Polyoxidovanadates a new therapeutic alternative for neurodegenerative and aging diseases

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Abstract

Aging is a natural phenomenon characterized by a progressive decline in physiological integrity, leading to a deterioration of cognitive function and increasing the risk of suffering from chronic-degenerative diseases, including cardiovascular diseases, osteoporosis, cancer, diabetes, and neurodegeneration. Aging is considered the major risk factor for Parkinson's and Alzheimer's disease develops. Likewise, diabetes and insulin resistance constitute additional risk factors for developing neurodegenerative disorders. Currently, no treatment can effectively reverse these neurodegenerative pathologies. However, some antidiabetic drugs have opened the possibility of being used against neurodegenerative processes. In the previous framework, Vanadium species have demonstrated a notable antidiabetic effect. Our research group evaluated polyoxidovanadates such as decavanadate and metforminium-decavanadate with preventive and corrective activity on neurodegeneration in brain-specific areas from rats with metabolic syndrome. The results suggest that these polyoxidovanadates induce neuronal and cognitive restoration mechanisms. This review aims to describe the therapeutic potential of polyoxidovanadates as insulin-enhancer agents in the brain, constituting a therapeutic alternative for aging and neurodegenerative diseases.

Key Words: Alzheimer's disease; antidiabetic; brain; cognition; diabetes; insulin; neurodegeneration; neuroinflammation; oxidative stress; Vanadium species

Introduction

Aging is a biological process of multifactorial etiology that involves decreased physiological functions and increased susceptibility to age-pathologies development, including cardiovascular diseases, diabetes, cancer, and neurodegenerative diseases (Baghel et al., 2019). It occurs at a different speed between species, with interindividual variations in the same species, depending on the organs and tissues (Campisi et al., 2019). According to the United Nations Organization, by 2050, one in six individuals will spend 65 years, and the number of people over 80 will triple worldwide (Cai et al., 2022). Meanwhile, economic expenses for treating age-related health disorders will increase as population aging increases. Therefore, effective and therapeutic preventive and therapeutic approaches will be needed, constituting a challenge for the health sector (Hou et al., 2019; Scott et al., 2021). Neurodegeneration and cognitive impairment receive particular importance within the range of age-related pathologies due to their high impact on health and quality of life. Several studies have shown that AD (the most common neurodegenerative disease) predominates in aging people (Hou et al., 2019).

In recent years, particular attention has been paid to the relationship between neurodegeneration and the prevalence of metabolic diseases such as diabetes. In particular, it has been observed that type 2 diabetes (T2D) and AD share some mechanisms, including abnormal insulin signaling, mitochondrial dysfunction, oxidative stress, lipid peroxidation (LPO) and neuroinflammation (Sims-Robinson et al., 2010; Carvalho and Moreira, 2023). Both are disorders linked to aging, and their incidence has increased worldwide (Labandeira et al., 2022). However, pharmacological treatments focus on symptomatology control, not preventing or improving the disease's progressivity. Additionally, clinical trials on AD have been relatively scarce in recent years, presenting a 99.6% failure rate (Cummings et al., 2014).

Consequently, developing a disease-modifying therapy takes a lot of work to achieve. Faced with the current problem, the need to implement effective therapeutic strategies that guarantee a better quality of life for the aging population arises. Based on published studies about diabetes and its association with neurodegenerative disease development, antidiabetic medicines have been proposed for their prevention and/or treatment (Labandeira et al., 2022). Metallodrugs have been used to treat various pathologies, such as diabetes, cancer, rheumatoid arthritis, infections, and cardiovascular diseases. Additionally, metallopharmaceuticals have been used to counteract the effects caused by LPO processes, exacerbated by oxidative stress, in particular pathologies such as cancer, diabetes, and neurodegenerative diseases (Aureliano et al., 2023). Especially, metallopharmaceuticals based on V have demonstrated broad euglycemic potential (**Figure 1**). However, it should be noted that speciation is extremely important to assess the therapeutic effect of V in biological systems (Aureliano et al., 2022, 2023).

