Toxicology Letters 410 (2025) 67–75

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.journals.elsevier.com/toxicology-letters

Mini review

Vanadium – good or bad – The role of vanadium in the central nervous system disorders, potential therapeutic targets and its toxicity

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ARTICLE INFO

Editor: Dr. Angela Mally.

Keywords:
Vanadium
Antidiabetic
Mental health
Toxicity
Therapeutic potential of vanadium

ABSTRACT

When we see dust particles floating in the sunlit air, we do not realize that these particles also contain vanadium. Vanadium (V) is a trace element in air, soil, water, and food. In living organisms, it occurs mainly as vanadyl (cation) or vanadate (anion). Vanadium has a wide range of applications in the industry. In addition, its therapeutic potential - particularly as an anti-diabetic agent - has been indicated. However, its therapeutic use is controversial due to postulated concerns regarding its toxicity and possible involvement in cognitive disorders. Recent research is focusing on the role of vanadium in the treatment of conditions such as depression or schizophrenia. This review attempts to summarize what is known about the potential of vanadium in the context of both metabolic and cognitive disorders. It highlights the need for further research into its safety, efficacy, and wider therapeutic applications.

1. Introduction

The name vanadium comes from Vanadis, the Norse goddess of happiness, fertility, and patroness of war. Vanadium (V) is a refractory metal of group 5, centered cubic lattice with a high melting point (Carpio et al., 2018). It was discovered by Andrés Manuel del Rio and named erythronium. The French Chemical Society changed the name of the metal due to the discovery of Sefstrom in 1830, who isolated vanadium, documenting that the earlier discovery was impure chromium (Carpio et al., 2018). Vanadium is a pervasive element found in air, dust, water, and soil. Its content is estimated at 135 mg/kg in soil (Carpio et al., 2018). In seawater, it is the second most common transition element (Pessoa et al., 2015). In the environment, vanadium constitutes a component of minerals, of which more than sixty have been counted (Carpio et al., 2018). It is also found in food (Carpio et al., 2018; Barceloux, 1999; Scibor et al., 2020). Its presence has been documented in seeds, vegetables, and mushrooms, among other things, but also in meat (Carpio et al., 2018; Barceloux, 1999; Scibor et al., 2020). It accounts for about 0.001–0.03 mg/kg in food (Rezk and Rezk, 2017). In air, it ranges from 0.000001 mg/m^2 (rural area) to 0.0001 mg/m^2 in cities (Rezk and Rezk, 2017).

Vanadium has found several industrial applications as a catalyst in the production of sulfuric acid in the manufacturing industries of plastics, glass, paint, ceramics, and electrochemistry (Carpio et al., 2018; Barceloux, 1999; Scibor et al., 2020). In addition, it is a component of superconducting magnets, which provide a magnetic field of 175,000 G; it is used in the nuclear power industry (Carpio et al., 2018). In this case, it coats reactor fuel elements (Carpio et al., 2018). Vanadium-containing steel has been used for springs, tools, and high-speed steel because of its hardness, strength, and flexibility (Scibor et al., 2020). This type of steel has been used to manufacture engines, aircraft, and automotive parts/components (Scibor et al., 2020). For example in 2023, vanadium consumption in the United States was 3.83 thousand metric tons (TMT), by ReportLinker, 2023.

The human body's vanadium concentration is about 0.3 μM (Pessoa et al., 2015). The value refers to the average serum concentration of vanadium in the human body under normal physiological conditions. This baseline level is maintained through dietary intake, environmental exposure (air and dust), and excretion, primarily via feces. The primary sources of the body's vanadium are food, air/dust, and water (Pessoa et al., 2015). The level of vanadium in the body is relatively constant. However, the element in the body represents a variable pool of vanadium supplied with food (absorption) and excreted in the feces (excretion) (Pessoa et al., 2015; Scibor et al., 2020). Food is a source that provides the human body with vanadium in daily doses of 0.01–0.03 mg/day (Scibor et al., 2020). Absorbed vanadium, as VO_4^- in the stomach's acidic environment, is transformed into a cationic form VO^{2+} and excreted with feces (Scibor et al., 2020; Gruziewska et al.,

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https://doi.org/10.1016/j.toxlet.2025.06.006
Received 24 February 2025; Received in revised form 5 May 2025; Accepted 2 June 2025
Available online 2 June 2025

2014). Thus, average absorption is 1–10 %, and 94–98 % of vanadium is excreted with feces (Scibor et al., 2020; Gruziewska et al., 2014). The kidneys remove the resorbed vanadium pool from the body at 12 % of the intake (Scibor et al., 2020). In the human body, + 4 and + 5 are oxidation states of vanadium, and in the form of + 4 (vanadyl cations), it permeates cell membranes by diffusion or using anion channels (Gruziewska et al., 2014). Intracellularly, it occurs as reduced by glutathione to VO^{2+} (Gruziewska et al., 2014). Inhaled with air, vanadium is absorbed in the lungs, solubilized, and enters the bloodstream in the form of $H_2VO_4^-$ (vanadate) (Carpio et al., 2018; Pessoa et al., 2015). In the bloodstream, vanadium complexes are transported mainly in the form of VO_4^{2-} bound to transferrin; it takes the place of iron (Fe^{3+}) and undergoes endocytosis (Carpio et al., 2018; Scibor et al., 2020). Alternatively, it can be up-taken via passive diffusion and bound by immunoglobulin G or phosphate, citrate, lactate, and oxalate (Scibor et al., 2020). When it is in the form of VO_4^{2-}, it may reach cells via anion channels (Scibor et al., 2020). However, in cells, it is reduced to VO^{2+} and binds to hemoglobin (Scibor et al., 2020). However, with its central role in metabolism and detoxification, the liver is critical in processing and distributing vanadium throughout the body, alongside its excretion through the feces and kidneys.

