

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,600

Open access books available

137,000

International authors and editors

170M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Alzheimer-Like Cell Alterations after Vanadium Pentoxide Inhalation

Claudia Dorado-Martínez, Enrique Montiel-Flores, Oscar A. Mejía-García, José Luis Ordoñez-Librado, Ana Luisa Gutierrez-Valdez, Jesús Espinosa-Villanueva, Leonardo Reynoso-Erazo, Rocío Tron-Alvarez, Vianey Rodríguez-Lara and Maria Rosa Avila-Costa

Abstract

Vanadium (V), a widely distributed transition metal, has been considered toxic, which depends on the valence of the compound. V pentoxide (V_2O_5) is considered the most harmful. Its long-term exposure produces neurotoxicity. Mice exposed to inhaled V_2O_5 displayed less tubulin⁺ in testicular cells and dendritic spines loss, cell death, and CA1 neuropil modifications, considered as the result of V interaction with the cytoskeleton, which made us suppose that V_2O_5 inhalation could initiate CA1 cell alterations comparable to what happen in the brains of Alzheimer disease (AD) patients. This study intends to demonstrate pyramidal CA1 cytoskeletal changes in rats which inhaled V_2O_5 . Twenty rats were exposed to V_2O_5 0.02 M one hour, three times a week for several months. Our findings showed that V_2O_5 -exposed rats had cell death that reached 56,57% after six months; we also observed collapsed strong argyrophilic nuclei and characteristic flame-shaped somas in all V_2O_5 -exposed animals hippocampus CA1 compared to controls. We also found somatodendritic deformations. Neurite's cytoskeleton exhibited visible thickening and nodosities and prominent dendritic spine loss. Our results demonstrate that V_2O_5 induces AD-like cell death with evident cytoskeletal and synaptic alterations.

Keywords: Vanadium pentoxide, Cell death, Bielschowsky silver stain, inhalation, dendritic spines, hippocampus

1. Introduction

Vanadium (V) is a transition metal abundant in nature; its atomic number is 23. Andres Manuel Del Rio was the first who reported it in 1801. But it was actually discovered in 1830 by a Swedish chemist named Nils Sefstrom [1]. V is a bright silver-white, soft and malleable metal and the 22nd most abundant element in the earth's crust, and it has become a matter of concern among nutritionists since various marine species contain this metal as an trace element [2]. Environmental air V acts as the primary source for the general population [3].

Although V is extensively dispersed in air, its role as human nutrient is not yet confirmed. Humans are exposed to V generally through the polluted atmosphere from combustion products of vanadium-bearing fuel oils, fumes, and dust. Food contains insignificant V concentrations, frequently below 1 ng/g. V enters the organism by inhalation, skin, and gastrointestinal tract and accumulates mainly in the kidney, liver, bones, spleen, lungs and brain, accumulate fewer V concentrations [3–5].

Neurotoxic effects of V are not well recognized yet. Still, it is known that acute exposure in animals by ingestion or inhalation leads to nervous system alterations, paralysis of legs, respiratory failure, convulsions, bloody diarrhea, and death [6]. V disrupts the blood–brain barrier [7] and alters some neurotransmitters concentrations such as serotonin, norepinephrine, and dopamine, and an inhibitory effect on the uptake and release of norepinephrine were observed in the rat brain during V poisoning [8–10].

The V oxidation states of biological importance are vanadate (V^{5+}) and vanadyl (V^{4+}) and are considered harmful to mammals depending on their levels. Workers occupationally exposed to vanadium pentoxide (V_2O_5) had presented cardiovascular alterations and a variety of symptoms involving the central nervous system (CNS), gastrointestinal and respiratory systems [11]. Moreover, it has been suggested that raised tissue levels of V may be of etiological importance in manic-depressive syndrome since V reduces serotonin concentration. Blood V levels in depressed patients were greater than non-V-exposed controls [11]. Besides, reduced cognitive abilities in humans chronically exposed to this metal were found [12].

2. Vanadium sources

Metallic V is not found in nature. The most common in mining is carnotite and vanadinite. V is also found in phosphate rock, iron ores, and some crude oils in organic complexes and in small percentages of meteorites [3]. The presence of V is related to other minerals; among them is iron, aluminum, uranium, and titanium, and is frequently used as alloy steel, in combination with nickel, boron, or manganese. Extraction of V from coal or fossil fuels, such as Vanadium-rich coal tars and oil, explains the high V concentrations registered in the atmosphere [11].

V is generally employed in metallurgy in alloy with steel. And, as nonferrous metal V is considered fundamental for aircraft's manufacture, atomic and space industries. In the chemical industry, V_2O_5 and metavanadates are remarkably important for plastics and sulfuric acid production. Emissions of V may be high near producing steel alloys industries. V is also released into the air: during the re-smelting of scrap steel and the transformation of titaniferous and vanadic magnetite iron ores into steel; from the roasting of V slags; from V_2O_5 smelting furnaces; and from electric furnaces in which ferrovanadium is smelted [11, 13].

2.1 Vanadium in the environment

As a profuse element in the earth's crust, the V average varies from 159 g/t to 0.14 mg/kg. The standard concentration of 135 mg/kg in soil positions V in 5th place, among all transitional metals [11, 13]. V recycling includes its release from anthropogenic and natural bases to the water, soil, and air [13–15]. Frequently, the places such as fuel plants and refineries showed the highest level of V [16, 17].

V geochemical characteristics depend on the oxidation state and pH. The moderately immobile V (III) prevails. Typically, V compounds with high oxidation states are more soluble [14]. The average concentration of V in different soils

fluctuates from 10 to 220 mg kg dry mass depending on the soil types and chemical characteristics [18, 19]. The soils directly under humans' use include a much higher V concentration [17, 18]. On the other hand, what most pollutes the soil and water is the mining V-derived [20]. Vanadium is the most profuse transition metal in the aqua sphere, with an average content similar to zinc [21]. Persian Gulf sediments have very high V concentrations [22].

It seems that over the last decades, V levels in the biosphere have been significantly growing, a fact that will be of concern in the future [23]. The primary sources are mining, fossil fuel combustion, atmospheric wet and dry accumulation, etc. [24]. V remains in the water, soil, and air for long periods and may react with other elements [2, 21]. Recently, it has been shown that atmosphere V levels are increasing every day, mainly due to fossil fuel burning [11, 14, 18]. For that reason, more than 60 thousand tons of V may be released into the big cities air [14, 25].

Apparently, V concentrations in ambient air fluctuate significantly; in rural areas, V levels are under $0.001 \mu\text{g}/\text{m}^3$, however, in areas where there is a high degree of fossil fuel burning, as in large cities, the average annual concentration goes from $0.02 \mu\text{g}/\text{m}^3$ to $0.3 \mu\text{g}/\text{m}^3$. It has been determined that near industrial zones, its level can reach $1 \mu\text{g}/\text{m}^3$ [26]. Fortoul et al. [26] reported that V has increased over time in lung parenchyma from Mexico City inhabitants since it has been demonstrated that Mexican petroleum has high V concentrations.

V concentration in plants and food is very low, from less than 0.001 to 0.005 mg [14]. Some foods, including oysters, parsley, and spinach, had a relatively higher amount of V than all other foods [27].

V occupational exposure. V levels near metallurgical industries usually average about $1 \text{ mg V}/\text{m}^3$, whereas ambient air near industries, which produce V metal or compounds, contain a few $\text{mg V}/\text{m}^3$ [11]. Very high levels of V result from boiler-cleaning procedures due to the high concentration (approximately 10–25%) of V oxides in the dust. During these procedures, 50–100 $\text{mg V}/\text{m}^3$ are frequent, with concentrations ranging from $500 \text{ mg V}/\text{m}^3$ [3].

The most critical V compounds are ferrovandium, V_2O_5 , vanadium trioxide, V carbide, and salts, such as ammonium and sodium vanadate. The salts and oxides are used in powder form. It has been reported that the metallurgical industry includes the production of vapor containing V_2O_5 , which condenses to form breathable aerosols. Also, residual fuels combustion with high V content have V_2O_5 aerosols [11].

2.2 Vanadium absorption, distribution and excretion

It appears that only 10% of ingested V is absorbed from the gastrointestinal tract [28]. This report suggests that most of the ingested V is transformed into the cationic vanadyl form in the stomach before being absorbed in the duodenum through an unknown mechanism [29]. In its anionic vanadate form, V is absorbed in much higher quantities (about five times more than vanadyl form) through an anionic transport system [29]. Multivalent existence of V in nature and living systems put forth the chemical complexity of this element. This multifaceted chemical character of V, in turn, echoes in its biological and biochemical properties, especially in metabolism and absorption. Again vanadate, after reaching the bloodstream, is converted into vanadyl ion, although the vanadate form also exists. Thus, vanadate (by transferrin) and vanadyl (by albumin and transferrin) are rapidly transported by blood proteins to various tissues [30]. Blood parameters showed little or no reflection of toxicity after a long-term supplementation of V compounds [31], which might be due to the transport of V from blood to the tissues. Upon supplementation, V is incorporated in various organs and tissues, including the liver,

kidney, brain, heart, muscles, and bone. The kidney, spleen, bone, and liver tissues of rats have been shown to accumulate distinctly high amounts of V in chronically treated animals through oral administration [32].

The effects of V persist even after it has been withdrawn for several days [33]. Unabsorbed V is excreted in feces. When V was administered through the parenteral route, 10% of the V was found in the feces of humans and rats [3]. V is excreted through bile and urine [34]. It is, thus, the bile route through which a significant amount of V may be eliminated through feces. Moreover, it may be suggested that V content in feces does not reflect V absorbed or unabsorbed (1).