Therefore, they have been considered a therapeutic alternative for treating T2D (Treviño et al., 2015). This review will address the different physiological properties of V in organisms, emphasizing the promising findings of using metallopharmaceuticals in managing diabetes, such as a potential therapeutic target in treating neurodegenerative diseases.

Database Search Strategy

The literature review was performed electronically with the help of the PubMed and Scopus databases to retrieve articles published in English, combining the key terms: cerebral aging, neurodegenerative diseases and diabetes, vanadium species, physiological role of vanadium, metformin, metformin decavanadate and abnormal insulin signaling in the central nervous system.

The highest percentage of the selected investigations was published during the 2010–2023 period. Some previous reviews were also included given its importance in the physiological properties of vanadium. Similarly, the references of eligible articles were carried out.

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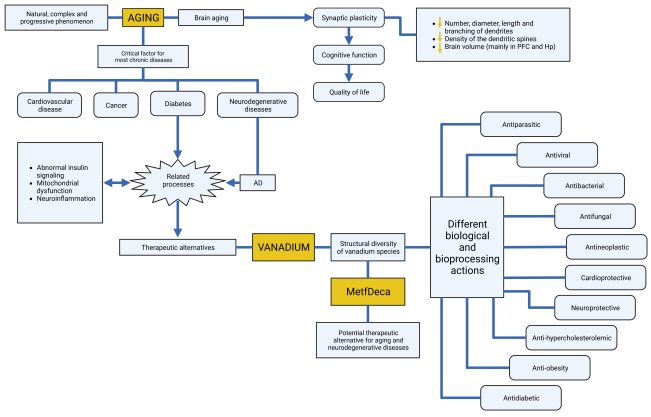

Figure 1 | **Vanadium, a therapeutic alternative for neurodegenerative diseases and aging.**
The schematic figure shows aging as a critical factor for the development of chronic diseases, including diabetes and AD, as well as the relationship between them. Likewise, it is observed how brain aging affects the cognitive function and the quality of life of the elderly. Finally, Vanadium is placed as a potential therapeutic alternative to mitigate the negative effects of aging and neurodegenerative diseases. Created with BioRender.com. AD: Alzheimer's disease; Hp: hippocampus; MetfDeca: metformin decavanadate; PFC: prefrontal cortex.

Brain Aging

At the biological level, aging is associated with progressive and cumulative damage in cells associated with an immune system depressed (inflammaging). Inflammaging impairment the body's capability to repair itself, which increases the risk of developing different pathologies (Epel, 2020). Notably, the brain is one of the most affected organs during aging (Flores et al., 2020; Tassinari et al., 2023). Brain aging is characterized by changes at all levels, reflected in reduced brain size, altered vasculature, and decreased motor and cognitive functions (Canevelli and Marsilli, 2022). Additionally, a decrease in the dendrites' number, diameter, length and branch, and density of dendritic spines has been associated with aging (Isaev et al., 2019; Blinkouskaya et al., 2021).

Other markers that have also been linked to brain deterioration include; mitochondrial alterations, deregulated energy metabolism, intracellular accumulation of protein, nucleic acids, and lipids oxidized, altered waste elimination mechanisms, aberrant response to adaptive stress, unusual DNA repair, abnormal neuronal networks, altered homeostasis of Ca^{2+} neuronal and inflammation (Mattson and Arumugam, 2018; Hou et al., 2019).

Therefore, a series of central nervous system (CNS) alterations could be presented as we age. The main affected regions are the prefrontal cortex and the hippocampus, critical areas in cognitive function (Isaev et al., 2019; Flores et al., 2020; Canevelli and Marsilli, 2022). The manifested alterations are decreased learning and memory, attention, decision-making, sensory perception, and motor coordination (Mattson and Arumugan, 2018). Since the brain function is based on the connectivity of the neuronal network, the consequences of aging are expressed at the level of synaptic plasticity, observing a decrease with age in the synapse number and an aberrant synaptic transmission in various regions of the brain (Sikora et al., 2021).