To date, it has not been established whether vanadium is an essential element for humans; it is undoubtedly an essential element for rats, chicks, birds, guinea pigs, goats, bacteria, fungi, and algae (Pessoa et al., 2015; Scibor et al., 2020). It is essential for living beings in amounts of 0.05 μM and toxic in amounts of 10 μM and above (Scibor et al., 2020). Vanadium can build complexes with many proteins, e.g., transferrin, albumin, hemoglobin, and α-aminoacids. Hence, it has good access to organs and tissues (Carpio et al., 2018). It has a wide range of physiological roles (Pessoa et al., 2015; Rezk and Rezk, 2017). Tissue deposition of vanadium determined 21 days after administration indicates from highest to lowest content in bones/liver, kidney, spleen/-blood/muscle/brain (Kordowiak and Holko, 2009). The half-life of vanadium in soft tissues is about 1–10 days (Kordowiak and Holko, 2009). Among the physiological roles of vanadium most recognized are anti-diabetic potential, anti-cancer, and mitogenic (Pessoa et al., 2015). Vanadium is suspected of regulating osteogenesis, bone collagen synthesis, counteracting oxidative drug demethylation, anti-viral, anti-HIV, anti-bacterial, anti-fungal, and anti-neoplastic actions (Pessoa et al., 2015; Scibor et al., 2020). One of the first reports on its physiological role documented the role of endogenous vanadium in inhibiting Na^+/K^+ ATPase *in vitro* (Cantley et al., 1977a,1977b). Furthermore, vanadium, e.g., vanadium(III)-L-cysteine complexes, have the potential to induce apoptosis of cancer cells, e.g., via induction of changes in mitochondrial function, pro-apoptotic factor release, ROS production, disruption of cellular metabolism, cell proliferation, changes in genetic expression and DNA damage (Carpio et al., 2018; Pessoa et al., 2015). The anti-viral potential of vanadium manifests, among others, through the inhibition of reverse transcriptase activity that blocks viral replication (Scibor et al., 2020). Fig. 1. presents sources, distribution, medical and industrial applications of vanadium:

Vanadium is used in medicine to treat diabetes Carpio et al., 2018; Pessoa et al., 2015; Barceloux, 1999; Scibor et al., 2020; Rezk and Rezk, 2017), although it is a controversial element due to its toxicity (Scibor et al., 2020; Rezk and Rezk, 2017; Jaiswal and Kale, 2020), a topic that will be developed in subsequent subsections of the manuscript.

2. Vanadium use in medicine

2.1. *Vanadium use in diabetes*

Diabetes is a serious metabolic disease that comes in two forms: type I and type II (Cloete, 2022). In type I diabetes, pancreatic beta cells do not produce insulin as a consequence of the autoimmune destruction of beta cells, while in type II, insulin secretion is impaired, resulting in hyperinsulinemia and insulin resistance (Cloete, 2022). Vanadium compounds have been identified as a competitive inhibitor of insulin metabolism, acting via protein tyrosine phosphatases 1B (PTP1B) (Treviño et al., 2019). PTP1B is a common intracellular prototypic non-receptor tyrosine phosphatase that dephosphorylates the insulin

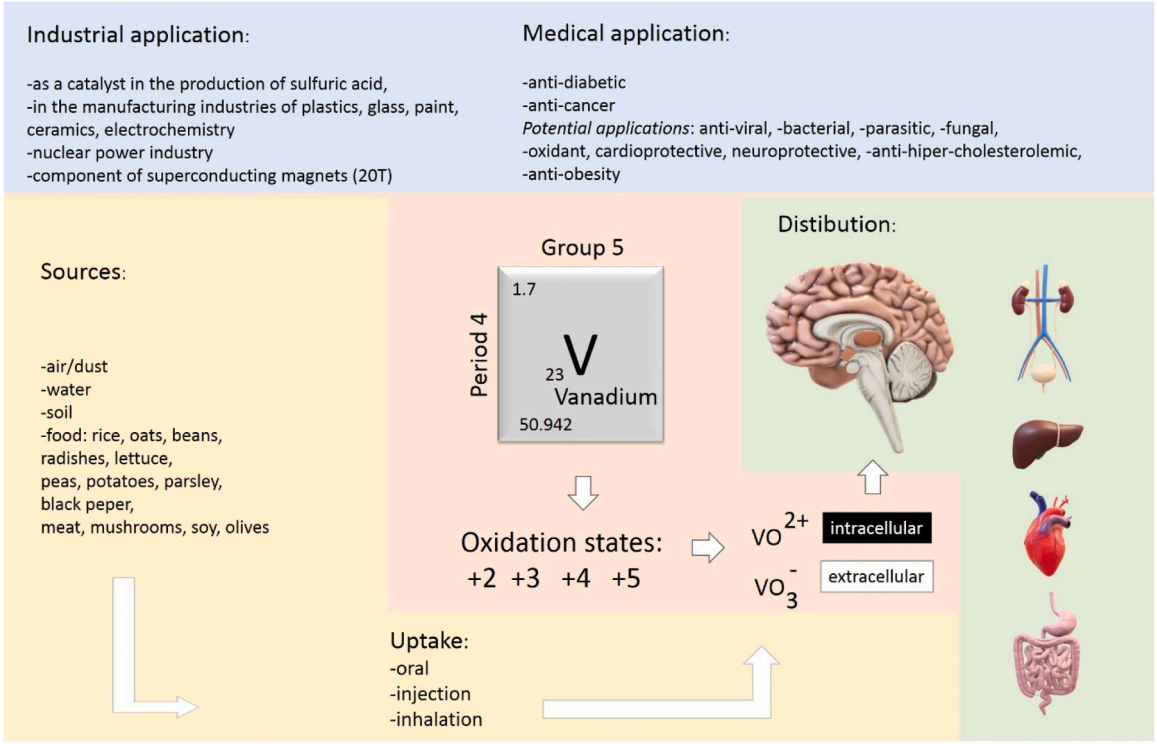

Fig. 1. Vanadium in the body: sources, distribution, and applications in medicine and industry (based on Carpio et al#, 2018; Pessoa et al#, 2015; Barceloux, 1999; Scibor et al#, 2020).

