

Kidney chronic disease (CKD) has increased worldwide. The main risk factors for the development of this disease are diabetes, metabolic syndrome, and hypertension. However, there are a segment of population that has none of these risk factors and there are other factors that are being studied as a possible cause of renal injury. One of them is the environmental pollution, particularly pollution by metals in atmosphere and water. Arsenic, cadmium, mercury, lead, and vanadium have been reported as nephrotoxic metals because of the production of ROS and the induction of oxidative stress. These metals enter the body by oral or inhaled exposure, then they are absorbed, enter into the systemic circulation, and distributed into the organs where they may accumulate. Finally, most of them are eliminated by the kidney, reason why this organ is one of the most affected structures by metals [38]. Also, there are reports that in CKD when there is a problem to eliminate pollutant metals, these can concentrate into kidney cells and the damage worsened when it occurs in humans, both in children and adults [39]. Oxidative stress and inflammation are the principal mechanisms of renal injury; in addition, arsenic, cadmium, mercury, and lead are associated to hyperglycemia that may aggravate the oxidative stress and the renal damage. Vanadium is an exception because it has a hypoglycemic effect, but this does not ameliorate its toxicity [40].

Vanadium is nephrotoxic, as it has been proved mainly in animal models, but also in humans [41]. In a report of human acute poisoning by oral ammonium metavanadate, hypoglycemia, bronchoconstriction, and acute renal insufficiency were the causes of death; in a chronic model of vanadium exposure reported glomerulonephritis, glomerular and tubular necrosis that lead to renal insufficiency and hypertension [42]. The reported findings in other study with ammonium metavanadate *p.o.* at doses of 30, 45, and 60 mg/kg were edema, vacuolization, and degeneration of epithelial tubular cells at 21st day of exposure [43]. Another research group, using different compounds and doses of vanadium (45 and 90 mg/kg) reported thickening of glomerular basement membrane, pyknotic nuclei, cellular vacuolization, and pyelonephritis [44]. In our group, in a subchronic model of vanadium inhalation, we found foci of inflammatory cells, vacuolation, loss of microvilli of epithelial tubular cells, and changes in urine parameters as proteinuria and hematuria associated to the increase, in a time dependent manner, of 4-hidroxynonenal (4-HNE) [45] (**Figure 1A** and **B**). Oxidative stress is also the toxic vanadium mechanism reported by other groups, for example, Marouane et al. [46] found lipid peroxidation, protein denaturation, DNA degradation, and cell membrane disintegration; in addition, Scibior et al. [47] reported elevated malonaldehyde (MDA) as a marker of oxidative stress and enhanced total antioxidant status in a rat model of 12-week oral sodium metavanadate exposure.

2.4.3 Immune system

The immune system is an interactive network of lymphoid organs, cells, humoral factors, and cytokines whose function is to distinguish between self and non-self-antigens in the host system, thus providing mechanisms against infections and tolerance to the components of the host. When an antigen attacks the host, two distinct, yet interrelated, branches of the immune system are activated, the nonspecific/innate and specific/adaptive immune response. Both of these systems

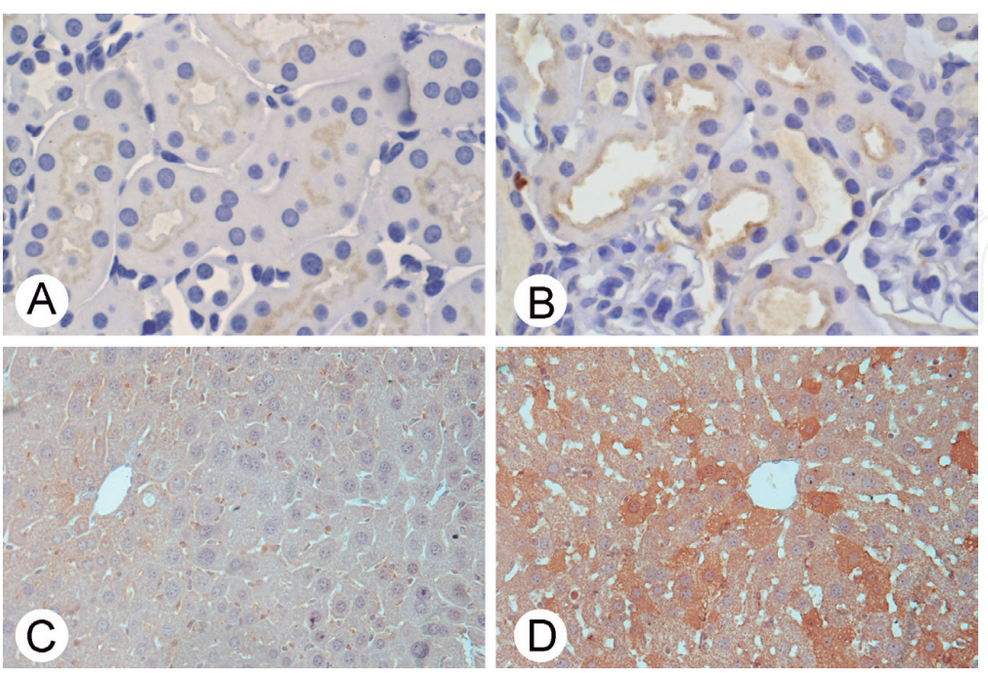

Figure 1.
4-hydrxynonenal (4-HNE) in kidney and liver as a marker of oxidative stress. (A) Kidney tubules in control group with a basal 4-HNE immunoreactivity. (B) In vanadium group, 4-HNE immunoreactivity increased in microvilli of proximal tubules after 8th-week exposure. (C) Liver of control group with a basal 4-HNE immunoreactivity. (D) Liver of vanadium group after 8th-week exposure with increase in 4-HNE immunoreactivity in hepatocytes, some of them with a very intense mark.

have certain physiological mechanisms, which enable the host to recognize foreign materials as foreign materials and to neutralize, eliminate, or metabolize them [48]. The immune system is a target of air pollutants, such as vanadium that might impair its function and induce oxidative stress.