The toxicity of V depends on various factors, including the administration route and the V compound toxicity. In general, the toxicity of V is low, and its toxicity is least following ingestion and greatest following parenteral administration. Inhalation is a route of exposure that produces intermediate toxicity [3, 11]. The toxicity of V increases with higher valences, and the pentavalent compounds (as V pentoxide) are usually the most toxic [3].

2.3 Vanadium effects in the nervous system

V crosses the blood–brain barrier [7], and its compounds can induce neurologic alterations through different routes of administration [3, 11]. It has been reported that V-exposed lactating rat pups developed neurological deficits [35]; other authors described neurological alterations and increased brain V concentration after sodium metavanadate intraperitoneal administration [36–38]. Also, our group [7, 8] reported neuroinflammation in the brain of mice that inhale V_2O_5 . We found a seven-fold peak increase in V brain concentration after one week of inhalation and remained constant (0.10–0.12 mg/g dry weight tissue) during eight weeks of V_2O_5 inhalation. The inhalation route seems to induce neurotoxicity [6], which is epidemiologically relevant since this is the main route to the brain during occupational and environmental exposure.

One of the first studies on the V neurological effects was made by Done [39], who found that humans exposed to V displayed tremor and depression. Other researchers demonstrated that occupationally exposed people present alterations in cognitive ability tasks [40]. Despite the route, duration, and compound, V exposure has affected nerve cells and glia. In a study of chronic intraperitoneal exposure at 3 mg/kg in mice, Folarin et al. [36] reported that the brain accumulates large amounts of V, mainly in the brain stem, cerebellum, and olfactory bulb. This study described disruption of the layering pattern in the prefrontal cortex with nuclear pyknosis, loss of pyramidal neurons and reduced apical dendrites in the hippocampal CA1, and loss of cerebellar Purkinje cells. These morphological alterations were accompanied by astrogliosis and microgliosis.

Demyelination has also been reported after drinking milk from mothers exposed to sodium metavanadate [41]. Our group also described that in male CD-1 mice exposed by inhalation to 0.02 M V_2O_5 2 h twice a week for four weeks, Golgi staining revealed a severe loss in dendritic spines in the striatum compared to the controls, showing that the inhalation of V_2O_5 causes severe neuronal damage in this nucleus [8]. We observed fewer dendritic spines in the olfactory bulb granule cells after three months of exposure using the same inhalation protocol, and electron microscopy alterations consisted in swelled mitochondria and endoplasmic reticulum, and neuronal death that can be correlated with the olfactory dysfunction [42]. In the hippocampus, we found a decrease in dendritic spines and necrosis of the pyramidal CA1 neurons, modifications that could be associated with spatial memory impairment [43].

2.4 Mechanisms of vanadium neurotoxicity

It has been reported that V induces reactive oxygen species (ROS) production, which several authors have proposed as a reasonable basis for its neurotoxicity [6, 44, 45]. V, as other catalytic transition metals, participate in the Fenton reaction [46]. V in body fluids exists mainly in the 5⁺ oxidation state as V pentoxide (V₂O₅) [47]. V enters the cell as vanadate via anion channels while as vanadyl ions by passive diffusion and endocytosis bound to transferrin [48]. When entering the cell, vanadate is reduced by intracellular antioxidants to vanadyl, with subsequent production of ROS [49]. H₂O₂ then oxidizes vanadyl into vanadate in a Fenton-like reaction with the consequent hydroxyl radical production [50]. With higher V levels, these reactions result in oxidative stress and toxic effects on lipids, proteins, and nucleic acids. With its high lipid content, the brain is vulnerable to oxidant-induced lipid peroxidation [51], and as such, V neurotoxicity is related to myelin deficits [45]. Moreover, as we mentioned above, earlier results from our group revealed substantia nigra tyrosine hydroxylase cell loss, and therefore, dendritic spine loss in the striatum medium-size spiny neurons [8], blood–brain barrier disruption [7], and hippocampal cells alterations [43].

Besides oxidative stress, it has been demonstrated that the cytoskeleton is an important target of V toxicity because of its ability to compete with phosphatases; due to this, V inhibits actin polymerization through the tyrosine phosphatases inhibition [52, 53], which, in consequence, by decreasing gamma-tubulin disturbs microtubules function and formation [54]. It is also well known that actin polymerization establishes the morphology of dendrites and dendritic spines [55]. These facts make us consider the possibility that V₂O₅ inhalation might induce hippocampus cell death similar to that seen in Alzheimer disease (AD).

2.5 Alzheimer disease

Today, aging human populations worldwide face an epidemic of AD, with an increasing number of cases to nearly 106 million by 2050 [56]. Several factors have been described to participate in the AD etiology including, aging, genetics [57], head injury [58], and exposure to certain chemicals and compounds [59].

AD is a neurodegenerative disease that represents the most common cause of dementia. Symptoms associated with dementia vary from difficulties with orientation, language, and problem-solving to memory alterations and other cognitive skill deficits that affect a person's ability to perform daily life activities [60]. The most noticeable symptoms at the beginning of the disease are disorientation and episodic and spatial memory loss [61]. The medial temporal lobe region, consisting of the hippocampal formation and related cortices, are essential for the adequate functioning of spatial and declarative memory systems [62, 63] and are the first areas affected in the progression of the disease [64].

Synaptic failure has been suggested as the leading cause of AD pathology [65]. The principal neuropathological hallmarks of the disease are the neurofibrillary tangles (NFTs) associated with abnormal phosphorylated tau protein and the accumulation of aberrant amyloid- β , features also found in the brains of old patients without cognitive impairments or AD [66]. Nonetheless, directly or indirectly, these proteins induce synapses alterations by changing dendritic spines morphology or causing their loss and neuronal degeneration [67, 68].

The development of intraneuronal lesions at selectively vulnerable brain structures is central to the pathological process in AD [69–71]. The lesions consist mainly of hyperphosphorylated tau protein. They include tangle material, NFTs in cell

bodies, neuropil threads (NTs) in neuronal processes, and material in dystrophic nerve cell processes of neuritic plaques (NPs) [72–74].

2.6 Alzheimer's disease experimental models

Experimental models are crucial in understanding AD pathogenesis for implementing novel therapeutics. So far, AD experimental models consist almost exclusively of transgenic mammals that express the human genes that result in the formation of amyloid plaques (by expression of human APP alone or in combination with human PSEN1) and NFTs (by the expression of human MAPT) [75–78]. Other experimental models have used invertebrates such as *C. elegans* and *Drosophila melanogaster* and vertebrates such as zebrafish; nevertheless, these models are very different from human physiology and less extensively used [79]. Nevertheless, some issues have been raised about this model's validity, mainly because the efficacy in clinical trials has been very low [80, 81]. Facts that make us wonder if the animals in the experimental models actually have AD, considering only the specific pathological features. Most animal models develop only the amyloid accumulation that defines AD. This often gives rise to specific memory-associated cognitive alterations. However, these models normally preset the absence of the main AD pathological features, including cell death and, most importantly, NFTs development [79]. The lack of NFTs could partly explain the failure between pre-clinical and clinical trials [80].

Therefore, in this chapter, we intend to demonstrate that the inhalation of V_2O_5 produces cellular alterations like those observed in AD, with synaptic alterations (shown by the loss of dendritic spines) and by the presence of NFTs, due to V directly interacts with the cytoskeletal components, and is a potent inhibitor of tyrosine phosphatases.

3. Experimental procedures

The experiments were accomplished in 24 male Wistar rats weighing 180–200 g at the beginning of the study. The rats were individually placed in plastic cages with controlled light conditions (12 h light/12 h dark) and fed with Purina Rat Chow and water *ad libitum*. Body weight was recorded daily. The experimental protocol was carried out following the Animal Act of 1986 for Scientific Procedures and the Rules for Research in Health Matters (Mexico). We made efforts to minimize the number of animals used and their suffering.

3.1 Vanadium pentoxide inhalation

V_2O_5 inhalations were performed as described by our group [8]. As part of our experiment with V, a pilot study was implemented with 0.005 and 0.01 M V_2O_5 , and we found no changes using light microscopy in lung tissue; therefore, a higher dose was utilized, 0.02 M, realizing that V half-life about 48 h [11] we designed a three times a week exposure protocol.

Twelve rats were placed in an acrylic chamber inhaling 0.02 M V_2O_5 (Sigma, St. Louis, MO, USA) (Sigma Aldrich, Co. Mexico) 1 h three times a week for two and six months. Twelve control rats inhaled only the vehicle—deionized water—for the same time. Inhalations were performed in closed acrylic boxes (40 cm wide x 70 cm long and 25 cm high) attached to an ultra-nebulizer (Shinmed, Taiwan), with 10 l/min continuous flux. The ultra-nebulizer is designed to produce droplets in a 0.5–5 μm range. A trap for the vapor was located on the opposite side with a

solution of sodium bicarbonate to precipitate the remaining metal. During the inhalation, animals were constantly monitored for respiration rate, depth, and regularity. The exposure system was monitored for temperature, oxygen level, and V concentration.

After two or six months, rats were sacrificed under sodium pentobarbital anesthesia (lethal dose) and perfused via the aorta with a saline solution followed by the fixative containing 10% formaldehyde in 0.2 M-phosphate buffer. The brains were removed and placed in the fixative solution for one hour.