receptor (IR) and its substrates (Liu et al., 2022). In that case, vanadium (vanadate) is a potent inhibitor of phosphatase activity by pretending the 5-coordinate transition state of phosphate formed during the phosphatase catalytic cycle (Treviño et al., 2019). Furthermore, it may oxidize the cysteine active site, affecting PTPases (Treviño et al., 2019). In PTP1B vanadate is bound to a tyrosine site and may also form a Cys-bound vanadate (Treviño et al., 2019). Geometries of protein structures with vanadium bound in the active site are square pyramidal and trigonal bipyramidal, which can support the phosphoryl group transfer in phosphatases and phosphorylates (Pessoa et al., 2015). Thus, the potential of vanadium in treating diabetes may result from the similarity in structure between vanadate and phosphate. However, vanadate occupies the active site in a way that is not quickly released once bound (Pessoa et al., 2015). Inhibition of PTP1B by vanadate was documented *in vitro* and *in vivo* (Treviño et al., 2019). The antidiabetic potential of vanadium depends on the coordination in which the vanadium salts are located, so vanadate (V) has cytosolic activity with beneficial effects on glucose and fat metabolism. In contrast, vanadium (IV) normalizes glucose concentrations through glucose uptake across cytoplasmic membranes and can inhibit lipolysis (Scior et al., 2016). In this regard oxidation of vanadium from + 4 to + 5 produces pervanadate intermediate that boosts glucose uptake by increasing autophosphorylation of the IR and prevents its dephosphorylation (Treviño et al., 2019). Further points of action of vanadium are mitogen-activated protein kinases (MAPK) ERK and p38, Akt, phosphorylation of Ser473, Thr308, activation of phosphoinosidide 3 kinase (PI3K) (Treviño et al., 2019).

One of the first clinical trials with vanadium was performed in 1995 on moderately obese non-insulin-dependent diabetes (NIDDM) subjects and obese nondiabetics with insulin resistance (Goldfine et al., 2000). Vanadyl sulfate was used orally for three weeks in seven NIDDM and six nondiabetic patients (Halberstam et al., 1996). The element was not effective in obese patients without diabetes but improved insulin sensitivity in patients with NIDDM (Halberstam et al., 1996). Similar results were obtained in subsequent years. Patients with type II diabetes were treated with vanadyl sulfate for six weeks in three doses divided into three daily portions with a meal (Goldfine et al., 2000). The study observed improved glucose utilization in some patients (Goldfine et al., 2000). A similar study on type II diabetes allowed the authors to conclude that vanadium acts via improvement in muscle and hepatic insulin sensitivity (Cusi et al., 2001). The vanadium potential was confirmed in rats treated for 24 weeks with vanadyl sulfate (Shah et al., 2016). The hypoglycemic effect was confirmed in healthy rats with a secondary decrease in insulin levels (Shah et al., 2016). However, insulin-mimetic vanadoorganic complexes of the second generation were found to be greater than inorganic vanadium salts (Scior et al., 2016). Thus compounds such as bis(2-ethyl-3-hydroxy-4-pyronato) oxovanadium(IV) (BEOV) and bis(3-hydroxy-2-methyl-4-pyronato) oxovanadium(IV) (BMOV) enter clinical stages (Scior et al., 2016). Basal and insulin-stimulated glucose uptake tested on rat adipocytes allowed the selection of vanadium compounds with the most favorable properties (Pereira et al., 2009). Decavanadate applied at a dose of 50 microM showed a 6-fold increase in glucose uptake compared to stock solutions, followed by BMOV (1 mM) and metavanadate (1 mM) (3-fold). In contrast, V5 dipic and amavadine showed no effect (Pereira et al., 2009). The highest insulin-like activity showed decavanadate in a dose of 100 microM (Pereira et al., 2009). Among the most studied compounds was still BEOV, an ethyl derivative of BMOV, entering clinical trial phase II in 2007/2008 (Scibor et al., 2020; Scior et al., 2016; Thompson et al., 2009). However, due to detected kidney problems, the program was stopped in 2009 (Scibor et al., 2020; Scior et al., 2016). In a 2013, the first attempt to correlate anti-diabetic activity with total serum V was made (Willsky et al., 2013). The discovery was made that vanadium pools other than total serum vanadium may be related to its insulin-like activity, thus pointing out the need for further investigations into the coordination chemistry of metabolites and the interaction of proteins with vanadium chelates (Willsky et al., 2013). Last year's results (2023), an analysis of covariance performed on patients with T2D showed that administration of VEY (vanadium pentoxide) significantly reduced anthropometric indices and glycemic parameters and increased insulin sensitivity after adjusting for potential concomitant variables, compared to the placebo group (Ghalichi et al., 2023). In addition, VEY supplementation was effective on MAPK, PTP1B, and NFƘB gene expression levels compared to the placebo group (Ghalichi et al., 2023). No significant changes were observed in dietary intake, quality of life, and lipid profile in the VEY group compared to the placebo group (Ghalichi et al., 2023).

Rodent studies in streptozocin (STZ)-induced diabetic rats treated with Vox2 (oxidovanadium(IV) complex) revealed that Vox2 in association with insulin caused a few times decrease in blood glucose (Lopes et al., 2024). Compared to insulin alone, a dose-dependent decrease in blood glucose was found as an additional decrease after Vox2 (Lopes et al., 2024). Further increases in pancreatic GSH levels were observed, and no side effects were linked with renal, hepatic toxicity or lipid profile (Lopes et al., 2024). Vanadium compounds were also tested in metabolic syndrome using new Zeland obese (NZO) mice (Krośniak et al., 2014). Experiments revealed improvement in glucose levels in mice treated for eight weeks with a fatty diet (Adam et al., 2017). Further studies with vanadium complex with vitamin A were adequate as antidiabetic in STZ-mice, additionally improving lipid profile, antioxidant activity, and kidney and liver function (Adam et al., 2017). Additionally, the effects of vanadium on organ weights and body mass in NZO mice revealed the impact of vanadium compounds on the liver, spleen, and heart weight of obese mice (Krośniak et al., 2019). Details on the role of vanadium in diabetes research are presented in Table 1.

Research into using vanadium compounds as antidiabetic agents shows promising, yet still preliminary, results. Vanadium has demonstrated insulin-mimetic and insulin-sensitizing effects by targeting key enzymes like protein tyrosine phosphatase 1B (PTP1B) and enhancing insulin receptor signaling. In both *in vitro* and *in vivo* models, vanadium compounds (e.g., vanadyl sulfate, BMOV, BEOV, decavanadate) have improved glucose uptake, insulin sensitivity, and lipid metabolism. Early clinical trials have confirmed some benefits, particularly in type II diabetes patients, with glucose utilization and insulin sensitivity improvements.