In previous studies, effects from vanadium inhalation on the immune system have been demonstrated. Changes in the spleen morphology and a decrease in humoral immune responses have been reported [49], as well as a decrease in the number of thymic dendritic cells, its expression of CD11c and MHC-II biomarkers, and an increase of thymic medullar epithelial cells [50]. Oxidative stress could be an important mechanism involved in these effects and some mechanisms are described as follows:

Sodium metavanadate ($NaVO_3$) induced oxidative stress through generation of ROS and depletion of the antioxidant defense systems. When the exposure is chronic, the oxidative stress turns out in severe damage [51].

The effect of vanadyl sulfate ($VOSO_4$) in blood glucose and in the spleen, in streptozotocin (STZ)-induced diabetic rats was evaluated. The levels of lipid peroxidation (LPO) and glutathione (GSH) in the spleen were analyzed. After 60 days of treatment, spleen LPO significantly increased, but spleen GSH levels significantly decreased in the diabetic group. On the other hand, treatment with $VOSO_4$ reversed these effects in STZ diabetic animals [52]. These studies show that vanadium induced oxidative stress in the spleen, which might disrupt the immune response.

2.4.4 Digestive system

The liver as the major site for metabolism, biotransformation and detoxification of drugs and foreign compounds, is constantly exposed to ROS resulting in oxidative stress and frequently, permanent and irreversible tissue damage [53]. Studies have shown that liver is one of the most important target tissues for vanadium toxicity with its capacity to form ROS by interacting with mitochondrial redox centers, mainly in mitochondrial respiratory processes I, II, and III [54]. Studies with HepG2 cell line have shown that exposure to vanadium causes damage to nuclear and mitochondrial DNA, as well as decreased cell viability [55]. *In vivo* studies from our group demonstrate that vanadium increases lipid peroxidation in V-exposed animals [56]. **Figure 1C** and **D** show the oxidative marker 4-HNE in liver parenchyma.

As a heavily irrigated, highly connected organ with neural, endocrine, digestive, absorptive, and immune functions, the gut can enter oxidative cycles mostly by two well-defined mechanisms:

1. Ambient-polluting microparticle swallowing: especially in heavily polluted areas (industrial centers, cities, mines, etc.), the air is charged with carbon PM, whose size varies between 10 and 2.5 (or even less) micrometers. Such particles are normally covered by metals (vanadium, for instance), which get trapped via natural defense mechanisms in the nasal and oral mucosa, slowly, descending into the pharynx and into the digestive tract carried on through saliva [30].

2. Direct toxic ingestion: recent research relates ingestion of food ingredients—especially sugar (sucrose or high fructose) present mostly in sugar-sweetened beverages (SSB)—with tissue damage. Although there is no specific data on gut tissue damage, it has been reported in other bodily systems—e.g., kidney [45]. This represents a particularly severe problem in a world where no matter the country, the SSB consumption increases steadily year after year [57].

Research on this matter has still a long path to walk. However, preliminary results from ongoing protocols at our laboratory show a significant rise in 4-HNE levels in the gut epithelium in response to air pollution and SSB consumption mice models, which indicate higher oxidative stress levels vs. control groups.

2.4.5 Cardiovascular system

Air pollution has been associated to thrombosis and cardiovascular risk. Pollutants, including PM and metals may induce oxidative stress and inflammation predisposing to endothelial dysfunction, platelet activation, and procoagulant state [58]. There is epidemiological evidence that elevated concentrations of pollutants, e.g., vanadium, are associated to an increase in ER visits for acute cardiovascular effects or exacerbations of preexisting cardiovascular diseases [59].

Vanadium induces oxidative stress, and there is evidence of their toxic effects on endothelium, platelets, and myocardium. An *in vitro* study using HUVEC (human umbilical vein endothelial cells) exposed to different V_2O_5 concentrations reported an increase in ROS that damaged endothelial cells leading to apoptosis and diminished proliferation. This might be involved in endothelial dysfunction and increased cardiovascular risk associated to metals [60]. An *in vivo* vanadium inhalation mice model, from our group, reported thrombocytosis that is an increase in platelet number, but also the presence of giant platelets that are associated to increase reactivity [61]. Also, we found a megakaryocytosis with an increase in megakaryocytes size and granularity because of the activation of JAK/STAT pathway [40, 62, 63]. Platelet aggregation after subchronic vanadium inhalation diminished, but activation markers of platelets P-selectin or CD-62p were increased after the 4th week of exposure, maybe because of the slow elimination of vanadium, so it is possible that this metal has on platelet aggregation a long-term effects [64]. Another effect of vanadium on cardiovascular system is arrhythmia; in our group, we studied its effect on myocardium N-cadherin and connexin-43, important proteins in the intercalated discs. The reduction of both proteins and its effect on the electric stimuli conduction was proposed to explain the pathophysiology of the arrhythmias induced by vanadium [65]. Vanadium and other metals induce oxidative stress that may damage several cells of cardiovascular system.

2.4.6 Respiratory system

The lung is one of the main targets of air pollution damage because it is the first site in contact with the pollutants suspended in the air. After reaching the alveolar epithelium, the pollutants can cross the alveoli-capillary barrier. There are various reports that demonstrate the damage caused to this organ by exposure to specific contaminants, such as vanadium that is part of the suspended particles.

In vivo, it has been reported that inhaled exposure to vanadium, mainly in the form of pentoxide induces histopathological changes in the lung, such as fibrosis [66], inflammation [30, 66, 67], hyperplasia and epithelial metaplasia [30, 67] and apoptotic cell death [68], among others.

Experimental evidence supports that exposure to V_2O_5 increases the production of ROS in lung cells. Wang et al. [68] reported increase in ROS production in mice bronchoalveolar lavage cells treated with a concentration of 10 μm of sodium metavanadate ($NaVO_3$), in a time-exposure dependent manner (3, 10, 30, and 60 minutes) through a spin trapping essay.

On the other hand, other evidence shows that exposure to V modifies in the lung glutathione concentrations, both in its oxidized (GSSG) and reduced (GSH) forms. It is known that oxidative stress results in the depletion of GSH and the increase in

GSS; so, the determination of their respective concentrations in blood and other tissues is considered a measure of intracellular oxidative stress [69].