3.2 Bielschowsky silver impregnation

After the routine paraffin processing, serial coronal brain sections were cut at 8 μm thickness in a sliding microtome (Leica SM2010 R, Germany). Brain sections were deparaffinized in xylene and alcohol before being disposed into 20% silver nitrate solution for 20 min at 37°C. After washing with distilled water, slides were submerged in 20% silver nitrate solution titrated with fresh sodium hydroxide and evaporated ammonia. After 15 min, slides were washed with ammonia before being individually revealed with 100 ml of a developer (20 ml of formaldehyde, 100 ml distilled water, 20 μl concentrated nitric acid, and 0.5 g citric acid) and then added to 50 ml of titrated silver nitrate solution. Slides were then rinsed in tap water, fixed in 5% sodium thiosulfate, and dehydrated through alcohols and xylene [82]. The hippocampus CA1 pyramidal cells were evaluated under a light Optiphot 2 microscope (Nikon, Japan).

3.3 Golgi stain

Brain tissue from the hippocampus CA1 was cut into 90 μm - thick sections and processed for the rapid Golgi method [83]. The histological analysis consisted in counting the number of dendritic spines in a 10 μm -long area from five secondary dendrites from 20 CA1 pyramidal neurons from each rat [8, 84].

Means from each group were compared for statistical differences by one-way ANOVA test ($p < 0.05$) followed by *posthoc* comparisons with Tukey test. The statistical analyses were conducted with GraphPad Prism 9 for Mac Software.

4. Results

The animals that inhaled V_2O_5 did not show changes in their weight or clinical alterations compared to the control group.

4.1 Dendritic spines

Brain sections were treated with the Golgi stain to determine if V_2O_5 inhalation induces synaptic alterations in the hippocampus CA1. The synaptic damage resulted in significant CA1 pyramidal neurons dendritic spine loss of exposed rats compared to controls (**Figures 1** and **2B, C**). As it is shown in **Figure 1**, spine loss was more evident with longer inhalation time.

4.2 Hippocampus CA1 neuronal alterations

With the Bielschowsky method, we found that rats exposed to V_2O_5 after two months have substantial CA1 pyramidal cell death (25%) (**Figures 3** and **5**), and after six months, the cell death reached 56.57%, being statistically different vs.

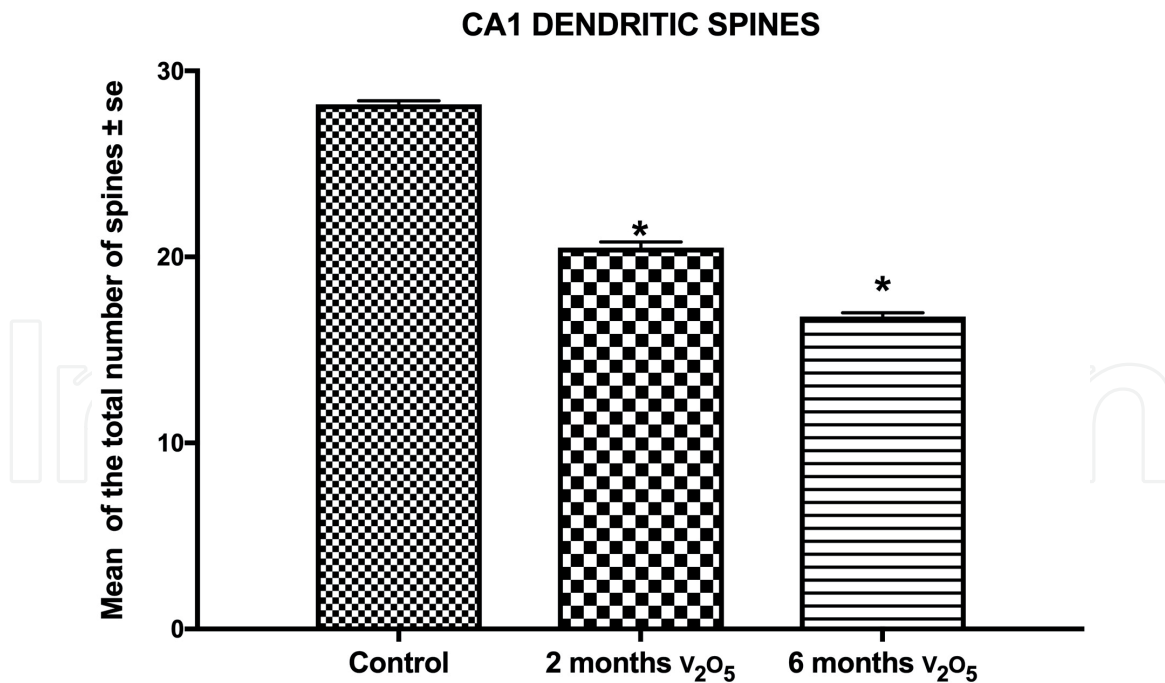


Figure 1. The number of pyramidal CA1 neurons dendritic spines, contrasting control and exposed rats after two and six months of V₂O₅ inhalation. One way ANOVA, **p* < 0.05 vs. control group.

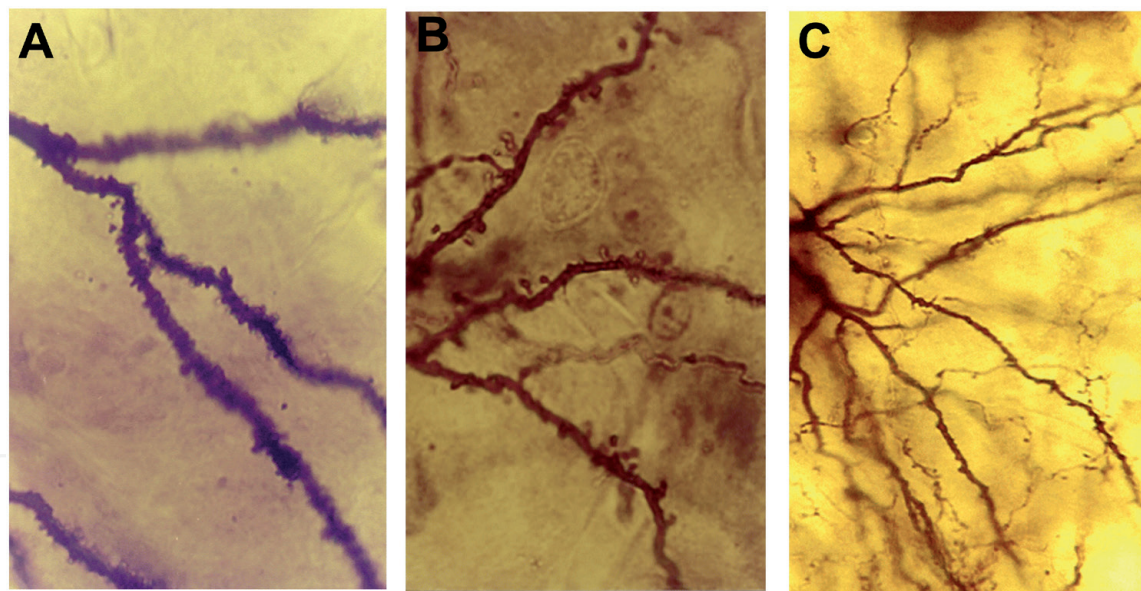


Figure 2. Dendritic spine density. Representative Golgi-stained pyramidal CA1 neurons of the control group (A), two months (B), and six months of V₂O₅ inhalation (C). Both exposure times provoked a significant decrease in the total number of spines, mainly after six months. (magnification 40X).

two months and control groups (**Figures 3 and 4**); we observed that in all V₂O₅-exposed rats the pyramidal hippocampus CA1 cells displayed strong argyrophilic and collapsed somas compared to control rats, the somas also revealed the typical flame-shaped (**Figures 4–6**). Also, somatodendritic deformations were identified. Axons and dendrites exhibited thick dark bands resembling thickening nodosities and fibrillary cytoskeleton proteins linear traces. The neurofibrils were fused, disordered, thickened, and crowded together into broadband, and the neurites were deeply stained; we also noticed curly fibers. Some neurites displayed neurofibrillary-type tangles (**Figure 6**).

5. Discussion

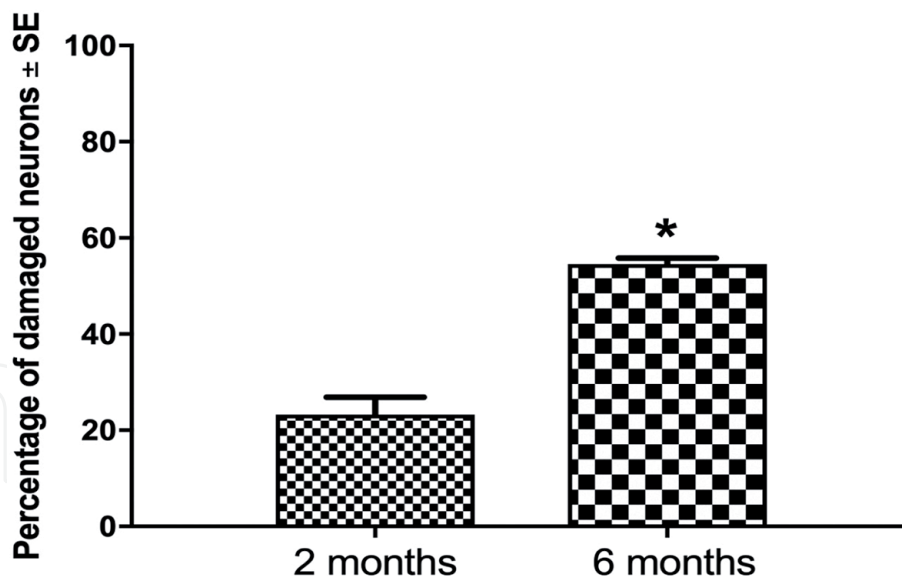


Figure 3.
Damaged pyramidal hippocampus CA1 neurons percentage after two or six months of V_2O_5 inhalation.
* $P < 0.05$ vs. two months group.