However, limitations remain. For example, BEOV reached phase II clinical trials but was halted due to kidney toxicity concerns. Furthermore, significant variability exists between different vanadium compounds regarding effectiveness and safety. More recent clinical work (e.g., Ghalichi et al., 2023) continues to show glycemic benefits without adverse effects, but results are not yet definitive. To advance the clinical potential of vanadium-based therapies for diabetes, several areas warrant further investigation. First, comprehensive toxicological profiling and long-term safety assessments are essential, particularly for newer organo-vanadium compounds such as Vox2. Additionally, pharmacokinetic studies and coordination chemistry analyses are needed to understand better the bioavailable vanadium pools responsible for its insulin-like activity. Future research should also focus on dose optimization and comparative trials to identify the most effective and safe formulations. Expanded clinical trials involving larger and more diverse patient populations are necessary, with particular attention to renal and hepatic safety outcomes. Finally, mechanistic studies exploring vanadium's impact on key cellular pathways—such as MAPK, PI3K/Akt, and PTP1B—will help clarify its mode of action and therapeutic potential.

2.2. *Vanadium use in mental health - focusing on depression and schizophrenia/manic depressive psychosis*

Despite years of research, the idea of using vanadium to treat depression or schizophrenia has not penetrated the clinic. This chapter will gather material to answer the question of whether vanadium does not have potential in the disorders above or is not sufficiently tested.

Table 1
The role of vanadium in diabetes, clinical and rodent studies.

Use	Dose	Form	Effects	Ref.
Clinic				
Clinic/ 7 NIDDM and 6 non diabetic obese	100 mg/day/3 weeks oral	Vanadyl sulfate	Improvement of insulin sensitivity in NIDDM but not obese nondiabetic	(Halberstam et al., 1996)
Clinic/16 diabetes type II	75 mg/day;150 mg/ day; 300 mg/day oral (Dose divided into three servings per day with meals)/ 6 weeks	Vanadyl sulfate	Glucose utilization improved in some patients. Modification basal insulin receptor and substrate tyrosine phosphorylation, activation of PI3-kinase; not additive with insulin	(Goldfine et al., 2000)
Clinic/11 diabetes type II	150 mg/day/6 oral (Dose divided into three servings per day with meals)	Vanadyl sulfate	Reduction of endogenous glucose production, lowered total plasma cholesterol; improvement in muscle and hepatic insulin sensitivity	(Cusi et al., 2001)
Clinic/ Single-blind, placebo-controlled 40 non-diabetic subjects. Single-blind, placebo-controlled 7 T2D patients	Phase I: 10–90 mg/day 2 weeks active. No-follow up Phase II: 20 mg/day 28 days 14 days follow-up	BEOV	No information about plasma glucose and HbA1c. No side effects. Reduction in plasma glucose and HbA1c. Renal side effects	(Thompson et al., 2009)
Clinic/16 T2D	25, 50, 100 mg V daily/ oral/ 6 weeks	Vanadyl sulfate	Serum accumulation of V - dose-dependent. No correlation between total serum V concentation and the insulin-like response. V pools other than total serum V may be related to the insulin-like effect.	(Willsky et al., 2013)
Clinic/ 44 T2D, randomized, double-blind, placebo-controlled clinical trial	0.9 mg/day 12 weeks	VEY (vanadium pentoxide)	decreased anthropometric indices and glycemic parameters and increased insulin sensitivity. effective on MAPK, PTP1B, and NFKB gene expression level, compared to the placebo group.	(Ghalichi et al., 2023)
Rodent studies				
Rats	0.25 mg/kg/day and 1.2 mg/ kg/day for 24 weeks/ oral	Vanadyl sulfate	Decrease in plasma glucose, insulin, HDL, increase in LDL, TC levels in a dose-dependent manner	(Shah et al., 2016)
Rats/ STZ-induced diabetes	30 and 100 mg/kg/ oral/ 12 days	Vox2	Decrease of blood glucose, increase pancreatic GSH levels. No side effects	(Lopes et al., 2024)
NZO mice	0.063 mmol/kg/ 5 weeks/ gavage	VOSO4, VOmal2, NaVO(O2) 2bpyxH2O	Decrease of glucose level	(Krośniak et al., 2014)
STZ-mice	100 mg/kg	VO(vitaminA)2 (H2O)2	Decrease glucose level, improvement I lipid profile, improvement I liver and kidney functions	(Adam et al., 2017)

Alternatively, it may participate in the mechanisms of psychiatric disorders, so used as an additional booster, it could increase the effectiveness of drugs.

As of today, we do not know the pathomechanism that initiates depression. The prevailing theory is the influence of multiple changes at the neurotransmission, molecular, and histopathological levels, as well as plastic changes that result from rearrangements of the glutamatergic, immune, serotonergic, and other systems (Stachowicz and Sowa-Kućma, 2022), which the single common name of interference changes can call. Vanadium's involvement in oxidative stress-related changes has been demonstrated (Nnama et al., 2022; Adebiyi et al., 2018). Sodium metavanadate used for seven days in mice induced reduction of superoxide dismutase (SOD), catalase (CAT), increase in hippocampal malondialdehyde (MDA) and H_2O_2 (Adebiyi et al., 2018). Similarly, vanadium pentoxide used for 21 days showed dose-dependent involvement in changes in oxidative stress biomarkers, total reduced glutathione (GSH), SOD, CAT, and production of reactive oxygen species (ROS) (Nnama et al., 2022). Furthermore, the involvement of vanadium in cyclooxygenase-2 (COX-2) expression was shown (Korbecki et al., 2015; Chien et al., 2006; Stachowicz, 2023). Vanadium in the form of vanadate may induce the expression of COX-2 mRNA (10 μM) and increase the expression of COX-2 protein (100 μM) (Korbecki et al., 2015). The activation of mitogen-activated protein kinase (MAPK) cascades, involvement of transcription factor NF-κB, p38, c-Jun N-terminal kinase (JNK) MAPK, extracellular-regulated kinase (ERK) MAPK in that process was described (Korbecki et al., 2015; Chien et al., 2006), thus mechanisms involved in depression (Stachowicz and Sowa-Kućma, 2022). Moreover, activation of microglia, astrocytes, tumor necrosis factor (TNF), and interleukin 1β (IL-1β) are effects of long-term exposure to vanadium (Azeez et al., 2016). However, these are not the only mechanisms connecting depressive and vanadium mechanisms. The involvement of glutamate (Glu) in depression is not in dispute (Stachowicz and Sowa-Kućma, 2022). Vanadium compounds exhibit the potential to inhibit Glu metabolism, influencing glutamate dehydrogenase (Kiersztan et al., 1998), but also may interfere with N-methyl--D-aspartate (NMDA) receptors, which was documented in the hippocampus (Ladagu et al., 2023). The potential of vanadium to affect other neurotransmitters such as acetylcholine (Ach), serotonin (5-HT) or gamma-aminobutyric acid (GABA) has also been presented (Sun et al., 2017). Another point of grip is the ability to modulate sodium, potassium-activated adenosine triphosphatase ($Na,^{+}K^{+}$-ATPase) signaling, both by vanadium (Cantley et al., 1977a,1977b), and it is mentioned as one of the mechanisms changed in bipolar disorder (Lichtstein et al., 2018). Since there are so many common pathways between depressive changes and vanadium exposure, it is essential to look at what *in vivo* studies present on the subject.