Schuler et al. reported that in their inhalation model of V_2O_5 at exposure concentrations of 0.25, 1, and 4 mg/m^3, there was an increase in the levels of oxidized glutathione (GSSG) in lung tissue, with the consequent reduction in the ratio between reduced and oxidized glutathione (GSH/GSSG) concentrations [70]. Kulkarni and colleagues reported the same finding in relation to GSH concentration in lung tissue in a model of exposure to V_2O_5 nanoparticles [66]. In addition to this finding in the same study, the significant increase in MDA levels in plasma was identified. The MDA is a final product of lipid peroxidation.

Another biomarker of oxidative damage that has been identified is the 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxoGuo) in the DNA. Schuler demonstrated the increase in the formation of 8-oxoGuoin at exposure concentrations of 1 and 4 mg/m^3 of V_2O_5 in lung cells [70].

2.4.7 Nervous system

Neurotoxic metals as vanadium can induce oxidative damage in the brain and develop blood brain barrier disruption, neuropathology, and neuronal damage that can trigger central nervous system alterations as depression, increase in anger, fatigue, and tremors between other clinical features [71]. Also, a decrease in tyrosine hydroxylase and dopamine levels has been reported after vanadium exposure [72]. Chronical exposure to $NaVO_3$ can cause, in mice, metal accumulation in the olfactory bulb, brain stem, and cerebellum, as well as histopathological alterations like nuclear shrinkage in the prefrontal cortex and cell death of the hippocampal pyramidal cells and cerebellum Purkinje cells [71]. The accumulation of vanadium in the brain depends more on the exposure time than on the concentration of the metal. In fact, it is reported that disruption of ependymal cells is observed after long periods of vanadium inhalation [73].

Recently, behavioral alterations due to vanadium occupational exposure have been reported. Vanadium exposed workers exhibited poor performance in the simple reaction time, digit span memory, and Benton visual retention tests [74]. Memory loss in mice exposed to vanadium for 3 months was observed; nevertheless, in these animals, memory was recovered 9 months after vanadium was removal [75]. Increased incidence of Parkinson's disease is related to environmental metal exposure. It has been reported that vanadium pentoxide (V_2O_5) is neurotoxic to dopaminergic neurons via caspase-3-dependent PKCδ cleavage, so maybe vanadium can promote nigral dopaminergic degeneration [76].

2.5 Antioxidative action of carnosine and ascorbate

The cells exposed continuously to oxidative stress are not defenseless against free radicals. All aerobic organisms count with a series of mechanisms protecting them against oxidative damage; among them are antioxidant molecules which represent a first line of defense. If the antioxidant mechanisms fail, the cell uses others such as: transient cell arrest, biomolecular repair systems or apoptosis death processes [7].

An antioxidant is any substance that when is present in low concentrations, compared to the oxidizable substrate, decreases or prevents the substrate oxidation. Oxidizable substrates comprise everything that is found in living tissues including proteins, lipids, carbohydrates, and nucleic acids [77].

Cells use a series of antioxidant compounds that react directly with oxidizing agents, functioning as "sweepers" or chemical shields [7]; these molecules have enzymatic or non-enzymatic actions. Non-enzymatic antioxidants carry out

the reduction of free radicals through electron donation, thus avoiding oxidative reactions. Glutathione (GSH), alpha-tocopherol (vitamin E), ascorbic acid (vitamin C), carnosine, bilirubin, and uric acid are the main molecules performing this function.

Ascorbate is an important water-soluble antioxidant in biological fluids, because it eliminates reactive oxygen species and radicals such as: alkoxy, hydroxyl, peroxyl, and hydroperoxyl radicals, singlet oxygen, superoxide anion, and ozone. It also eliminates reactive species and radicals derived from nitrogen and chlorine and even radicals that come from other antioxidants [78].

In general, a large number of studies have been carried out to show the beneficial effects of ascorbate. Evidence indicates that supplementation with this compound protects against lipid oxidation *in vivo*, particularly in individuals exposed to exacerbated conditions of oxidative stress, such as smokers [79].

Epidemiological studies of treatment with this antioxidant have shown consistently favorable effects in patients with cardiovascular disease or coronary risk. In addition, it has been suggested that the increase in ascorbate consumption significantly decreases the incidence and mortality from cardiovascular diseases. Even in pathologies related to free radicals and the inability of the organism defenses against them, as is the case of cancer, epidemiological studies show that increased consumption of ascorbate decreases the incidence and mortality from cancer [79].

Experimental evidence indicates that ascorbic acid works as an antidote against acute vanadium poisoning. In mice, Jones and Basinger [80] examined several compounds and concluded that ascorbate was the most promising for human use.

Domingo et al. [81] administered $NaVO_3$ to mice intraperitoneally and observed, as did Jones and Basinger, that ascorbate proved to be the most effective antidote against vanadium poisoning. In another study, Domingo et al. [82] showed that ascorbate stimulates urinary excretion of vanadium when mice are injected intramuscularly with $VOSO_4$.

Another water-soluble antioxidant is carnosine which is a dipeptide composed of β-alanine and L-histidine; it is found naturally in many mammalian species, mainly in the skeletal muscle. It is estimated that 99% of the carnosine in the organism is found in muscular tissue [83].

It has been reported that carnosine may form complexes with transition metals and has antioxidant activity, which implies mechanisms such as chelation of metals, scavenging of ROS, and peroxyl radicals [83].

The antioxidant efficiency of carnosine in the nervous system, when mice are exposed to vanadium inhalation was successfully tested by our group. It was observed that in those groups with carnosine treatment, a larger size granulose cells with a greater number of dendritic spines, and in general less adverse ultrastructural morphological changes, as well as less lipid peroxidation were observed [84].

3. Conclusions

Air pollution has been continuously mentioned as one of the problems that decrease the quality and life expectancy of all living organisms, included humankind. It is true that not all the sources of pollution are from anthropological origin; however, a great deal of it are generated by humans and can be prevented or controlled by those who generate it.