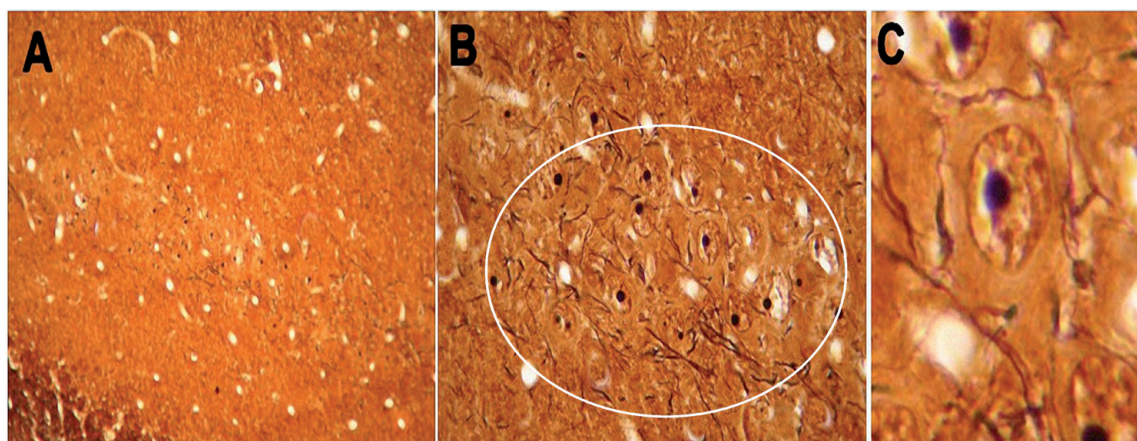


Figure 4.
Representative photomicrographs of Hippocampus CA1 control group stained with the Bielschowsky method. As can be seen in B (white oval), the pyramidal neurons of the hippocampus CA1 are healthy, in terms of size and shape. Figure C depicts the detail of B white oval. A 10X, B 40X and C 100X.

Our results show significant alterations in the cytoskeleton and synaptic activity, demonstrated by the loss of dendritic spines and Alzheimer-like fibrillary tangles.

It is essential to stand out that V concentrations in the environment vary substantially; in rural areas, V concentrations are below $0.001 \mu\text{g}/\text{m}^3$, in big cities, where there are high levels of fossil fuel burning, the average V concentration range from $0.02 \mu\text{g}/\text{m}^3$ to $0.3 \mu\text{g}/\text{m}^3$. It has been shown that near industrial zones, its concentrations can reach $1 \mu\text{g}/\text{m}^3$. In this experiment, V concentrations in the inhalation chamber was $1436 \mu\text{g}/\text{m}^3$ [54], exceeding the highest concentration reported in ambient air ($1 \mu\text{g}/\text{m}^3$). In this regard, we know that the concentrations used here are higher than those subjects with occupational exposure, but animal models permit amplifying the impact that V has on the nervous system.

Our results demonstrated that V_2O_5 inhalation generates a significant loss of pyramidal CA1 neurons dendritic spines and notorious cytoskeleton distortions resulting in the alteration of the synaptic transmission and, therefore, possibly in

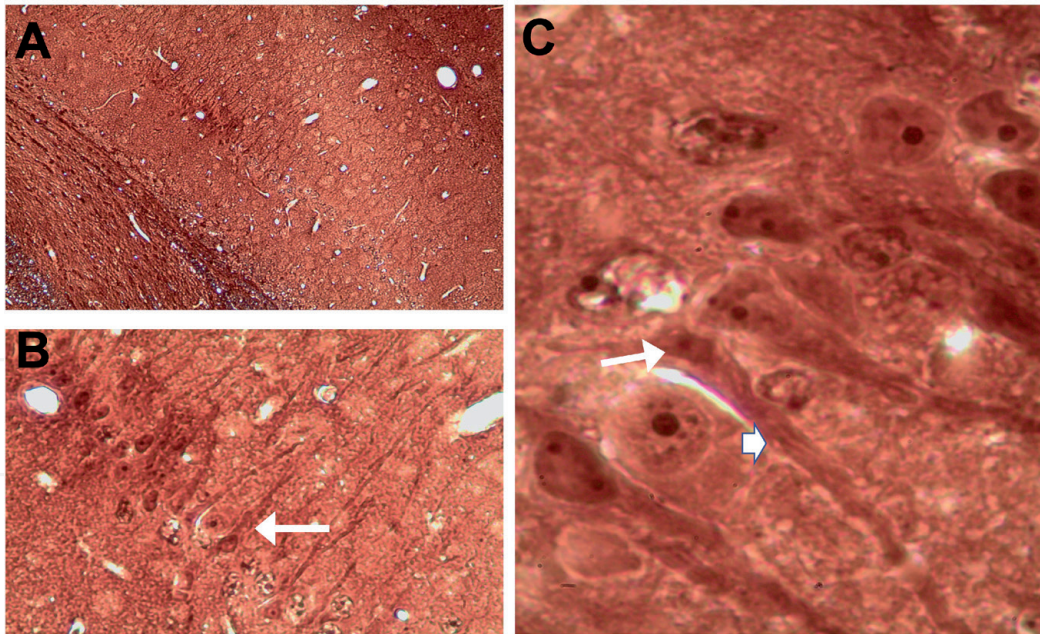


Figure 5. Representative photomicrographs of Hippocampus CA1 Bielschowsky staining from the experimental group after two months of V_2O_5 inhalation. Neuronal soma deformation is observed (arrows). The axons displayed thicker and darker bands (arrowhead); A (10x), B (40x), and C (100x)

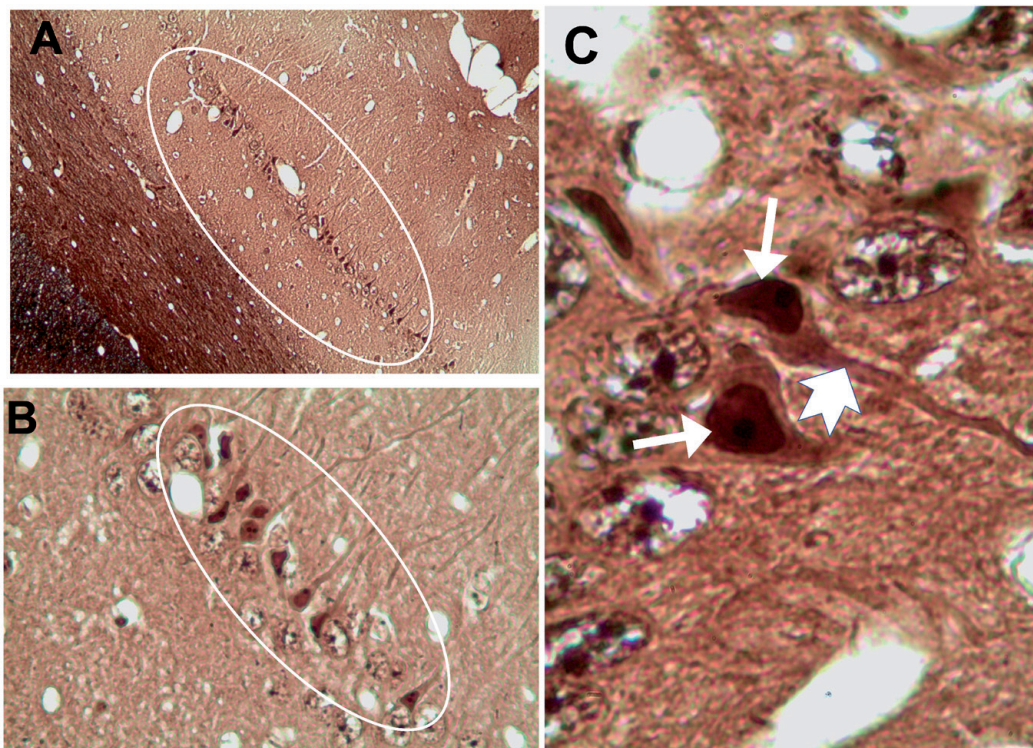


Figure 6. Hippocampus CA1 representative photomicrographs of Bielschowsky staining from the experimental group after six months of V_2O_5 inhalation. It can be observed strong argyrophilic nuclei (white oval in a and B; arrows in C) typical flame-shaped and intensely stained neurites (white oval in a, B and C), forming similar structures to neurofibrillary tangles (arrowhead); A (10x), B (40x), and C (100x).

memory disturbances. It is well known that many neurological conditions lead to a decreased number of dendritic spines [85], for instance, epilepsy, alcoholism, and others disorders, imply that the decline in the number and availability of axo-spinous synapses are the consequence of the dendritic spines loss (85). Previously, our group informed significant dendritic spine loss after ozone inhalation in the

hippocampus, correlated with memory alterations [84], also, dendritic spines loss in the corpus striatum and cerebral cortex with motor impairments [86] as well as olfactory bulb modifications [87]. Furthermore, we found dendritic spine loss in the corpus striatum after V_2O_5 inhalation [8]. Since V interacts with the cytoskeleton, this interaction may be the cause of dendritic spine loss since it seems that actin is a critical element for dendritic spine architecture preservation. It orchestrates the spine's morphology and number [88]. In this context, Pelucchi and cols. [88] mention that Rho activation is essential for the dendritic spine functionality, cofilin phosphorylation, and, consequently, spine actin stabilization. According to Wang et al. [89], cofilin phosphorylation prevents binding to the F- and G-actin binding, and only a dephosphorylated cofilin can initiate the actin-binding. Consequently, their activity is synchronized by phosphorylation/dephosphorylation. It is important to mention again that V is practically a structural and electronic phosphate analog and a phosphatase inhibitor [90]. In humans, the resemblance between phosphate and V explains V and phosphate-dependent enzymes interplay. Therefore, V may achieve a regulatory function in phosphate-depending metabolic processes [90].