The relationship between locomotor behavior and depression in rodents remains complex and requires further elaboration. Research has produced contradictory results, complicating the interpretation of locomotor activity as an indicator of depression. This variability has significant implications for depression screening tests in animal models (Sanchez et al., 1998; Dyer and Butte, 2022; Sampath et al., 2022; Gilbert et al., 2021). Sanchez et al. (1998) were among the first to report on this topic, observing that rats treated with sodium metavanadate for eight weeks showed reduced locomotor activity, as evidenced by a decrease in the total distance traveled in an open-field test. In contrast, studies on mice have demonstrated dose-dependent effects of vanadium on motor function. For example, low doses of vanadium were associated with improved motor development and muscle strength in pups, whereas higher doses resulted in significant motor impairments (Gilbert et al., 2021). Similar findings were reported with neonatal female mice subjected to the elevated open space test (Franklin et al., 2021).

Other studies reported neurobehavioral deficits in vanadium-treated rat pups, as observed in the rotarod and open-field tests, suggesting a

potential negative impact on locomotor function (Usende et al., 2016). However, these results contrast those described by Sampath et al. (2022), where no significant changes in locomotor behavior were observed in the open field. Furthermore, a decreased activity duration was recorded in the forced swim test, suggesting a pro-depressant effect of vanadium. Additional research has reported decreased motion, weakness, and weight loss in adult rats exposed to vanadium for eight days (de la Torre et al., 1999), reinforcing the possible depressive effects of vanadium at higher doses. On the other hand, chronic low doses of vanadium administered to young male rats did not appear to affect their behavior in the open-field test (Dyer and Butte, 2022), suggesting that lower doses may not significantly alter locomotor activity. While some of our own research suggests that vanadium-treated mice exhibit prolonged immobility in the tail suspension test, these findings must be interpreted cautiously, as vanadium also affects locomotor activity, complicating the conclusion of any antidepressant or pro-depressant effects (manuscript in preparation). To better elucidate the relationship between locomotor behavior and depression, it is important to consider how changes in motor activity can serve as potential behavioral indicators of depressive states in animal models. A decrease in locomotor activity in response to specific compounds or stimuli, such as vanadium, may reflect a general decline in locomotion. However, these changes may also result from disruptions in the neurotransmitter system, changes in neuroplasticity or other factors affecting the brain's emotional regulation circuitry. Moreover, the variability in the results of locomotor activity tests in rodents may be attributed to different dosages, treatment durations, and animal species, highlighting the complexity of assessing depression-related behavior through motor performance alone. Further research is needed to delineate the mechanisms by which changes in locomotion are linked to depressive symptoms and how such behavior can be reliably used to evaluate potential therapeutic compounds.

People exposed to vanadium exhibit neurobehavioral alterations, as described by Chinese workers using the Neurobehavioral Core Test Battery (NCTB) (Simonoff et al., 1987). People exposed every day to vanadium compounds exhibited increased anger-hostility, depression-dejection, fatigue-inertia, longer mean reaction time, impaired reaction speed, and coordination problems (Simonoff et al., 1987). Effects were correlated with the duration of exposure (Simonoff et al., 1987). Clinical reports documented changes in serum levels of vanadium in patients (Naylor, 1984). The clinical group was divided into the beginning of the depression, depressed patients with medication, and the control group (Naylor, 1984). Depressed patients had higher serum vanadium levels compared to controls, and treatment resulted in a decrease in this parameter (Naylor, 1984). Average values were found in neurotic depression (Naylor, 1984). The results were confirmed in subsequent years when differences were shown in vanadium levels in the sera of depressed patients - before and after treatment (Sampath et al., 2022). Moreover, post-mortem studies have documented reduced vanadium content in the prefrontal cortex (PFC) of depressed patients (Sampath et al., 2022). Most literature on vanadium and human studies dates back to the 1980s. However, the manuscript cites data from the last ten years by a margin, so they will not be quoted here, but they are available in databases (examples: Naylor et al., 1983; Naylor and Smith, 1981; Aucoin et al., 2020).

As it states to schizophrenia, there are no clear reports on the subject. However, some vital data can be found on the topic of manic-depressive psychosis. A review by Aucoin et al. (2020) indicated the importance of diet in manifesting schizophrenia with the weight of minerals and fatty acids. Unfortunately, vanadium was not included in the manuscript. However, the study of Lakhan and Vieira took into account the effect of vanadium, showing its negative impact, which was reduced by the use of vitamin C (Naylor et al., 2018). Schizophrenia spectrum disorder (SSD) is a severe mental illness whose symptoms are both positive (delusions, hallucinations) and negative and cognitive symptoms (Lakhan and Vieira, 2008). Only one study out of many met the criteria of studies done in the last ten years on the topic of depressive psychosis. A clinical study of depressive psychosis showed a significant effect of vanadium in a manic episode (McCutcheon et al., 2023). Vanadium concentrations were monitored in hair, whole blood, serum, urinary vanadium excretion, and renal clearance (McCutcheon et al., 2023). Renal clearance of vanadium was lower, and serum vanadium concentration was higher in depressed patients than in the controls (McCutcheon et al., 2023). A strong negative correlation was found between vanadium and Na-K-ATPase activity, which concluded that vanadium concentration is vital in sodium changes during depressive psychosis (McCutcheon et al., 2023). Details are described in Table 2, which collects data on vanadium's contribution to depression and schizophrenia/manic depressive psychosis in *in vivo* studies.