The use of fossil fuels as the quasi unique source of energy and limited use of other sources of energy will maintain the air pollutant levels high enough to keep its deleterious health effects.

As it is revised in this chapter, metals are one of the air pollutants that enter through the respiratory tract, reaching by the systemic circulation every cell in living organisms. Vanadium is one of the elements adhered to PM which results from the incomplete combustion of fossil fuels. PM generates ROS, mainly those that contains transition metals (e.g., Fe, V, and Mn).

Reported previously in this chapter, one of the main toxic mechanisms of metals is oxidative stress which affects all biomolecules. DNA oxidative damage may conduct the cell to genotoxic and mutagenic changes and further to cell death or cancer.

When proteins are oxidized: cell structure, cell signaling modification, and/or disruption of cellular enzymatic processes could be noticed. The reactive molecules which results from these interactions with proteins and ROS may interplay with specific peptide residues such as: lysines, arginines, histidines, and cysteines. The result of these actions causes the formation of reactive carbonyls and protein carbonylation, and its accumulations have been related with chronic diseases and aging.

If lipids are in contact with ROS, peroxidation occurs producing MDA, a biomarker of oxidative stress that could interact with proteins forming protein adducts and inactivating the protein. Another lipid peroxidation product is 4-HNE with cytotoxic effects and the induction of pro-inflammatory cytokines, which could result in cellular dysfunction and death [85].

If the sources of V or other pollutants are not reduced and the oxidative insults prevail, we can supplement our system with antioxidants such as vitamin C. This water-soluble molecule is not synthesized by humans, and its supplementation is obtained by different dietary sources such as fruits and vegetables or by vitamin C supplements. One of the benefits of vitamin C is its antioxidant action, scavenging ROS and NOS species. In addition, it helps to regenerate alpha-tocopherol and coenzyme Q; also, vitamin C inhibits NAD(P)H oxidase decreasing ROS formation [86]. Another less known endogenous and exogenous antioxidant is carnosine that in our laboratory showed promising antioxidant effects in the nervous system [84].

The systems and organs affected by the oxidative potential of vanadium and the protective effect of antioxidants are summarized in **Figure 2**.

While humankind decide to work together in order to find a common solution for controlling air pollution, scientist should be working in finding more and better

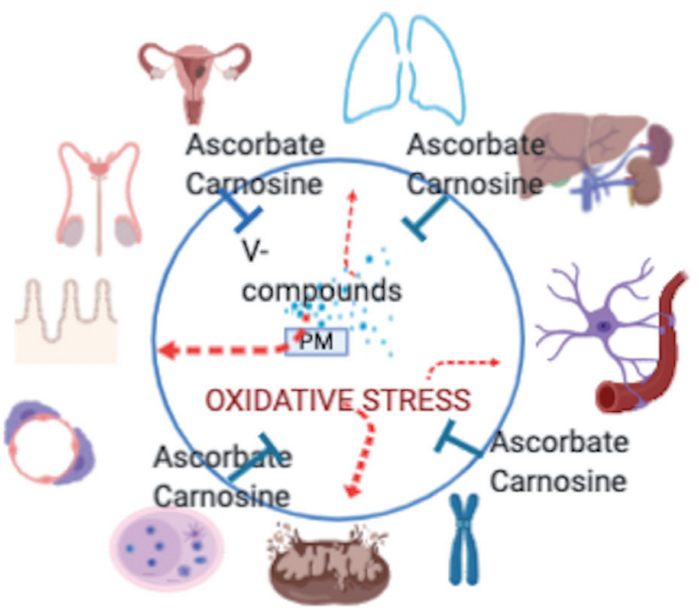

Figure 2.
Oxidative stress by vanadium and antioxidants protective effects (this figure was created by Biorender software in www.biorender.com).

antioxidants to prevent and ameliorate the effects that metals, such as V adhered to PM, have on living organisms, that meanwhile might reduce oxidative stress, its injurious effects and improves the quality of life on the planet.

Acknowledgements

This work was partially supported by project PAPIIT-DGAPA UNAM IN200418.

Author details

Marcela Rojas-Lemus[1], Patricia Bizarro-Nevares[1], Nelly López-Valdez[1,3], Adriana González-Villalva[1], Gabriela Guerrero-Palomo[1], María Eugenia Cervantes-Valencia[1,4], Otto Tavera-Cabrera[1], Norma Rivera-Fernández[2], Brenda Casarrubias-Tabarez[1,3], Martha Ustarroz-Cano[1], Armando Rodríguez-Zepeda[1], Francisco Pasos-Nájera[1] and Teresa Fortoul-van der Goes[1*]

1 Department of Cellular and Tissular Biology, Faculty of Medicine, National Autonomous University of Mexico (UNAM), Mexico City, Mexico

2 Department of Microbiology and Parasitology, Faculty of Medicine, National Autonomous University of Mexico (UNAM), Mexico City, Mexico

3 Doctoral Fellow, Biological Sciences, UNAM

4 Postdoctoral Fellow, Faculty of Medicine, UNAM

*Address all correspondence to: fortoul@unam.mx

References

[1] Fernandez A, Wendt JOL, Wolski N, Hein KRG, Wang S, Witten ML. Inhalation health effects of fine particles from the co-combustion of coal and refuse derived fuel. Chemosphere. 2003;**51**:1129-1137. DOI: 10.1016/S0045-6535(02)00720-8

[2] Sorensen M, Schins RPF, Hertel O, Loft S. Transition metals in personal samples of PM2.5 and oxidative stress in human volunteers. Cancer Epidemiology, Biomarkers and Prevention. 2005;**14**:1340-1343. DOI: 10.1158/1055-9965.EPI-04-0899

[3] Marconi A. Materiale particellare aerodisperso: definizioni, effetti sanitari, misura e sintesi del leindagani ambientali effettuate a Roma. Annali dell'Istituto Superiore di Sanità. 2003;**39**:329-342

[4] Leonard SS, Bower JJ, Shi X. Metal-induced toxicity, carcinogenesis, mechanisms and cellular responses. Molecular and Cellular Biochemistry. 2004a;**255**:3-10. DOI: 10.1023/b:mcbi.0000007255.72746.a6