The molecular modifications in glucose and lipid metabolism cause synaptic transmission impairment during aging (Epel, 2020). Glycemia commonly increases in aged persons because the cells gradually lose the ability to transport glucose and respond to insulin signals (Mattson and Arumugam, 2018). Glucose is one of the most important brain energy substrates; thereby, alterations in its metabolism result in significant consequences in the functioning of this organ. A decrease in hippocampal volume has been reported in the elderly with glucose intolerance, accompanied by decreased performance on cognitive tests. It should be noted that glucose hypometabolism was most marked in the frontal, parietal, and temporal cortices (Tondo et al., 2020).

Additionally, hyperinsulinemia, low insulin sensitivity, and insulin resistance (IR) associated with aging alter the molecular pathways involved in synaptic plasticity, leading to cognition alterations (Hou et al., 2019; Epel, 2020). Cognitive function is considered an essential factor determining the quality of life in the aging population. It should be noted that cognitive functioning is altered with the development of neurodegenerative diseases (Setién et al., 2022). Given that, in the elderly population, neurodegenerative diseases are frequent and healthy brains are rare. Therefore, it is appropriate to consider aging as a critical factor for neurodegeneration (Tassinari et al., 2023). Among the most common neurodegenerative diseases associated with brain aging, AD has the highest incidence and is seen predominantly in people older than 65 years (Hou et al., 2019; He et al., 2021; Cai et al., 2022; Tassinari et al., 2023).

A correlation has recently been observed between the prevalence of peripheral metabolic diseases, such as diabetes, and the increase in the incidence of AD (He et al., 2021; Labandeira et al., 2022). Hence, it is the importance of studying the link between these pathologies.

Diabetes and Alzheimer's Disease

Diabetes is a metabolic disorder characterized by chronic hyperglycemia with alterations in carbohydrate, lipid, and protein metabolism due to alterations in insulin secretion, insulin action, or both. This pathology represents a global public health problem, estimating that 1 in 10 adults presents it (Sapra and Bhandari, 2022). Type 1 diabetes (T1D) and type 2 diabetes (T2D) commonly result from a deficit of insulin production (T1D) and action (T2D). It should be noted that diabetes is the final stage of a heterogeneous and progressive syndrome characterized by a range of metabolic disorders (dysglycemia and dyslipidemia) of multifactorial etiology (Sapra and Bhandari, 2022).

On the other hand, AD is one of the neurodegenerative disorders with the highest incidence that mainly affects older people. It is estimated that around 50 million people suffer from it, which is expected to triple by 2050 (Arvanitakis et al., 2019). AD is characterized by progressive memory loss and deterioration of cognitive function, in addition to exhibiting biochemical and inflammatory markers, within these are; a decrease in extracellular insulin levels, accumulation of amyloid-beta peptide (Aβ), hyperphosphorylation of tau protein, and pro-inflammatory cytokines and interleukins (Volicer, 2020).

In recent years it has been observed that diabetes and AD share some pathogenic characteristics, such as oxidative stress (Verdile et al., 2015), adiponectin deficiency (Ng et al., 2016), chronic inflammation (Verdile et al., 2015), and abnormal plasma cholinesterase expression (Hosoi et al., 2015). Therefore, several studies have reported an increased risk of AD in patients with T2D (Hamzé et al., 2022). In addition, obesity, hyperinsulinemia, and metabolic syndrome (MS) have also been considered risk factors for AD development (Treviño et al., 2020).