It is well known that V neurotoxic properties have been predominantly attributed to its capacity to induce oxidative stress by the generation of ROS, which in turn initiates the peroxidative decomposition of the cellular membranes

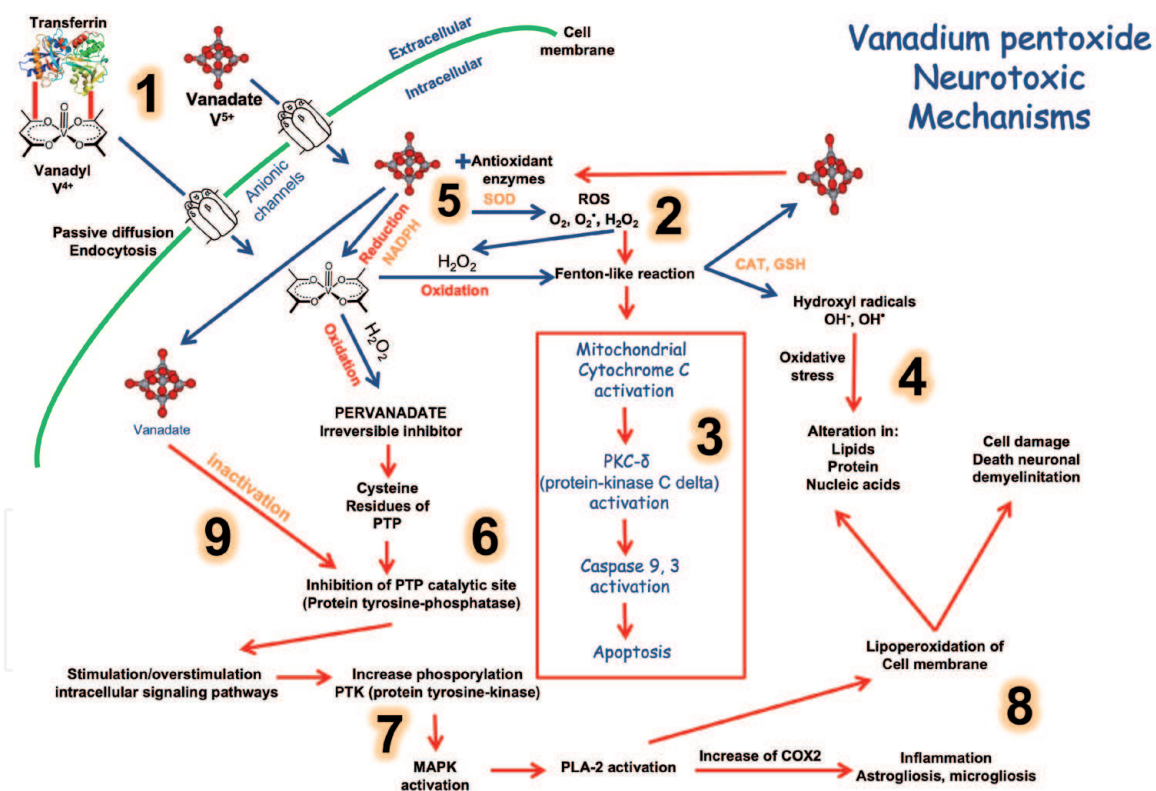


Figure 7.

When vanadium enters the body, it enters as a tetravalent ((vanadyl) or as a pentavalent (V^{5+}) [3]; then, it is transported via the blood by albumin and transferrin (1). V with these two valences enters cells through anionic channels. These two forms arrive the cells through anionic channels; once in the cell, V^{5+} reacts with some antioxidant enzymes such as superoxide dismutase (SOD) (2) [12], producing H_2O_2 through Fenton-like reaction, where the mitochondrion initiates the cytochrome C pathway inducing the apoptosis route through the activation of caspases 3 and 9 (3) [95], then, vanadate generates free radicals (OH^+ OH^-) by reacting with GSH and CAT enzymes (4) [94], stimulating oxidative stress triggering lipids, proteins, and DNA alterations. V^{5+} reduces to vanadyl through NADPH-oxidase (5), which in turn, forms pervanadate, oxidized by H_2O_2 , that will permanently inhibit protein tyrosine phosphatases (PTP) [96] (6), which will aggregate the phosphorylated protein tyrosine kinase (PTK) activating intracellular signaling pathways (7) [1], triggering the inflammation mechanisms through phospholipase-A2 (PLA-A2) and COX-2 formation, activating the gliosis process (8) [97], similarly DNA, cell death, demyelination and damage to proteins through lipid peroxidation. Finally, the PTP is inactivated by vanadate (9) [98], which results in the activation of intracellular death signaling pathways.

phospholipids [6, 44, 45] and neuron inflammation [91]. It is also associated with hypomyelination correlated with oxidative stress [92] and a decrease in myelin essential protein [93]. It has also been reported that V produces DNA cleavage, apoptosis and induces iron-mediated oxidative stress in brain cell cultures [94] and hippocampus neuronal death [36]. Likewise, it has been reported that V inactivates protein-tyrosine-phosphatases (PTP) because it binds to the cysteine catalytic residue, which leads to an increase in phosphorylation of PTP, increasing the phosphorylation of the MAPK pathways, which probably causes tau protein hyperphosphorylation, to generate or induce neurofibrillary tangles (NFTs) [94]. Thus, according to our findings and the revised literature, V neurotoxic effects are summarized in **Figure 7**.

Likewise, an increased body of evidence implicates oxidative stress as involved in at least the propagation of cellular injury, which leads to neuropathology in various conditions, such as AD. Moreover, oxidative stress is intimately linked with an integrated series of cellular phenomena, which all seem to contribute to neuronal death [51, 99].

The facts mentioned above provide evidence that V_2O_5 disrupts critical neuronal processes and leads to alterations that include ROS generation, producing cell death. Further work should be done to answer questions, such as identifying the signaling pathways that induced the changes reported here.

Furthermore, as formerly reported, V_2O_5 modifies cytoskeletal proteins such as γ -tubulin [54], inducing actin alterations [52]. Some studies have demonstrated the interaction between V with actin. V has a high affinity for cytoskeletal actin-binding sites. G- and F- actin interact with oxovanadium (IV), with 4:1 and 1:1 stoichiometries, respectively, and it has been demonstrated that G-actin-V interaction might occur close to the actin adenosine triphosphate binding position [100–102]. Likewise, decavanadate can modify actin's structure by oxidizing its cysteines in its polymerized form [103].

Remarkably, earlier results demonstrate that V induces Tau hyperphosphorylation [104, 105], ROS, and neuronal inflammation [106], occasioning AD-like damage. Moreover, the substantial hippocampal CA1 cell damage might result from the affinity of G-actin for V, and its association with the metal, since neurons have a particularly dynamic cytoskeleton, which requires continuous polymerization of actin filaments [107].

6. Conclusion

Our results show that vanadium pentoxide, when inhaled, produces important synaptic alterations, manifested in this case, by the significant loss of dendritic spines of CA1 pyramidal neurons and by the presence of Alzheimer-type fibrillar tangles, an aspect considered to be the main neuropathological feature in AD [107], related to the evident alterations of the cytoskeleton. Therefore, more research is needed to establish the relationship between V_2O_5 and Tau hyperphosphorylation, not only in the hippocampus but also in the amygdala, neocortex, and entorhinal, structures involved in AD [108, 109], and whether spatial memory is altered.

Moreover, these data must encourage research efforts towards environmental health effects, with the final purpose of intervening in decrease metals atmospheric pollution such as V. We have to promote viable schemes to safeguard the CNS from toxicants, which have redoubled in the atmosphere during the last decades and represent an important health challenge since metal pollution has been related to neurodegenerative diseases.

Acknowledgements

This work was supported by the research grants from PAPCA–Iztacala UNAM 2016-2113 and PAPIIT-DGAPA IN216821.

We are very grateful to Veronica Rodríguez Mata and Patricia Aley Medina for their excellent photographic and technical assistance.

Conflict of interest

The authors declare no conflict of interest.