[5] Leonard SS, Harris GK, Shi X. Metal-induced stress and signal transduction. Free Radical Biology and Medicine. 2004b;**37**:1921-1942. DOI: 10.1016/j.freeradbiomed.2004.09.010

[6] Chihuailaf RH, Contreras PA, Wittwer FG. Patogénesis del estrés oxidativo: consecuencias y evaluación en salud animal. Veterinaria México. 2002;**33**:265-283

[7] Davies KJ. Oxidative stress, antioxidant defenses, and damage removal, repair, and replacement systems. IUBMB Life. 2000;**50**:279-289. DOI: 10.1080/713803728

[8] Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chemico-Biological Interactions. 2006;**160**:1-40. DOI: 10.1016/j.cbi.2005.12.009

[9] Martínez-Cayuela M. Toxicidad de xenobióticos mediada por radicales libres de oxígeno. Ars Pharmaceutica. 1998;**39**:5-18

[10] Cooke MS, Evans MD, Dizdaroglu M, Lunec J. Oxidative DNA damage: Mechanism, mutation and disease. The FASEB Journal. 2003;**17**:1195-1214. DOI: 10.1096/fj.02-0752rev

[11] NTP. Technical Report on the Toxicology and Carcinogenicity Studies of Vanadium Pentoxide (CAS No. 1314-62-1) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). National Toxicology Program, Research Triangle Park NC. NTP TR 507, NIH Publication No. 03-44412002. p. 352

[12] Duffus JH. Carcinogenicity classification of vanadium pentoxide and inorganic vanadium compounds, the NTP study of carcinogenicity of inhaled vanadium pentoxide, and vanadium chemistry. Regulatory Toxicology and Pharmacology. 2007;**47**:110-114. DOI: 10.1016/j.yrtph.2006.08.006

[13] Starr TB, Macgregor JA, Ehman KD, Kikiforov AI. Vanadium pentoxide: Use of relevant historical control data shows no evidence for carcinogenic response in F344/N rats. Regulatory Toxicology and Pharmacology. 2012;**64**:155-160. DOI: 10.1016/j.yrtph.2012.06.017

[14] Rodríguez-Mercado JJ, Mateos-Nava RA, Altamirano-Lozano MA. DNA damage induction in human cells exposed to vanadium oxides in vitro. Toxicology In Vitro. 2011;**25**:1996-2002. DOI: 10.1016/j.tiv.2011.07.009

[15] Altamirano-Lozano M, Valverde M, Alvarez BL, Molina B, Rojas E.

Genotoxic studies of vanadium pentoxide (V_2O_5) in male mice. II. Effects in several mouse tissues. Teratogenesis, carcinogenesis, and. Mutagenesis. 1999;**19**:243-255. DOI: 10.1002/(sici)1520-6866(1999)19:4<243::aid-tcm1>3.0.co;2-j

[16] Rojas-Lemus M, Altamirano-Lozano MA, Fortoul TI. Sex differences in blood genotoxic and cytotoxic effects as a consequence of vanadium inhalation: Micronucleus assay evaluation. Journal of Applied Toxicology. 2014;**34**:258-264. DOI: 10.1002/jat.2873

[17] Mitra S, Izumi T, Boldolgh I, Bhadak KK, Hill JW, Hazra TK. Choreography of oxidative damage and repair in mammalian genomes. Free Radical Biology and Medicine. 2002;**33**:15-28. DOI: 10.1016/s0891-5849(02)00819-5

[18] Léonard A, Gerber GB. Mutagenicity, carcinogenicity and teratogenicity of vanadium compounds. Mutation Research. 1994;**317**:81-88. DOI: 10.1016/0165-1110(94)90013-2

[19] Shlomovitz I, Speir M, Gerlic M. Flipping the dogma-phosphatidylserine in non-apoptotic cell death. Cell Communication and Signaling: CCS. 2019;**17**:139. DOI: 10.1186/s12964-019-0437-0

[20] Trevino S, Diaz A, Sanchez-Lara E, Sanchez-Gaytan BL, Perez-Aguilar JM, Gonzalez-Vergara E. Vanadium in biological action: Chemical, pharmacological aspects, and metabolic implications in diabetes mellitus. Biological Trace Element Research. 2019;**188**:68-98. DOI: 10.1007/s12011-018-1540-6

[21] Capella MA, Capella LS, Valente RC, Gefe M, Lopes AG. Vanadate-induced cell death is dissociated from H_2O_2 generation. Cell Biology and Toxicology. 2007;**23**:413-420. DOI: 10.1007/s10565-007-9003-4

[22] Guerrero-Palomo G, Rendon-Huerta EP, Montaño LF, Fortoul TI. Vanadium compounds and cellular death mechanisms in the A549 cell line: The relevance of the compound valence. Journal of Applied Toxicology. 2019;**39**:540-552. DOI: 10.1002/jat.3746

[23] Balaji B, Balakrishnan B, Perumalla S, Karande AA, Chakravarty AR. Photocytotoxic oxovanadium(IV) complexes of ferrocenyl-terpyridine and acetylacetonate derivatives. European Journal of Medicinal Chemistry. 2015;**92**:332-341. DOI: 10.1016/j.ejmech.2015.01.003

[24] Zhang Y, Wang L, Zeng K, Wang K, Yang X. Vanadyl complexes discriminate between neuroblastoma cells and primary neurons by inducing cell-specific apoptotic pathways. Journal of Inorganic Biochemistry. 2018;**188**:76-87. DOI: 10.1016/j.jinorgbio.2018.08.005

[25] Cunha-de Padua MM, SuterCorreia Cadena SM, de Oliveira Petkowicz CL, Martinez GR, Merlin-Rocha M, Merce AL, et al. Toxicity of native and oxovanadium (IV/V) galactomannan complexes on HepG2 cells is related to impairment of mitochondrial functions. Carbohydrate Polymers. 2017;**173**:665-675. DOI: 10.1016/j.carbpol.2017.06.027