Although the exact relationship between diabetes and AD is not yet fully understood, a link between abnormal insulin signaling and the amyloid cascade has been proposed, thereby increasing the risk of AD in diabetic patients (Hou et al., 2019). It should be noted that the brain was previously considered an organ with insulin-independent activity. However, current evidence shows that insulin plays a significant role in the CNS. Besides presenting metabolic functions, this hormone is also related to cell growth, trophic activity, cognition, behavior, and neuroprotection (Mazucanti et al., 2019). The acute increase in insulin level has been shown to play an essential role in cognition under healthy conditions. However, chronic hyperinsulinemia significantly diminishes its actions at the brain level (Komleva et al., 2021).

Elevated insulin levels in the brain are also associated with increased Aβ deposition because insulin and Aβ are broken down by the insulin-degrading enzyme (IDE) (Hölscher, 2019). The IDE expression is limited and downregulated by high insulin levels. Consequently, insulin could hurt neurogenesis (Spinelli et al., 2019). This conclusion is supported by studies that show impairment in the learning process in animal models of T2D. Similarly, a cognitive deficit has been observed in clinical studies of patients with this disease (Pignalosa et al., 2021). Post-mortem studies have shown a greater nitrosylation and oxidation of IDE in AD brains compared to healthy brains in the same age range (Tarasoff-Conway et al., 2015). In addition, IDE was decreased in AD patients' brains, particularly in the cortical and hippocampal regions (Zhang et al., 2018). In recent decades, it has been more frequently observed that the pathological events accompanying AD are closely related to IR (Kandimalla et al., 2017). Although brain hyperinsulinemia, and thereby IR origin, is controversial because insulin crosses the blood-brain barrier, it can also be synthesized and secreted by hippocampal neurons and adult neural progenitors. Therefore, Aβ generated in an insulin-resistant environment causes astrocytic bidirectional modifications between the alteration of insulin signaling in the brain and the deposit of Aβ observed in AD patients (Spinelli et al., 2019). In addition, it has been confirmed that the brain with IR diminishes task processing speed, cognitive flexibility, and motor skills (Komleva et al., 2022).

Metabolic stress and neuroinflammation that cause neurodegeneration in AD are similar to those seen in peripheral tissues from models and diabetic patients (Talbot et al, 2014; Song et al., 2023). Therefore, these processes could modify central insulin transduction in AD patients (Komleva et al., 2022). Several mechanisms have been proposed that alter insulin transduction in the AD brain, such as a decrement in extracellular insulin levels (assayed in cerebrospinal fluid), total or partial lack of the insulin receptor, and decreased affinity of insulin receptor to the hormone (Talbot, 2014). For example, in the hippocampus, a critical area in learning and memory processes, insulin activated only 10% of the basal levels of insulin receptor substrate (IRS) (Talbot et al., 2014).

Currently, IR has been proposed as a mechanism of decreased insulin signaling in the AD brain (**Figure 2**). In the IR process, the serine phosphorylation in IRS is affected, which could activate microglia after Aβ increase, generating a vicious cycle between pro-inflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-α (Hemonnot et al., 2019). Impairment insulin signaling and low-grade inflammation explain why peripheral IR, obesity, and T2D are potential risk factors linked to AD development (Pugazhenthi et al., 2017). Therefore, it has been suggested that IR and glucose metabolism alterations can be used as risk biomarkers to prevent AD and other neurodegenerative disorders (Hölscher, 2019; Spinelli et al., 2019).