Author details

Claudia Dorado-Martínez¹, Enrique Montiel-Flores¹, Oscar A. Mejía-García¹, José Luis Ordoñez-Librado¹, Ana Luisa Gutierrez-Valdez¹, Jesús Espinosa-Villanueva¹, Leonardo Reynoso-Erazo², Rocío Tron-Alvarez², Vianey Rodríguez-Lara³ and Maria Rosa Avila-Costa^{1*}

¹ Neuromorphology Lab, Facultad de Estudios Superiores Iztacala, UNAM, Tlalnepantla, Edo. Mex., Mexico

² Health Education Project, Facultad de Estudios Superiores Iztacala, UNAM, Tlalnepantla, Edo. Mex., Mexico

³ Faculty of Medicine, Department of Cell and Tissue Biology, UNAM, Mexico City, Mexico

*Address all correspondence to: nigraizo@unam.mx

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Mukherjee B, Patra B, Mahapatra S, Banerjee P, Tiwari A, Chatterjee M. Vanadium--an element of atypical biological significance. *Toxicol Lett.* 2004;150(2):135-143 DOI: 10.1016/j.toxlet.2004.01.009.
- [2] Almeida M, Filipe S, Humanes M, Maia MF, Melo R, Severino N, et al. Vanadium haloperoxidases from brown algae of the Laminariaceae family. *Phytochemistry.* 2001;57(5):633-642. DOI: 10.1016/S0031-9422(01)00094-2
- [3] Barceloux DG. Vanadium. *J Toxicol. Clin Toxicol.* 1999;37(2):265-278. DOI: 10.1081/CLT-100102425
- [4] Hansen TV, Aaseth J, Alexander J. The effect of chelating agents on vanadium distribution in the rat body and on uptake by human erythrocytes. *Arch Toxicol.* 1982;50(3-4):195-202. DOI: 10.1007/bf00310851
- [5] Bracken WM, Sharma RP, Elsner YY. Vanadium accumulation and subcellular distribution in relation to vanadate induced cytotoxicity in vitro. *Cell Biol Toxicol.* 1985;1(4):259-268. DOI: 10.1007/BF00118191
- [6] Olopade JO, Connor JR. Vanadium and neurotoxicity: a review. *Curr Topics Toxicol.* 2011; 1;7:33-39.
- [7] Avila-Costa MR, Colín-Barenque L, Zepeda-Rodríguez A, Antuna SB, Saldivar L, Espejel-Maya et al. Ependymal epithelium disruption after vanadium pentoxide inhalation: a mice experimental model. *Neurosci Lett.* 2005. 10;381(1-2):21-5. DOI: 10.1016/j.neulet.2005.01.072
- [8] Avila-Costa MR, Montiel Flores E, Colin-Barenque L, Ordoñez JL, Gutiérrez AL, Niño-Cabrera HG, et al. Nigrostriatal modifications after vanadium inhalation: an immunocytochemical and cytological approach. *Neurochem Res.* 2004;29(7):1365-1369. DOI: 10.1023/B:NERE.0000026398.86113.7d
- [9] Witkowska D, Brzezinski J. Alteration of brain noradrenaline, dopamine and 5-hydroxytryptamine levels during vanadium poisoning. *Pol J Pharmacol Pharm.* 1979;31(4):393-398. PMID: 523342
- [10] Witkowska D, Brzezinski J. Effect of metavanadate on the uptake and release of noradrenaline in rat brain cerebral cortex slices. *Toxicol Lett.* 1983;17(3-4):223-231. DOI: 10.1016/0378-4274(83)90230-8
- [11] World Health Organization. Vanadium-Environmental Health Criteria 81. 1988.
- [12] Barth A, Schaffer AW, Konnaris C, Blauensteiner R, Winker R, Osterode W, et al. Neurobehavioral effects of vanadium. *J Toxicol Environ Health A.* 2002;65(9):677-683. DOI: 10.1080/15287390252900377
- [13] 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. *J Immunotoxicol.* 2014;11(1):13-18. DOI: 10.3109/1547691x.2013.789940
- [14] Imtiaz M, Rizwan MS, Xiong S, Li H, Ashraf M, Shahzad SM, et al. Vanadium, recent advancements and research prospects: A review. *Environ Int.* 2015;80:79-88. DOI: 10.1016/j.envint.2015.03.018
- [15] Amorim FA, Welz B, Costa AC, Lepri FG, Vale MG, Ferreira SL.

- Determination of vanadium in petroleum and petroleum products using atomic spectrometric techniques. *Talanta*. 2007;72(2):349-359. DOI: 10.1016/j.talanta.2006.12.015
- [16] Khan S, Kazi TG, Kolachi NF, Baig JA, Afridi HI, Shah AQ, et al. Hazardous impact and translocation of vanadium (V) species from soil to different vegetables and grasses grown in the vicinity of thermal power plant. *J Hazard Mater*. 2011;190(1-3):738-743. DOI: 10.1016/j.jhazmat.2011.03.105
- [17] Teng Y, Yang J, Sun Z, Wang J, Zuo R, Zheng J. Environmental vanadium distribution, mobility and bioaccumulation in different land-use districts in Panzhihua Region, SW China. *Environ Monit Assess*. 2011;176(1-4):605-620. DOI: 10.1007/s10661-010-1607-0
- [18] Panichev N, Mandiwana K, Moema D, Molatlhegi R, Ngobeni P. Distribution of vanadium(V) species between soil and plants in the vicinity of vanadium mine. *J Hazard Mater*. 2006;137(2):649-653. DOI: 10.1016/j.jhazmat.2006.03.006
- [19] McLauchlan CC, Murakami HA, Wallace CA, Crans DC. Coordination environment changes of the vanadium in vanadium-dependent haloperoxidase enzymes. *J Inorg Biochem*. 2018;186:267-279. DOI: 10.1016/j.jinorgbio.2018.06.011
- [20] Ortiz-Bernad I, Anderson RT, Vrionis HA, Lovley DR. Vanadium respiration by *Geobacter metallireducens*: novel strategy for in situ removal of vanadium from groundwater. *Appl Environ Microbiol*. 2004;70(5):3091-3095. DOI: 10.1128/aem.70.5.3091-3095.2004
- [21] Kustin K. Aqueous vanadium ion dynamics relevant to bioinorganic chemistry: A review. *J Inorg Biochem*. 2015;147:32-38. DOI: 10.1016/j.jinorgbio.2014.12.009
- [22] Pourang N, Nikouyan A, Dennis JH. Trace element concentrations in fish, surficial sediments and water from northern part of the Persian Gulf. *Environ Monit Assess*. 2005;109(1-3):293-316. DOI: 10.1007/s10661-005-6287-9
- [23] Ringelband U, Hehl O. Kinetics of Vanadium Bioaccumulation by the brackish water hydroid *Cordylophora caspia* (Pallas). *Bull Environ Contam Toxicol*. 2000;65(4):486-493. DOI: 10.1007/s001280000150
- [24] Morrell BG, Lepp NW, Phipps DA. Vanadium uptake by higher plants: Some recent developments. *Environ Geochem Health*. 1986;8(1):14-18. DOI: 10.1007/bf02280116
- [25] Aragon AM, Altamirano-Lozano M. Sperm and testicular modifications induced by subchronic treatments with vanadium (IV) in CD-1 mice. *Reprod Toxicol*. 2001;15(2):145-151. DOI: 10.1016/s0890-6238(01)00117-4
- [26] Fortoul TI, Quan-Torres A, Sanchez I, Lopez IE, Bizarro P, Mendoza ML, et al. Vanadium in ambient air: concentrations in lung tissue from autopsies of Mexico City residents in the 1960s and 1990s. *Arch Environ Health*. 2002;57(5):446-449. DOI: 10.1080/00039890209601436
- [27] Myron DR, Givand SH, Nielsen FH. Vanadium content of selected foods as determined by flameless atomic absorption spectroscopy. *J Agric Food Chem*. 1977;25(2):297-300. DOI: 10.1021/jf60210a036
- [28] Poucheret P, Verma S., Grynypas M.D., McNeill J.H. (1998) Vanadium and diabetes. In: Pierce G.N., Izumi T., Rupp H., Grynberg A. (eds) *Molecular and Cellular Effects of Nutrition on Disease Processes*.

- Developments in Molecular and Cellular Biochemistry, vol 26. Springer, Boston, MA. DOI: 10.1007/978-1-4615-5763-0_9
- [29] Hirano S, Suzuki KT. Exposure, metabolism, and toxicity of rare earths and related compounds. *Environ Health Perspect.* 1996;104 Suppl 1:85-95. DOI: 10.1289/ehp.96104s185
- [30] Fantus I.G., Deragon G., Lai R., Tang S. (1995) Modulation of insulin action by vanadate: evidence of a role for phosphotyrosine phosphatase activity to alter cellular signaling. In: Srivastava A.K., Chiasson JL. (eds) *Vanadium Compounds: Biochemical and Therapeutic Applications.* Developments in Molecular and Cellular Biochemistry, vol 16. Springer, Boston, MA. DOI: 10.1007/978-1-4613-1251-2_12
- [31] Fawcett JP, Farquhar SJ, Thou T, Shand BI. Oral vanadyl sulphate does not affect blood cells, viscosity or biochemistry in humans. *Pharmacol Toxicol.* 1997;80(4):202-206. DOI: 10.1111/j.1600-0773.1997.tb00397.x
- [32] Hamel F.G., Duckworth W.C. (1995) The relationship between insulin and vanadium metabolism in insulin target tissues. In: Srivastava A.K., Chiasson JL. (eds) *Vanadium Compounds: Biochemical and Therapeutic Applications.* Developments in Molecular and Cellular Biochemistry, vol 16. Springer, Boston, MA. DOI: 10.1007/978-1-4613-1251-2_11
- [33] Cam MC, Brownsey RW, McNeill JH. Mechanisms of vanadium action: insulin-mimetic or insulin-enhancing agent? *Can J Physiol Pharmacol.* 2000;78(10):829-847. DOI: 10.1139/y00-053
- [34] Alimonti A, Petrucci F, Krachler M, Bocca B, Caroli S. Reference values for chromium, nickel and vanadium in urine of youngsters from the urban area of Rome. *J Environ Monit.* 2000;2(4):351-354. DOI: 10.1039/b001616k
- [35] Edel J, Sabbioni E. Vanadium transport across placenta and milk of rats to the fetus and newborn. *Biol Trace Elem Res.* 1989;22(3):265-275. DOI: 10.1007/BF02916615
- [36] Folarin OR, Snyder AM, Peters DG, Olopade F, Connor JR, Olopade JO. Brain Metal Distribution and Neuro-Inflammatory Profiles after Chronic Vanadium Administration and Withdrawal in Mice. *Front Neuroanat.* 2017;11:58. DOI: 10.3389/fnana.2017.00058
- [37] Mustapha O, Oke B, Offen N, Siren AL, Olopade J. Neurobehavioral and cytotoxic effects of vanadium during oligodendrocyte maturation: a protective role for erythropoietin. *Environ Toxicol Pharmacol.* 2014;38(1):98-111. DOI: 10.1016/j.etap.2014.05.001
- [38] Ladagu AD, Olopade FE, Folarin OR, Elufioye TO, Wallach JV, Dybek MB, et al. Novel NMDA-receptor antagonists ameliorate vanadium neurotoxicity. *Naunyn Schmiedebergs Arch Pharmacol.* 2020;393(9):1729-1738. DOI: 10.1007/s00210-020-01882-6
- [39] Done A. Of metals and chelation. *Emer Med.* 1979;11:186-218.
- [40] 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
- [41] Mustapha O, Oke B, Offen N, Sirén A-I, Olopade J. Neurobehavioral and cytotoxic effects of vanadium during oligodendrocyte maturation: a protective role for erythropoietin. *Environ Toxicol Pharmacol.* 2014;38(1):98-111. DOI: 10.1016/j.etap.2014.05.001