[26] Naso LG, Lezama L, Rojo T, Etcheverry SB, Valcarcel M, Roura M, et al. Biological evaluation of morin and its new oxovanadium(IV) complex as antioxidant and specific anti-cancer agents. Chemico-Biological Interactions. 2013;**206**:289-301. DOI: 10.1016/j.cbi.2013.10.006

[27] Kowalski S, Wyrzykowski D, Hac S, Rychlowski M, Radomski MW, Inkielewicz-Stepniak I. New oxidovanadium(IV) coordination

complex containing 2-methylnitrilotriacetate ligands induces cell cycle arrest and autophagy in human pancreatic ductal adenocarcinoma cell lines. International Journal of Molecular Sciences. 2019;**20**(2);261. DOI: 10.3390/ijms20020261

[28] Wang J, Huang X, Zhang K, Mao X, Ding X, Zeng Q, et al. Vanadate oxidative and apoptotic effects are mediated by the MAPK-Nrf2 pathway in layer oviduct magnum epithelial cells. Metallomics. 2017;**9**:1562-1575. DOI: 10.1039/c7mt00191f

[29] Chandra AK, Ghosh R, Chatterjee A, Sarkar M. Protection against vanadium-induced testicular toxicity by testosterone propionate in rats. Toxicology Mechanisms and Methods. 2010;**20**:306-315. DOI: 10.3109/15376516.2010.485623

[30] Fortoul TI, Rodriguez-Lara V, González-Villalva A, Rojas-Lemus M, Cano-Gutiérrez G, Ustarroz-Cano M, et al. Inhalation of vanadium pentoxide and its toxic effects in a mouse model. Inorganica Chimica Acta. 2014;**420**:8-15

[31] Morgan AM, El-Tawil OS. Effects of ammonium metavanadate on fertility and reproductive performance of adult male and female rats. Pharmacological Research. 2003;**47**:75-85. DOI: 10.1016/s1043-6618(02)00241-4

[32] Aprioku JS. Pharmacology of free radicals and the impact of reactive oxygen species on the testis. Journal of Reproduction and Infertility. 2013;**14**:158-172

[33] Vijaya Bharathi B, Jaya Prakash G, Krishna KM, Ravi Krishna CH, Sivanarayana T, Madan K, et al. Protective effect of alpha glucosyl hesperidin (G-hesperidin) on chronic vanadium induced testicular toxicity and sperm nuclear DNA damage in male Sprague Dawley rats. Andrologia. 2015;**47**(5):568-578. DOI: 10.1111/and.12304

[34] Chandra AK, Ghosh R, Chatterjee A, Sarkar M. Amelioration of vanadium-induced testicular toxicity and adrenocortical hyperactivity by vitamin E acetate in rats. Molecular and Cellular Biochemistry. 2007a;**306**:189-200. DOI: 10.1007/s11010-007-9569-4

[35] Chandra AK, Ghosh R, Chatterjee A, Sarkar M. Effects of vanadate on male rat reproductive tract histology, oxidative stress markers and androgenic enzyme activities. Journal of Inorganic Biochemistry. 2007b;**101**:944-956. DOI: 10.1016/j.jinorgbio.2007.03.003

[36] Lu J, Wang Z, Cao J, Chen Y, Dong Y. A novel and compact review on the role of oxidative stress in female reproduction. Reproductive Biology and Endocrinology. 2018;**16**:80. DOI: 10.1186/s12958-018-0391-5

[37] Shrivastava S, Joshi D, Bhadauria M, Shukla S, Mathur R. Cotherapy of tiron and selenium against vanadium induced toxic effects in lactating rats. Iranian Journal of Reproductive Medicine. 2011;**9**:229-238

[38] Rinaldi M, Micali A, Marini H, Adamo E, Puzzolo D, Pisani A, et al. Cadmium organ toxicity and therapeutic approaches: A review on brain, kidney and testis damage. Current Medicinal Chemistry. 2017;**24**:3879-3893. DOI: 10.2174/0929867324666170801101448

[39] Orr S, Bridges C. Chronic kidney disease and exposure to nephrotoxic metals. International Journal of Molecular Sciences. 2017;**18**:1039. DOI: 10.3390/ijms18051039

[40] González-Villalva A, Colín-Barenque L, Bizarro-Nevares P, Rojas-Lemus M, Rodríguez-Lara V, García-Peláez I, et al. Pollution by

metals: Is there a relationship in glycemic control? Environmental Toxicology and Pharmacology. 2016;**46**:337-343. DOI: 10.1016/j.etap.2016.06.023

[41] Wilk A, Szypulska-Koziarska D, Wiszniewska B. The toxicity of vanadium on gastrointestinal, urinary and reproductive system, and its influence on fertility and fetuses malformations. Postępy Higieny i Medycyny Doświadczalnej. 2017;**71**:850-859. DOI: 10.5604/01.3001.0010.4783

[42] Boulassel B, Sadeg N, Roussel O, Perrin M, Belhadj-Tahar H. Fatal poisoning by vanadium. Forensic Science International. 2011;**206**:79-81. DOI: 10.1016/j.forsciint.2010.10.027

[43] Liu J, Cui H, Liu X, Peng X, Deng J, Zuo Z, et al. Dietary high vanadium causes oxidative damage-induced renal and hepatictoxicity in broilers. Biological Trace Element Research. 2012;**145**:189-200. DOI: 10.1007/s12011-011-9185-8

[44] Roy S, Majumdar S, Singh AK, Ghosh B, Ghosh N, Manna S, et al. Synthesis, characterization, antioxidant status, and toxicity study of vanadium-rutin complex in Balb/c mice. Biologial Trace Elements Research. 2015;**166**:183-200. DOI: 10.1007/s12011-015-0270-2

[45] Espinosa-Zurutuza M, González-Villalva A, Albarrán-Alonso JC, Colín Barenque L, Bizarro-Nevares P, Rojas-Lemus M, et al. Oxidative stress as a mechanism involved in kidney damage after subchronic exposure to vanadium inhalation and oral sweetened beverages in a mouse model. International Journal of Toxicology. 2018;**37**:45-52. DOI: 10.1177/1091581817745504