In addition to the research described here, many vanadium studies are conducted in the context of cognitive changes, a topic to which the following subsection will be devoted.

2.3. *Vanadium use in cognition*

Cognitive changes, disorders of attention, and memory co-create many diseases, both neurodegenerative as well as depression or schizophrenia (He et al., 2020; Stachowicz and Sowa-Kućma, 2022). The effect of vanadium on cognitive changes has been demonstrated in many experiments; for example, studies conducted on rats have shown that vanadium exposure resulted in striatal learning and memory changes (Sun et al., 2017). Rats treated with vanadium for 12 weeks had alterations in memory manifested with increased time to find a platform; results were dose-dependent (Sun et al., 2017). Degradation of the striatum was observed histopathologically (Sun et al., 2017). Also, similar results were found in BALB/c mice in the Morris water test (Adebiyi et al., 2018). Mice treated with vanadium for seven days exhibited cognitive decline (Adebiyi et al., 2018). However, a lower dose of vanadium used chronically improved the learning skills of rats in the Morris water test (Dyer and Butte, 2022). On the second day of the treatment with vanadium, rats exhibited significantly better spatial memory and found the platform easier than controls (Dyer and Butte, 2022).

Furthermore, similar results were found in neuropathological Alzheimer's disease (AD) mice (APPSwe/PSIdE9 mice), where improvement of spatial learning was documented when vanadium treatment was implemented for 90 days (Xu et al., 2020). Based on these few research papers, it can be suggested that vanadium has both positive and negative effects on memory as measured by the Morris test. Studies suggest that lower doses of vanadium positively affect memory, while higher doses negatively affect memory parameters. At the same time, studies on AD transgenic mice suggest a positive effect of vanadium on pathology (Xu et al., 2020). Indeed, there is very little research on the subject. It is necessary to expand the experimental workshop with various tests, doses of vanadium, and chemical compounds that are carriers of vanadium to clarify the picture. One should also not forget the studies on workers exposed to vanadium in the work environment, who showed memory disorders, as discussed earlier in the manuscript (Simonoff et al., 1987). Table 3 shows data collected on role of vanadium in cognition.

3. Mechanisms of vanadium's biological activity in neurotransmission, mitochondrial function, and myelin integrity

The primary mechanism of vanadium activity was described earlier as a potent inhibitor of Na,K-ATPase (Cantley et al., 1977a,1977b). One of the first reports on a topic was done in 1977 (Cantley et al., 1977a, 1977b). Authors using microwave-induced emission spectroscopy detected vanadium as a potent Na,K-ATPase inhibitor in ATP derived from muscle (Cantley et al., 1977a,1977b). It was proposed as a substitute for the phosphate site on the Na,K-ATPase (Cantley et al., 1977a, 1977b). The mechanism of Na,K-ATPase inhibition is vital in a context

Table 2
The role of vanadium in mental health.

Use	Dose/methodology	Form/assessment	Effects	Ref.
Depression-like/locomotor activity				
BALB/c mice	3 mg/kg/i.p./7 days	Sodium metavanadate	Open field test – decreased line crossing, exploration, increased anxiety, decreased hanging latency in hanging wire test	(Adebiyi et al., 2018)
Sprague-Dawley rats/	4.1 mg/kg/day 8.2 mg/kg/day 16.4 mg/kg/day 8 weeks/ in drinking water	Sodium metavanadate	Decrease in total distance traveled in an open-field test	(Sanchez et al., 1998)
Pups from nursing mice (PND 90)	3 months/i.p./0.15 mg/kg and 3 mg/kg	Sodium metavanadate	Low-dose – improvement in motor development and muscle strength High-dose – impairment in motor development and muscle strength	(Gilbert et al., 2021)
Neonatal female mice	3 mg/kg/i.p./4 weeks	Sodium metavanadate	Open field test – increased latency to first entry, decrease in time spent and number of entries/ anxiety	(Franklin et al., 2021)
Sprague-Dawley rat-pups	3 mg/kg/i.p./21 days	Sodium metavanadate	Deficits in rotarod, and open field test – deficits in centre square entries, centre square duration, line crossing	(Usende et al., 2016)
BALB/c mice	i.c.v. injection of 10 mM in aCSF into the lateral ventricle	Sodium metavanadate	Pro-depressive in forced swim test/ no effects in open field test	(Sampath et al., 2022)
Sprague-Dawley rats/young 22 days/ and adult 62 days old	10 mg/kg/ 8 days/i.p.	Sodium othovanadate	No effects on locomotion, but adult rats showed weight loss, decreased locomotion, general weekness.	(de la Torre et al., 1999)
Sprague-Dawley rats/young	Chronic low dose 0.04 mg/ week/4 weeks	Sodium metavanadate	No effects on exploration, locomotion, anxiety in open-field test	(Dyer and Butte, 2022)
C57Bl/6 J mice	2 mg/kg; 5 mg/kg; 20 mg/ kg/i.p./acute	Sodium orthovanadate	Tail suspension test – increased immobility/ locomotor activity –decreased. Thus observed effects are not due to pro-depressant activity of vanadium compound. The dose of 20 mg/kg – disturbed rotarod performance.	[manuscript in preparation]
Depression – clinic				
Workers in China/ The Neurobehavioral Core Test Battery (NCTB)	463 vanadium-exposed workers and 251 non-exposed workers (control group)	Vanadium exposure in Steel and Iron Group in Sichuan, China	Neurobehavioral alterations, increased anger-hostility, depression-dejection, fatigue-inertia, longer mean reaction time, impaired reaction speed, coordination	(Simonoff et al., 1987)
Clinic/26 depressed patients/group at the beginning of depression and group after few months of antidepressant therapy/ 23 healthy controls	Collection of blood samples	Assessment of vanadium concentration in serum	Higher vanadium levels in the depressed group. No differences between psychotics and neurotics. Five patients with neurotic depression - intermediate value. Lower serum vanadium levels after 6 months of antidepressant treatment	(Naylor, 1984)
Clinic/ 11 female patients/ post mortem studies of 20 patients and 20 controls	Collection of blood samples/ post mortem prefrontal cortex (PFC)	Assessment of vanadi-um concentration in serum and in PFC (post mortem)	Decrease in vanadium serum level after treatment/ decreased PFC content of vanadium in post mortem depression	(Sampath et al., 2022)
Schizophrenia/manic depressive psychosis				
Clinic/three studies	1. neutron activation analysis/13 patients depressive psychosis 2. neutron activation analysis/21 patients with depressive psychosis and 27 controls 3. erythrocyte Na-K ATPase activity and serum concentration/58 patients	1. Assessment of vanadium concentration in hair, whole blood, serum, urine 2. serum, urine 3. serum	1. Vanadium concentration decreased with recovery, no changes in 24-h urinary excretion or renal clearance 2. mean renal clearance of vanadium lower, and mean serum concentration, mean 24-h excretion with no difference 3. strong negative correlation between Na-K ATPase and vanadium	(McCutcheon et al., 2023)