- [42] Fortoul TI, Rodriguez-Lara V, Gonzalez-Villalva A, Rojas-Lemus M, Cano-Gutierrez G, Ustarroz-Cano M, et al. Vanadium inhalation in a mouse model for the understanding of air-suspended particle systemic repercussion. *J Biomed Biotechnol.* 2011;2011:951043. DOI: 10.1155/2011/951043
- [43] Avila-Costa MR, Fortoul TI, Niño-Cabrera G, Colín-Barenque L, Bizarro-Nevarés P, Gutiérrez-Valdez AL, et al. Hippocampal cell alterations induced by the inhalation of vanadium pentoxide (V₂O₅) promote memory deterioration. *Neurotoxicology.* 2006;27(6):1007-1012. DOI: 10.1016/j.neuro.2006.04.001
- [44] Cuesta S, Proietto R, Garcia GB. Astrogliosis and HSP 70 activation in neonate rats' brain exposed to sodium metavanadate through lactation. *Neurotoxicol Teratol.* 2013;37:57-62. DOI: 10.1016/j.ntt.2013.03.002
- [45] Todorich B, Olopade JO, Surguladze N, Zhang X, Neely E, Connor JR. The mechanism of vanadium-mediated developmental hypomyelination is related to destruction of oligodendrocyte progenitors through a relationship with ferritin and iron. *Neurotox Res.* 2011;19(3):361-373. DOI: 10.1007/s12640-010-9167-1
- [46] Valko M, Morris H, Cronin MT. Metals, toxicity and oxidative stress. *Curr Med Chem.* 2005;12(10):1161-1208. DOI: 10.2174/0929867053764635
- [47] Nechay BR. Mechanisms of action of vanadium. *Annu Rev Pharmacol Toxicol* 1984;24:501-24. DOI: 10.1146/annurev.pa.24.040184.002441
- [48] Yang X, Wang K, Lu J, Crans DC. Membrane transport of vanadium compounds and the interaction with the erythrocyte membrane. *Coord Chem Rev.* 2003;237(1-2):103-111. DOI: 10.1016/S0010-8545(02)00247-3
- [49] Ding M, Gannett PM, Rojanasakul Y, Liu K, Shi X. One-electron reduction of vanadate by ascorbate and related free radical generation at physiological pH. *J Inorg Biochem.* 1994;55(2):101-112. DOI: 10.1016/0162-0134(94)85032-1
- [50] Capella LS, Gefé MR, Silva EF, Affonso-Mitidieri O, Lopes AG, Rumjanek VM, et al. Mechanisms of vanadate-induced cellular toxicity: role of cellular glutathione and NADPH. *Arch Biochem Biophys.* 2002;406(1):65-72. DOI: 10.1016/s0003-9861(02)00408-3
- [51] Wang X, Michaelis EK. Selective neuronal vulnerability to oxidative stress in the brain. *Front Aging Neurosci.* 2010;2:12. DOI: 10.3389/fnagi.2010.00012
- [52] Rodríguez-Lara V, Morales-Rivero A, Rivera-Cambas AM, Fortoul TI. Vanadium inhalation induces actin changes in mice testicular cells. *Toxicol Ind Health.* 2016;32(2):367-374. DOI: 10.1177/0748233713501364
- [53] Mailhes JB, Hilliard C, Fuseler JW, London SN. Vanadate, an Inhibitor of Tyrosine Phosphatases, Induced Premature Anaphase in Oocytes and Aneuploidy and Polyploidy in Mouse Bone Marrow Cells. *Mutat Res.* 2003;538(1-2):101-107. DOI: 10.1016/s1383-5718(03)00108-6
- [54] Mussali-Galante, P., Rodríguez-Lara, V., Hernández-Tellez, B., Ávila-Costa, M.R., Colín-Barenque, L., Bizarro-Nevarés, P., et al. Inhaled vanadium pentoxide decrease gamma-tubulin of mouse testes at different exposure times. *Toxicol Ind Health.* 2005; 21(7-8), pp.215-222. DOI: 10.1191/0748233705th232oa
- [55] Lee JR. Protein tyrosine phosphatase PTPRT as a regulator of synaptic formation and neuronal development.

BMB Reports. 2015;48(5):249. DOI: 10.5483/BMBRep.2015.48.5.037

[56] Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement*. 2007;3(3):186-191. DOI: 10.1016/j.jalz.2007.04.381

[57] Coon KD, Myers AJ, Craig DW, Webster JA, Pearson JV, Lince DH, et al. A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. *J Clin Psychiatry*. 2007;68(4): 613-618. DOI: 10.4088/jcp.v68n0419.

[58] Guo Z, Cupples L, Kurz A, Auerbach S, Volicer L, Chui H, et al. Head injury and the risk of AD in the MIRAGE study. *Neurology*. 2000;54(6):1316-1323. DOI: 10.1212/wnl.54.6.1316

[59] Calderón-Garcidueñas L, Reed W, Maronpot RR, Henriquez-Roldán C, Delgado-Chavez R, Calderón-Garcidueñas A, et al. Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. *Toxicol Pathol*. 2004;32(6):650-658. DOI: 10.1080/01926230490520232

[60] Alzheimer's Association. 2018 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2018;14(3):367-429. DOI: 10.1016/j.jalz.2018.02.001

[61] Wilson RS, Arnold SE, Schneider JA, Kelly JF, Tang Y, Bennett DA. Chronic psychological distress and risk of Alzheimer's disease in old age. *Neuroepidemiology*. 2006;27(3):143-153. DOI: 10.1159/000095761

[62] Dickerson BC, Eichenbaum H. The episodic memory system: neurocircuitry and disorders.

Neuropsychopharmacology. 2010;35(1):86-104. DOI: 10.1038/npp.2009.126

[63] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2011;1(1):a006189. DOI: 10.1101/cshperspect.a006189. 2011;1(1):a006189. DOI: 10.1101/cshperspect.a006189

[64] Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol*. 1991;82(4):239-259. DOI: 10.1007/BF00308809

[65] Selkoe DJ. Alzheimer's disease is a synaptic failure. *Science*. 2002;298(5594):789-791. DOI: 10.1126/science.1074069

[66] Ferrer I. Defining Alzheimer as a common age-related neurodegenerative process not inevitably leading to dementia. *Prog Neurobiol*. 2012;97(1):38-51. DOI: 10.1016/j.pneurobio.2012.03.005

[67] Forner S, Baglietto-Vargas D, Martini AC, Trujillo-Estrada L, LaFerla FM. Synaptic impairment in Alzheimer's disease: a dysregulated symphony. *Trends Neurosci*. 2017;40(6):347-357. DOI: 10.1016/j.tins.2017.04.002

[68] Chen Y, Fu AK, Ip NY. Synaptic dysfunction in Alzheimer's disease: mechanisms and therapeutic strategies. *Pharmacol Ther*. 2019;195:186-198. DOI: 10.1016/j.pharmthera.2018.11.006

[69] Duyckaerts C, Delaère P, He Y, Camilleri S, Braak H, Piette F, Hauw JJ (1995) The relative merits of tau- and amyloid markers in the neuropathology of Alzheimer's disease. In: Bergener M,