[46] Marouane W, Soussi A, Murat JC, Bezzine S, El Feki A. The protective effect of Malva sylvestris on rat kidney damaged by vanadium. Lipids in Health and Disease. 2011;**10**:65. DOI: 10.1186/1476-511X-10-65

[47] Scibior A, Golebiowska D, Adamczyk A, Niedfwiecka I, Fornal E. The renal effects of vanadate exposure: Potential biomarkers and oxidative stress as a mechanism of functional renal disorders-preliminary studies. BioMed Research International. 2014;**2014**:740105. DOI: 10.1155/2014/740105

[48] Parkin J, Cohen B. An overview of the immune system. Lancet. 2001;**357**:1777-1789. DOI: 10.1016/S0140-6736(00)04904-7

[49] Piñon-Zarate G, Rodriguez-Lara V, Rojas-Lemus M, Martinez-Pedraza M, Gonzalez-Villalva A, Mussali-Galante P, et al. Vanadium pentoxide inhalation provokes germinal center hyperplasia and suppressed humoral immune response. Journal of Immunotoxicology. 2008;**5**:115-122. DOI: 10.1080/15476910802085749

[50] Ustarroz-Cano M, López-Ángel M, López-Valdez N, García-Peláez I, Fortoul TI. The Effect of Atmospheric Pollution on the Thymus. Rijeka, Croatia: IntechOpen; 2019. DOI: 10.5772/intechopen.87027

[51] Usende IL, Olopade JO, Emikpe BO, Oyagbemi AA, Adedapo AA. Oxidative stress changes observed in selected organs of African giant rats (*Cricetomys gambianus*) exposed to sodium metavanadate. International Journal of Veterinary Science and Medicine. 2018;**6**:80-89. DOI: 10.1016/j.ijvsm.2018.03.004

[52] Tunali S, Yanardag R. Effect of vanadyl sulfate on the status of lipid parameters and on stomach and spleen tissues of streptozotocin-induced diabetic rats. Pharmacological Research. 2006;**53**:271-277. DOI: 10.1016/j.phrs.2005.12.004

[53] Bataller R, Brenner DA. Liver fibrosis. Journal of Clinical Investigation. 2005;**115**:209-218. DOI: 10.1172/JCI200524282.The. 2005

[54] Soares SS, Gutiérrez-Merino C, Aureliano M. Decavanadate induces mitochondrial membrane depolarization and inhibits oxygen consumption. Journal of Inorganic Biochemistry. 2007;**101**:789-796. DOI: 10.1016/j.jinorgbio.2007.01.012

[55] Rivas-García L, Quiles JL, Varela LA, Arredondo M, Lopez P, Dieguez AR, et al. In vitro study of the protective effect of manganese against vanadium-mediated nuclear and mitochondrial DNA damage. Food and Chemical Toxicology. 2019;**2019**:110900. DOI: 10.1016/j.fct.2019.110900

[56] Cano-Gutiérrez G, Acevedo NS, Santamaria A, Altamirano LM, Cano RM, Fortoul TI. Hepatic megalocytosis due to vanadium inhalation: Participation of oxidative stress. Toxicology and Industrial Health. 2012;**28**:353-360. DOI: 10.1177/0748233711412424

[57] Shoham DA, Durazo-Arvizu R, Kramer H, Luke A, Vopputuri S, Kshirsagar A, et al. Sugary soda consumption and albuminuria: Results from the national health and nutrition examination survey 1999-2004. PLoS One. 2008;**3**:e3431. DOI: 10.1371/journal.pone.0003431

[58] Vidale S, Campana C. Ambient air pollution and cardiovascular diseases: From bench to bedside. European Journal of Preventive Cardiology. 2018;**25**:818-825. DOI: 10.1177/2047487318766638

[59] Ye D, Klein M, Mulholland J, Russell A, Weber R, Edgerton E, et al. Estimating acute cardiovascular effects of ambient PM2.5 metals. Environmental Health Perspectives. 2018;**126**:027007. DOI: 10.1289/EHP2182

[60] Montiel-DávalosA,González-VillavaA, Rodriguez-Lara V, Montaño LF, Fortoul TI, López-Marure R. Vanadium pentoxide induces activation and death of endothelial cells. Journal of Applied Toxicology. 2012;**32**:26-33. DOI: 10.1002/jat.1695

[61] González-Villalva A, Fortoul TI, Avila-Costa MR, Piñón-Zárate G, Rodríguez Lara V, Martínez-Levy G, et al. Thrombocytosis induced in mice after subacute and subchronic V_2O_5 inhalation. Toxicology and Industrial Health. 2006;**22**:113-116. DOI: 10.1191/0748233706th250oa

[62] Fortoul TI, Gonzalez-Villalva A, Piñón-Zarate G, Rodriguez V, Montaño LF. Ultrastructural megakaryocyte modifications after vanadium inhalation in spleen and bone marrow. Journal of Electron Microscopy. 2009;**58**:375-380. DOI: 10.1093/jmicro/dfp031

[63] Fortoul TI, Piñón-Zárate G, Díaz-Bech ME, González-Villalva A, Mussali-Galante P, Rodríguez Lara V, et al. Spleen and bone marrow megakaryocytes as targets for inhaled vanadium. Histology and Histopathology. 2008;**23**:1321-1326. DOI: 10.14670/HH-23.1321

[64] González-Villalva A, Piñón-Zárate G, De la Peña-Díaz A, Flores-García M, Bizarro-Nevares P, Rendón-Huerta Erika P, et al. The effect of vanadium on platelet function. Environmental Toxicology and Pharmacology. 2011;**32**:447-456. DOI: 10.1016/j.etap.2011.08.010

[65] Fortoul TI, Rojas-Lemus M, Rodriguez-Lara V, Gonzalez-Villalva A, Ustarroz-Cano M, Cano-Gutierrez G, et al. Overview of environmental and occupational vanadium exposure and associated health outcomes: An article based on a presentation at the 8th international symposium on vanadium chemistry, biological chemistry, and toxicology;

Washington DC, August 15-18 2012. Journal of Immunotoxicology. 2014;**11**:13-18. DOI: 10.3109/1547691X.2013.789940