discussed in the manuscript, while it was described in bipolar disorder (Lichtstein et al., 2018). Na,K-ATPase represents an enzyme in the plasma membrane of most eukaryotic cells that hydrolyzes ATP and uses the free energy to maintain potassium transport into the cell and sodium out of the cell against their electrochemical gradients (Lichtstein et al., 2018). However, later studies confirmed the involvement of Na, K-ATPase in the action of vanadium (Sampath et al., 2022). A report by Sampath et al. (2022) revealed that vanadium inhibits Na,K-ATPase activity in mice brains via direct inhibition of transport. The ion transport of Na^+ and K^+ ensures neuronal electrical activity, synaptic plasticity, and brain functions (Lichtstein et al., 2018). Furthermore, alterations in intracellular signaling with ERK, AKT, and NFκB were described (Lichtstein et al., 2018).

Secondly, vanadium may influence the activity of mitochondria and hepatocytes via changes in glutamate dehydrogenase (Kiersztan et al., 1998). Studies were done in rabbit liver mitochondria (Kiersztan et al., 1998); however, glutamate dehydrogenase acts to lead glutamate to the tricarboxylic acid cycle, influencing glutamine-glutamate-GABA metabolic system in brain structures involved in depression and cognition, that are striatum, hippocampus, or cerebellum (Imura et al., 2013). Among genes involved in glutamine-glutamate metabolic changes during chronic unpredictable mild stress (CUMS) are GS, GLS2, GLT1, SSADH in the striatum, GS, SNAT1, GAD1, SSADH, VGAT, ABAT in the hippocampus, and GS, ABAT, SNAT1, VGAT, GDH in the cerebellum (Imura et al., 2013). Dysfunction of GABAergic signaling is characteristic of depression and schizophrenia (Imura et al., 2013). Thus, studies involving vanadium would be highly recommended. Results of Sun et al. (2017) showed degenerative damage in the striatum exposed to high doses of vanadium, with an increase in neurotransmitter content that is Ach, 5-HT, and GABA.

Table 3
The role of vanadium in cognition.

Use	Dose	Form	Effects	Ref.
Sprague-Dawley rats	0.5 g/l, 1 g/l, 2gl in drinking water/12 weeks	Sodium metavanadate	Morris water maze – increased time to find platform, dose-dependent effects. Accumulation of vanadium in striatum and degenerative damage. Increased content of acetylcholine and serotonin, GABA in a striatum.	(Sun et al., 2017)
BALB/c mice	3 mg/kg/i.p./7 days	Sodium metavanadate	Morris water test – longer latency to find platform, lower time spent in target quadrant	(Adebiyi et al., 2018)
Sprague-Dawley rats	Chronic low dose 0.04 mg/week/4 weeks	Sodium metavanadate	Morris water test – improvement in tasks learning and memory	(Dyer and Butte, 2022)
APPSwe/PSIdE9 mice	68.4 μg/ml, 342 μg/ml in drinking water/90 days	BEOV	Morris water maze – improvement of spatial learning in AD mice, shorter time to find platform, more time spent in target quadrant	(Xu et al., 2020)

Conversely, vanadium has a positive impact when neuropathology occurs (Xu et al., 2020). In that case, vanadium's biological function was related to the reduction of Aβ generation in AD mice by increasing the expression of peroxisome proliferator-activated receptor γ (PPARγ) and insulin-degrading enzyme (IDE) and decreasing β-secretase in the hippocampus and the cortex (Xu et al., 2020). Via that mechanism, vanadium can decrease Aβ by inhibiting β-site APP cleaving enzyme 1 (BACE1) expression and promoting IDE expression (Xu et al., 2020).

Another mechanism triggered by vanadium is associated with changes in myelin (Adebiyi et al., 2018). It was documented the downregulation of myelin essential protein (MBP) in the hippocampus of vanadium-exposed BALB/c mice (Adebiyi et al., 2018). Furthermore, discontinuity of myelin was observed (Adebiyi et al., 2018). The toxic effects of vanadium on myelin and oligodendrocyte death may correspond with the impaired learning observed by the authors (Adebiyi et al., 2018). The toxicity of vanadium is known and will be discussed in the following subsection of the manuscript.

4. Vanadium toxicity - another face of the element

Vanadium toxicity depends mainly on the type of vanadium compound - inorganic or organic, the nature of the attached ligand, the valence, and the dose (Scibor et al., 2020). The most toxic is vanadium, which has a + 5 degree of oxidation and is a product of industry (Scibor et al., 2020). Among the symptoms of vanadium exposure are gastrointestinal problems, abdominal pain, nausea, vomiting, weight loss, chest pain, bronchitis, and headache (Scibor et al., 2020). Symptoms depend on the oral or inhalation route of poisoning (Scibor et al., 2020). The mortality of mice treated with ammonium metavanadate (AMV) depended on mice metabolism, while high mortality was detected in mice on a high-fat diet (Mustapha et al., 2022). The mechanism of this action was documented as impairing lipid metabolism, resulting in lipid accumulation, mucosal epithelial cells and the small intestine necrosis (Mustapha et al., 2022). Secondly, age may be a predictor of vanadium toxicity (de la Torre et al., 1999). Vanadium-induced morphologic changes in the kidney were more pronounced with age (de la Torre et al., 1999).