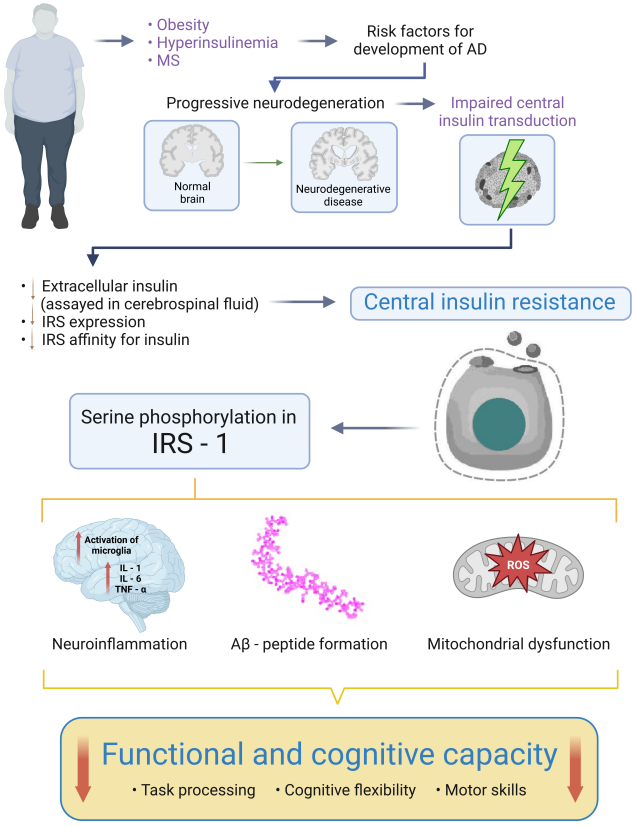

Figure 2 | **Relationship between type 2 diabetes and Alzheimer's disease.**
Conditions such as obesity, hyperinsulinemia, and MS in individuals with T2D are considered risk factors for the development of AD. During the characteristic neurodegeneration of AD, there is an alteration in the central transduction of insulin, probably due to changes in the expression and/or function of the IRS. This promotes alterations in mitochondrial function, neuroinflammation, increased Aβ production, and insulin resistance in the brain. This general condition decreases cognitive function and quality of life in older adults. Created with BioRender.com. AD: Alzheimer's disease; Aβ: amyloid-beta; IL: interleukin; IRS: insulin receptor; IRS-1: insulin receptor type 1; MS: metabolic syndrome; ROS: reactive oxygen species; T2D: type 2 diabetes; TNF-α: tumor necrosis factor alpha.

After reviewing the evidence for the relationship between diabetes and neurodegeneration and considering the pathological mechanisms they share, it is reasonable to consider using drugs with antidiabetic potential for treating neurodegenerative disorders and aging. However, today, the therapeutic options for these pathologies continue to be limited and unsuccessful. In this sense, it is essential to find novelty pharmacological strategies to prevent or delay neuronal damage in patients with metabolic diseases.

Since the 1980s, vanadium compounds have been shown to act as insulin mimetics, improving metabolic disorders (Treviño et al., 2020). For this reason, V is proposed as a new therapeutic alternative in treating neurodegenerative diseases and adverse aging effects.

Vanadium

Vanadium, symbol V, is a transition element located in the 4th period, group 5, with an atomic number of 23 and an atomic weight of 50.942. It constitutes the twentieth most abundant chemical element in the earth's crust (Ścibior et al., 2021) and is the second most abundant transition element, even above iron (Rehder, 2017). It was discovered in 1801 by Andrés Manuel del Río, a Spanish mineralogist, who called it "erythronium", indicative of the red color that the compound presented (Rehder, 2017). V is distributed ubiquitously in nature; it is present in water, air, soil, fossils, and living organisms. It has the potential to form various compounds, acting as a cation or anion (Ścibior et al., 2021). V shows a wide range of oxidation states, +2, +3, +4, and +5, found at a biological level in tetravalent and pentavalent forms (Aureliano et al., 2022). The pentavalent form predominates in body fluids and the extracellular space, such as vanadate ion (VO^{3+}). Intracellularly, the tetravalent state prevails, exhibiting itself as a protein-bound vanadyl ion (VO^{2+}). However, it highlights that the V specie in biological systems depends on redox balance (Aureliano et al., 2022).