- Finkel SI (eds) *Treating Alzheimer's and other dementias*. Springer, Heidelberg Berlin New York, pp 81-89.
- [70] Feany MB, Dickson DW. Neurodegenerative disorders with extensive tau pathology: a comparative study and review. *Ann Neurol*. 1996;40(2):139-148. DOI: 10.1002/ana.410400204
- [71] Goedert M. Tau protein and the neurofibrillary pathology of Alzheimer's disease. *Trends Neurosci*. 1993;16(11):460-465. DOI: 10.1016/0166-2236(93)90078-z
- [72] Bancher C, Brunner C, Lassmann H, Budka H, Jellinger K, Wiche G, et al. Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer's disease. *Brain Res*. 1989;477(1-2):90-99. DOI: 10.1016/0006-8993(89)91396-6
- [73] Braak F, Braak H, Mandelkow E-M. A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuropil threads. *Acta Neuropathol*. 1994;87(6):554-567. DOI: 10.1007/BF00293315
- [74] Braak H, Braak E, Grundke-Iqbal I, Iqbal K. Occurrence of neuropil threads in the senile human brain and in Alzheimer's disease: a third location of paired helical filaments outside of neurofibrillary tangles and neuritic plaques. *Neurosci Lett*. 1986;65(3):351-355. DOI: 10.1016/0304-3940(86)90288-0
- [75] Boutajangout A, Wisniewski T. Tau-based therapeutic approaches for Alzheimer's disease-a mini-review. *Gerontology*. 2014;60(5):381-385. DOI: 10.1159/000358875
- [76] Dujardin S, Colin M, Buee L. Animal models of tauopathies and their implications for research/translation into the clinic. *Neuropathol Appl Neurobiol*. 2014. DOI: 10.1111/nan.12200
- [77] Barrett J, McGonigle P. Rodent models for Alzheimer's disease in drug discovery. In: Adeboye Adejare (Ed.) *Drug Discovery Approaches for the Treatment of Neurodegenerative Disorders*: Academic Press, 2017. p. 235-247. DOI: 10.1016/B978-0-12-802810-0.00012-X
- [78] Wisniewski T, Goñi F. Immunotherapeutic approaches for Alzheimer's disease. *Neuron*. 2015;85(6):1162-1176. DOI: 10.1016/j.neuron.2014.12.064
- [79] Drummond E, Wisniewski T. Alzheimer's disease: experimental models and reality. *Acta Neuropathol*. 2017;133(2):155-175. DOI: 10.1007/s00401-016-1662-x
- [80] Banik A, Brown RE, Bamburg J, Lahiri DK, Khurana D, Friedland RP, et al. Translation of Pre-Clinical Studies into Successful Clinical Trials for Alzheimer's Disease: What are the Roadblocks and How Can They Be Overcome? 1. *J Alzheimers Dis*. 2015;47(4):815-843. DOI: 10.3233/JAD-150136
- [81] Schneider LS, Mangialasche F, Andreasen N, Feldman H, Giacobini E, Jones R, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. *J Intern Med*. 2014;275(3):251-283. DOI: 10.1111/joim.12191
- [82] Nobakht M, Hoseini SM, Mortazavi P, Sohrabi I, Esmailzade B, Roosh NR, Omidzahir S. Neuropathological changes in brain cortex and hippocampus in a rat model of Alzheimer's disease. *Iranian Biomed J*. 2011;15(1-2):51. PMID: PMC3639737
- [83] Valverde F. The Golgi Method. A Tool for Comparative Structural

Analyses. In: Nauta WJH, Ebbesson SOE, editors. *Contemporary Research Methods in Neuroanatomy*. Berlin, Heidelberg: Springer Berlin Heidelberg; 1970. p. 12-31.

[84] Avila-Costa MR, Colin-Barenque L, Fortoul TI, Machado-Salas P, Espinosa-Villanueva J, Rugerio-Vargas C, et al. Memory deterioration in an oxidative stress model and its correlation with cytological changes on rat hippocampus CA1. *Neurosci Lett*. 1999;270(2):107-109. DOI: 10.1016/s0304-3940(99)00458-9

[85] Fiala JC, Spacek J, Harris KM. Dendritic spine pathology: cause or consequence of neurological disorders? *Brain Res Rev*. 2002;39(1):29-54. DOI: 10.1016/s0165-0173(02)00158-3

[86] Avila-Costa MR, Colín-Barenque L, Fortoul TI, Machado-Salas JP, Espinosa-Villanueva J, Rugerio-Vargas C, et al. Motor impairments in an oxidative stress model and its correlation with cytological changes on rat striatum and prefrontal cortex. *Int J Neurosci*. 2001;108(3-4):193-200. DOI: 10.3109/00207450108986514

[87] Colín-Barenque L, Avila-Costa M, Fortoul T, Rugerio-Vargas C, Machado-Salas J, Espinosa-Villanueva J, et al. Morphologic alteration of the olfactory bulb after acute ozone exposure in rats. *Neurosci Lett*. 1999;274(1):1-4. DOI: 10.1016/s0304-3940(99)00639-4

[88] Pelucchi S, Stringhi R, Marcello E. Dendritic spines in Alzheimer's disease: how the actin cytoskeleton contributes to synaptic failure. *International Journal of Molecular Sciences*. 2020;21(3):908. DOI: 10.3390/ijms21030908

[89] Wang Q, Yuan W, Yang X, Wang Y, Li Y and Qiao H. Role of Cofilin in Alzheimer's Disease. *Front. Cell Dev. Biol*. 2020; 8:584898. DOI: 10.3389/fcell.2020.584898

[90] Hanus-Fajerska E, Wiszniewska A, Kamińska I. A Dual Role of Vanadium in Environmental Systems-Beneficial and Detrimental Effects on Terrestrial Plants and Humans. *Plants (Basel)*. 2021;10(6):1110. DOI:10.3390/plants10061110

[91] Jaiswal MR, Kale PP. Mini review-vanadium-induced neurotoxicity and possible targets. *Neurol Sci*. 2020;41(4):763-768. DOI: 10.1007/s10072-019-04188-5

[92] Sasi MM, Haider SS, El-Fakhri M, Ghwarsha KM. Microchromatographic analysis of lipids, protein, and occurrence of lipid peroxidation in various brain areas of vanadium exposed rats: a possible mechanism of vanadium neurotoxicity. *Neurotoxicology*. 1994;15(2):413-420. PMID: 7991230.

[93] Adebisi OE, Olayemi FO, Olopade JO, Tan NH. Beta-sitosterol enhances motor coordination, attenuates memory loss and demyelination in a vanadium-induced model of experimental neurotoxicity. *Pathophysiology*. 2019; 26(1):21-29. DOI: 10.1016/j.pathophys.2018.12.002

[94] Fatola OI, Olaolorun FA, Olopade FE, Olopade JO. Trends in vanadium neurotoxicity. *Brain Res Bull*. 2019;145:75-80. DOI: 10.1016/j.brainresbull.2018.03.010

[95] Goc A. Biological activity of vanadium compounds. *Cent Eur J Biol*. 2006;1(3):314-332. DOI: 10.2478/s11535-006-0029-z

[96] Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun*. 1984;120(3):885-890. DOI: 10.1016/s0006-291x(84)80190-4

[97] Tsave O, Petanidis S, Kioseoglou E, Yavropoulou MP, Yovos JG, Anastakis D,

- et al. Role of vanadium in cellular and molecular immunology: association with immune-related inflammation and pharmacotoxicology mechanisms. *Oxid Med Cell Longev*. 2016;2016:4013639. DOI: 10.1155/2016/4013639
- [98] Irving E, Stoker AW. Vanadium compounds as PTP inhibitors. *Molecules*. 2017;22(12):2269. DOI: 10.3390/molecules22122269
- [99] Andersen JK. Oxidative stress in neurodegeneration: cause or consequence? *Nat Med*. 2004;10 Suppl: S18-S25. DOI: 10.1038/nrn1434.
- [100] Combeau C, Carlier MF. Probing the mechanism of ATP hydrolysis on F-actin using vanadate and the structural analogs of phosphate BeF₃ and AlF₄⁻. *The J Biol Chem*. 1988;263(33):17429-17436. DOI: 10.1016/S0021-9258(19)77854-5.
- [101] Ramos S, Almeida RM, Moura JJ, Aureliano M. Implications of oxidovanadium(IV) binding to actin. *J Inorg Biochem*. 2011;105(6):777-783. DOI: 10.1016/j.jinorgbio.2011.02.010
- [102] Ramos S, Manuel M, Tiago T, Duarte R, Martins J, Gutierrez-Merino C, et al. Decavanadate interactions with actin: inhibition of G-actin polymerization and stabilization of decameric vanadate. *J Inorg Biochem*. 2006;100(11):1734-1743. DOI: 10.1016/j.jinorgbio.2006.06.007
- [103] Ramos S, Duarte RO, Moura JJ, Aureliano M. Decavanadate interactions with actin: cysteine oxidation and vanadyl formation. *Dalton Trans*. 2009(38):7985-7994. DOI: 10.1039/b906255f
- [104] Derkinderen P, Scales TM, Hanger DP, Leung KY, Byers HL, Ward MA, et al. Tyrosine 394 is phosphorylated in Alzheimer's paired helical filament tau and in fetal tau with c-Abl as the candidate tyrosine kinase. *J Neurosci*. 2005;25(28):6584-6593. DOI: 10.1523/JNEUROSCI.1487-05.2005
- [105] Jhang KA, Park J-S, Kim H-S, Chong YH. Resveratrol Ameliorates Tau Hyperphosphorylation at Ser396 Site and Oxidative Damage in Rat Hippocampal Slices Exposed to Vanadate: Implication of ERK1/2 and GSK-3 β Signaling Cascades. *J Agric Food Chem*. 2017;65(44):9626-9634. DOI: 10.1021/acs.jafc.7b03252
- [106] Korbecki J, Baranowska-Bosiacka I, Gutowska I, Chlubek D. Vanadium compounds as pro-inflammatory agents: effects on cyclooxygenases. *Int J Mol Sci*. 2015;16(6):12648-12668. DOI: 10.3390/ijms160612648
- [107] Coles CH, Bradke F. Coordinating neuronal actin-microtubule dynamics. *Curr Biol*. 2015;25(15):R677-R691. DOI: 10.1016/j.cub.2015.06.020
- [108] Kiuchi A, Otsuka N, Namba Y, Nakano I, Tomonaga M. Presenile appearance of abundant Alzheimer's neurofibrillary tangles without senile plaques in the brain in myotonic dystrophy. *Acta Neuropathol*. 1991;82(1):1-5. DOI: 10.1007/BF00310916
- [109] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuro pathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2011;1(1):a006189-a. DOI: 10.1101/cshperspect.a006189