However, vanadium toxicity has also been demonstrated in the central nervous system, where changes have been described at the neuronal level and in astrocytes (Scibor et al., 2020; Rezk and Rezk, 2017; Jaiswal and Kale, 2020; Adebiyi et al., 2018; Ladagau et al., 2023). Lipid peroxidation, free radical generation, and oxidative stress induced by vanadium result in morphological changes in neurons and astroglial cells (Jaiswal and Kale, 2020). In the hippocampus, vanadium neurotoxicity manifested as demyelination, microgliosis, and neuronal cell loss (Ladagau et al., 2023). Pathologies of the hippocampus were the most spectacular in dentate gyrus and CA3, where a decrease in neuronal density, disruption of the cytoarchitecture, loss of dendritic arborizations, and axonal extensions were observed (Ngawa et al., 2024). Moreover, simultaneous exposure to vanadium and manganese has been postulated as a risk factor for Parkinsonism (Mustapha et al., 2014). More pronounced changes in olfactory dysfunction and nigrostriatal system were documented when vanadium and manganese were coexpressed than when the elements were used separately (Gruziewska et al., 2014). The mechanism for these changes was oxidative stress manifested by increased levels of 4-hydroxynonenal (4HNE) in the striatum; increased expression of α-synuclein was also observed (Mustapha et al., 2014).

Through a Fenton-like mechanism, vanadium generates reactive oxygen species (ROS) in redox reactions (Jaiswal and Kale, 2020; Ladagau et al., 2023). Furthermore, it generates iron in redox active form from ferritin, which leads to ROS generation and apoptosis, inducing the destruction of progenitors of oligodendrocytes and cell toxicity (Jaiswal and Kale, 2020). Moreover, iron deficiency and increased divalent metal transporter-1 (DMT-1) expression may be observed (Jaiswal and Kale, 2020). Lipid peroxidation induced by vanadium leads to the loss of oleic, linoleic, and arachidonic acids (Jaiswal and Kale, 2020). Increased levels of COX-2 expression were observed to be induced by the MAPK cascade (Jaiswal and Kale, 2020). Vanadium also shows its toxicity during perinatal brain development and maturation (Mustapha et al., 2014). Toxic effects were due to the reduction of 2,3-cyclic nucleotide 3-phosphodiesterase (CNP-ase) and oligodendrocyte-specific protein (OSP/Claudin) (Mustapha et al., 2014).

5. Research prospects

Despite the growing body of evidence on vanadium's biological activity, several key areas remain underexplored, and future research is essential to fully understand its therapeutic potential, mechanisms of action, and safety profile. Future studies should focus on assessing the long-term safety of vanadium supplementation or therapeutic use, particularly in relation to kidney, liver, and neural health. Comprehensive studies are needed to determine the chronic toxicity of vanadium in both humans and animals, including clinical trials to better understand threshold doses for toxicity and the effects of prolonged exposure. The potential role of vanadium in treating neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) warrants further investigation. Specific mechanisms by which vanadium influences amyloid-beta (Aβ) production, tau phosphorylation, and oxidative stress in the brain need to be clarified. Additionally, the interaction between vanadium and other neurodegenerative pathways, such as glutamate regulation and synaptic plasticity, should be explored. Recent studies suggest vanadium may have antidepressant and anxiolytic effects. However, the precise mechanisms underlying these effects are not yet fully understood. Future research should focus on elucidating how vanadium affects neurotransmitter systems, particularly those related to GABAergic and glutamatergic signaling, in the context of psychiatric disorders like depression and schizophrenia. Animal models could be instrumental in advancing our understanding of vanadium's influence on mood regulation and behavioral changes.

Vanadium's absorption, distribution, metabolism, and excretion (ADME) need to be better understood, particularly regarding its bioavailability in human systems. Investigating how different vanadium compounds (e.g., vanadyl sulfate, vanadate, or organovanadium complexes) are processed by the body could reveal more efficient therapeutic strategies. This research could lead to the development of vanadium formulations with optimized bioavailability and minimal side effects.

Expanding clinical trials with diverse patient populations (e.g., diabetic, neurodegenerative, and psychiatric patients) will be crucial to determine the clinical efficacy of vanadium-based therapies. Additionally, comparative studies between different vanadium compounds and other existing treatments could provide valuable insights into their relative effectiveness and safety. Emphasis should be placed on personalized medicine approaches, considering the genetic and environmental factors that may affect the response to vanadium treatment. Given vanadium's complex pharmacokinetics and potential toxicity, there is an increasing need to explore advanced drug delivery systems. Nanoparticle-based or targeted delivery methods could allow for more precise administration of vanadium, minimizing systemic exposure while enhancing its therapeutic effects at specific sites of action. By addressing these research gaps, to better assess the potential of vanadium as a therapeutic agent and to enhance the understanding of its role in human health and disease.

6. Conclusions

Vanadium certainly has two faces: the positive and the negative. The ultimate effect of vanadium depends heavily on factors such as dosage, exposure time, and the carrier compound used. At times, vanadium demonstrates a negative impact on healthy organisms. However, it shows promise in addressing diseases, as evidenced by studies on Alzheimer's disease mice, where vanadium exhibited beneficial effects. However, it is important to acknowledge that much of the research on vanadium's therapeutic potential is still in its early stages. In particular, there is limited evidence regarding its role in depression, cognition, or schizophrenia. Thus, while vanadium shows potential for therapeutic use, further extensive research is required to fully understand its mechanisms, therapeutic window, and risks before any conclusions can be drawn about its overall effectiveness and safety. Vanadium holds both promise and risk. Its future in medicine will depend on continued research to determine the optimal balance between these two aspects.

CRediT authorship contribution statement

Katarzyna Stachowicz: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors state no conflict of interest.

Acknowledgments

This study was supported by the statutory fund of the Maj Institute of Pharmacology, PAS, Poland.

Data availability

No data was used for the research described in the article.

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