Different organisms store and/or use V in metabolic processes. In young adult humans, the average concentration of V present amounts to approximately 1 mg (Rehder, 2017), finding a balance between the quantity excreted and V intake through food (Ścibior et al., 2021). Some of the main sources of exposure to V in the atmosphere are the dust released from the different levels of soil erosion, volcanic emissions, mining, industries, and the combustion of crude oil (Rehder, 2016). The maximum accepted concentration in air is 0.005 mg/m^3, according to the California Office of Environmental Health Hazard Assessment. If a single exposure, the immediate health risk limit value rises to 7 mg of V by intravenous administration and 35 mg/m^3 by inhalation (Rehder, 2012). In the case of oral intake, a permitted dose of 10 mg/kg has been reported (Rehder, 2012).

Vanadium Metabolism

The amounts of V ingested through diet are approximately 15–20 µg/day (Sitprija and Eiam-Ong, 1998). After ingestion, the vanadate ion (VO^{4-}) reaches the gastrointestinal tract. Due to the acid pH of the stomach, the highest percentage of VO^{4-} is converted into VO^{2+}. Meanwhile, due to a slightly alkaline environment of the intestine, VO^{2+} precipitates as insoluble vanadyl hydroxide [$VO(OH)_2$] and is finally excreted in feces (94–98%) (Rehder, 2008, 2013). Kidneys eliminate the excess of V from the bloodstream (Sitprija and Eiam-Ong, 1998). The urinary V level has been established in approximately 12% of the amount ingested (Sitprija and Eiam-Ong, 1998). In the bloodstream, from 80 to 90% of V in its +4 and +5 oxidation state is binding to albumin and transferrin, respectively (Rehder, 2016). Besides, both V^{4+} and V^{5+} can be binding by apo-transferrin and holo-transferrin. Globulins and hemoglobin also can transport vanadium species in low quantities (Treviño et al., 2019).

Vanadium species can be efficiently uptaken by cells through receptor-mediated endocytosis processes. In addition, V species can enter cells through citrate transporters, organic anion transporters, and lactate transporters located at the membrane level (Treviño et al., 2019). Likewise, VO^{2+} can be assimilated by passive diffusion (Sanna et al., 2014) and bind to immunoglobulin G or low molecular weight plasmatic components, such as citrate, lactate, oxalate, and phosphate (Sanna et al., 2014). Meanwhile, V^{5+} ions can ingress cells through sulfate or phosphate channels. Into cells, V^{5+} can be reduced to VO^{2+} by ascorbic acid, cysteine, peptides, and proteins rich in thiol groups (Rehder, 2016).

Finally, it has been reported that V content in adult persons ranges from 100 to 200 µg (Rehder et al., 2017). The 50% is located in the bone, constituting the main long-term reservoir to V because VO^{4-} ion can displace the phosphate from hydroxyapatite [$(Ca_5PO_4)_3$] (Rehder, 2016). The remaining percentage is deposited in organs such as the liver, spleen, and kidney since their participation in detoxifying and excreting harmful substances (De Cremer et al., 2002). Likewise, the brain, lungs, and muscles also store V (De Cremer et al., 2002). V compounds can undergo speciation and redox modifications upon cell recapture, affecting their bioavailability, binding targets, and therapeutic and/or toxic effects (Ścibior et al., 2021).

Vanadium Therapeutic Effects

In the last 15 years, research on the therapeutic properties of V has intensified (Pessoa, 2015). Vanadium salts and compounds have shown potential as an antibacterial, antiviral, antifungal, antiparasitic, antihypercholesterolemic, antidiabetic agent, antiobesity, cardioprotective, neuroprotective, antineoplastic, and inhibition of the aggregation of amyloid β-peptides related to AD (**Figure 3**; He et al., 2020, 2021; Díaz et al., 2021, 2023; Scibior et al., 2021; Aureliano et al., 2022, 2023).