[66] Kulkarni A, Santosh Kumar G, Kaur J, Tikoo K. A comparative study of the toxicological aspects of vanadium pentoxide and vanadium oxide nanoparticles. Inhalation Toxicology. 2014;**26**:772-788. DOI: 10.3109/08958378.2014.960106

[67] López-Valdez N, Guerrero G, Rojas-Lemus M, Bizarro-Nevares P, Gonzalez-Villalva A, Ustarroz-Cano M, et al. The role of the non-ciliated bronchiolar cell in the tolerance to inhaled vanadium of the bronchiolar epithelium. Histology and Histopathology. 2019:18165. DOI: 10.14670/HH-18-165

[68] Wang L, Medan D, Mercer R, Overmiller D, Leornard S, Castranova V, et al. Vanadium-induced apoptosis and pulmonary inflammation in mice: Role of reactive oxygen species. Journal of Cellular Physiology. 2003;**195**:99-107. DOI: 10.1002/jcp.10232

[69] Zitka O, Skalickova S, Gumulec J, Masarik M, Adam V, Hubalek J, et al. Redox status expressed as GSH:GSSG ratio as a marker for oxidative stress in paediatric tumour patients. Oncology Letters. 2012;**4**:1247-1253. DOI: 10.3892/ol.2012.931

[70] Schuler D, Chevalier HJ, Merker M, Morgenthal K, Ravanat JL, Sagelsdorff M, et al. First steps towards an understanding of a mode of carcinogenic action for vanadium pentoxide. Journal of Toxicologic Pathology. 2011;**24**:149-162. DOI: 10.1293/tox.24.149

[71] Oluwabusayo RF, Snyder AM, Peters DG, Funmilayo O, Connor JR, Olopade JO. Brain metal distribution and neuro-inflammatory profiles after chronic vanadium administration and withdrawal in mice. Frontiers in Neuroanatomy. 2017;**11**:58. DOI: 10.3389/fnana.2017.00058

[72] Avila-Costa MR, Montiel-Flores E, Colin-Barenque L, Ordoñez JL, Gutierrez AL, Niño-Cabrera HG, et al. Nigrostriatal modifications after vanadium inhalation: An immunocytochemical and cytological approach. Neurochemical Research. 2004;**29**:1365-1369. DOI: 10.1023/b:nere.0000026398.86113.7d

[73] Avila-Costa MR, Colín BL, Zepeda RA, Antuna S, Saldivar L, Espejel G, et al. Ependymal epithelium disruption after vanadium pentoxide inhalation: A mice experimental model. Neuroscience Letters. 2005;**381**:21-25. DOI: 10.1016/j.neulet.2005.01.072

[74] Li H, Zhou D, Zhang Q, Feng C, Zheng W, He K, et al. Vanadium exposure-induced neurobehavioral alterations among Chinese workers. Neurotoxicology. 2013;**36**:49-54. DOI: 10.1016/j.neuro.2013.02.008

[75] Folarin O, Olopade F, Onwuka S, Olopade J. Memory deficit recovery after chronic vanadium exposure in mice. Oxidative Medicine and Cellular Longevity. 2016;**2016**:4860582. DOI: 10.1155/2016/4860582

[76] Afeseh Ngwa H, Kanthasamy A, Anantharam V, Song C, Witte T, Houk R, et al. Vanadium induces dopaminergic neurotoxicity via protein kinase Cdelta dependent oxidative signaling mechanisms: Relevance to etiopathogenesis of Parkinson's disease. Toxicology and Applied Pharmacology. 2009;**240**:273-285. DOI: 10.1016/j.taap.2009.07.025

[77] Halliwell B, Gutteridge JM. Oxygen toxicity, oxygen radicals, transition metals and disease. Biochemistry Journal. 1984;**219**:1-14. DOI: 10.1042/bj2190001

[78] Carr AC, Frei B. Chapter 9: Vitamin C and cardiovascular diseases. In: Cadenas E, Packer L, editors. Handbook of Antioxidants. 2nd ed. New York, NY; 2001. pp. 75-84

[79] Enstrom JE. Chapter 16: Epidemiology and clincial aspects of ascorbate and cancer. In: Cadenas E, Packer L, editors. Handbook of Antioxidants. 2nd ed. New York, NY; 2001. pp. 167-187

[80] Jones MM, Basinger MA. Chelate antidotes for sodium vanadate and vanadyl sulfate intoxication in mice. Journal of Toxicology and Environmental Health. 1983;**12**:749-756. DOI: 10.1080/15287398309530466

[81] Domingo JL, Llobet JM, Corbella J. Protection of mice against the lethal effects of sodium metavanadate: A quantitative comparison of a number of chelating agents. Toxicology Letters. 1985;**26**:95-99. DOI: 10.1016/0378-4274(85)90151-1

[82] Domingo JL, Gomez M, Llobet JM, Corbella J. Chelating agents in the treatment of acute vanadyl sulphate intoxication in mice. Toxicology. 1990;**62**:203-211. DOI: 10.1016/0300-483x(90)90110-3

[83] Boldyrev AA, Giancarlo A, Wim D. Physiology and pathophysiology of carnosine. Physiological Reviews. 2013;**93**:1803-1845. DOI: 10.1152/physrev.00039.2012

[84] Colín-Barenque L, Bizarro NP, González VA, Pedraza CJ, Medina-Campos O, Jimenez MR, et al. Neuroprotective effect of carnosine in the olfactory bulb after vanadium inhalation in a mouse model. International Journal of Experimental Pathology. 2018;**99**:180-188. DOI: 10.1111/iep.12285

[85] Valavanidis A, Vlachogianni T, Flotakis K, Lloridas S. Pulmonary oxidative stress, inflammation and cancer: Respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms. International Journal of Environmental Research and Public Health. 2013;**10**:3886-3907. DOI: 10.3390/ijerph10093886

[86] Li Y, Vitamin C. Chapter 20. In: Yumbo L, editor. Antioxidants in Biology and Medicine: essentials, advances and clinical applicarions. New York: Nova Science Publishers, Inc; 2011. pp. 265-279. ISBN 13-9781611225020