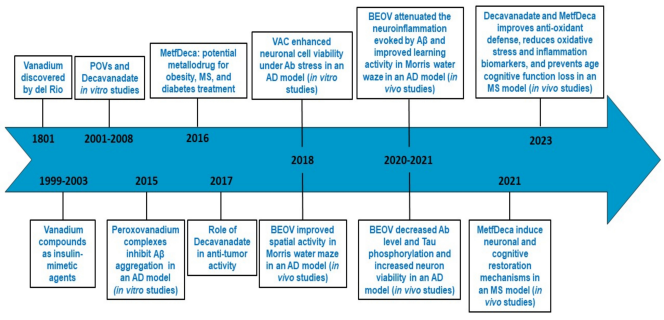

Figure 3 | **Timeline of the first *in vitro* and *in vivo* studies described for Vanadium species in various pathologies, including AD.**
Created with BioRender.com. AD: Alzheimer's disease; Aβ: amyloid-beta; BEOV: bis(ethylmaltolate)oxidovanadium (IV); del Rio: Andrés Manuel del Río; MetfDeca: metformin decavanadate; MS: metabolic syndrome; POVs: polyoxidovanadates; VAC: Vanadyl (IV) acetylacetonate.

It has recently been discovered that V complexes, such as POVs, have shown high efficacy as anticancer agents (Carvalho and Aureliano, 2023). In particular, isopolyoxovanadate decavanadate is related to various biochemical and cellular processes (Aureliano et al., 2022). Likewise, in the study carried out by Carvalho and Aureliano (2023), the action of POVs in cell cycle arrest is highlighted, specifically in lung and breast cancer. The authors note that, for most POVs, cell cycle arrest occurs at the level of the S phase (56%), where DNA is synthesized, while 36% block the G_2/M phase. Although the

studies are limited and the mechanisms of action are not entirely clear, they constitute a potential strategy in the future as antitumor drugs. Similarly, the anticancer properties of V compounds have begun to be used in skin cancer (Amante et al., 2021). Melanoma is the most aggressive type of skin cancer, and its incidence has been increasing alarmingly worldwide (Leonardi et al., 2018). The effects of V on this pathology were carried out in various human melanoma cell lines, such as A375, CN-mel, amelanotic melanoma, and murine cutaneous melanoma B16F10 cells, as well as *in vivo* studies in mice. Among the actions of the V species, the following are described: alterations in cell morphology, apoptosis, cell viability, cell cycle, mitochondrial dysfunction, reactive oxygen species (ROS) production and *in vivo* tumor regression and survival rates. The results indicate that the potency of cellular inhibition depends on the types of cancer cells. In this way, research shows that the applications of V in melanoma are viable, placing it as a possible therapeutic option (Amante et al., 2021).

Besides, *in vitro*, *in vivo*, and clinical studies have shown that pharmacological doses of V (10 to 100 times higher than regular intake) modulate lipid metabolism (stimulating lipogenesis and inhibiting lipolysis), influence the morphology of red blood cells, and promote the glycogen synthesis and glucose oxidation in hepatocytes (Aureliano and Ohlin, 2014). Additionally, V co-participates in the redox balance, as a pro-oxidant molecule, capable of interacting with other oxidants and synergistically improving oxidative stress as well as LPO (Aureliano et al., 2023). This is relevant because ROS affect various molecules of biological importance and induce different pathologies (Juan et al., 2021). There is a correlation between LPO products and an imbalance between the generation and accumulation of ROS that leads to oxidative stress (Aureliano et al., 2023). V compounds can reduce ROS formation through particular mechanisms. For example, the administration of a V complex increased glutathione concentration in the visceral adipose tissue of Wistar chow-fed rats (Francik et al., 2022). On the other hand, treatment with vanadyl sulfate ($VOSO_4$) in diabetic male Swiss albino rats restored the modified levels of oxidative stress markers in skeletal muscle, thus avoiding diabetic complications in these animals (Kurt et al., 2012).

Also, V participation has been described in the thyroid metabolism, bone mineralization, cell storage and transport of Ca^{2+}, and synthesis of secondary transmitters involved in intracellular signal transduction. *In vitro* studies performed in cell-free systems have associated effects of V derivatives on the activity of many enzymes that participate in the phosphorylation and dephosphorylation of kinases and phosphatases (Pessoa et al., 2015). Therefore, V influences carbohydrate and lipid metabolism and plays a specific role in cell proliferation and differentiation processes (Pessoa et al., 2015).

On the other hand, there are a growing number of studies that have demonstrated the therapeutic use of V compounds in neurodegenerative diseases such as AD (He et al., 2021). Although there is no single etiology of AD, it has been reported that LPO and oxidative stress may play an important role in the development of the disease (Aureliano et al., 2023). Recent research shows that vanadyl acetylacetonate improves glucose metabolism and energy in neurons; however, it fails to decrease the formation of β-amyloid plaques (Dong et al., 2019). Likewise, it was reported that two peroxovanadium complexes inhibit fibril formation. On the other hand, He et al. (2015) demonstrated that peroxovanadium complexes increased cell viability, probably due to their ability to reduce methionine residues. They also found that the bis(2-ethyl-3-hydroxy-4-pyronadium)oxovanadium(IV) (BEOV) complex improved AD symptoms through various mechanisms, including inhibition of Aβ aggregate formation (He et al., 2021). The previous results place V as a possible treatment for neurodegenerative diseases.

Vanadium Antidiabetic Function

Antidiabetic V potential has been widely reported (Crans et al., 2019; Aureliano et al., 2023). As previously mentioned, diabetes is a metabolic disease featured by hyperglycemia and impaired insulin action, whose etiology is multifactorial (Sapra and Bhandari, 2022). The V therapeutic effect is attributable mainly to vanadate species $(H_2VO_4)^-$, which have structural and electronic similarities to phosphate (Crans et al., 2019). Vanadate can adopt a trigonal bipyramidal geometry stable enough to mimic the phosphate transition state, thereby inhibiting the biological activity of the involved enzymes (Pessoa et al., 2015; Crans et al., 2019; Kowalski et al., 2020). Since most enzymes inhibited by $(H_2VO_4)^-$ participate in critical intracellular signaling mechanisms, V is considered a transition element with far-reaching therapeutic applications (Kowalski et al., 2020). For this reason, V organic and inorganic salts and compounds have been widely studied in treating diabetes. In animal models of diabetes streptozotocin-induced, compounds such as bis(2-ethyl-3-hydroxy-4-pyronadium)oxovanadium(IV) (BEOV) and bis(3-hydroxy-2-methyl-4-pyronadium)oxovanadium(IV) (BMOV) have shown better antidiabetic properties than vanadyl sulfate treatment (Hussain et al., 2016).

The hypoglycemic capacity of V species has been evaluated in animal models that present similar characteristics to those observed in T1D and T2D (Treviño et al., 2019). In T1D rat models, V compounds and inorganic V salts have been evaluated. Vanadium coordination compounds (III-, IV-, and V-chlorodipicolinate (Vdipic-Cl) or inorganic salts of V (vanadyl sulfate or sodium metavanadate) were administered orally through water for 28 days, showed hyperglycemic effects and improved glucose tolerance (Xie et al., 2014). Regarding T2D, V salts, and V compounds were administered in animal models: db/db mice, sucrose-fed rats, and fa/fa Zucker rats. The results showed improvement in the glycogen synthase activity in diabetes models, whereas, in the non-diabetic controls, there were no alterations in the enzymatic activities (Treviño and Díaz, 2020). By seven weeks, in the STZ model, the BMOV treatment did not improve insulin-stimulated glycogen synthase activity in skeletal muscle. In contrast, a similar treatment enhanced the enzyme activity in the fa/fa Zucker rat model (Treviño and Díaz, 2020).

The properties of V have also been tested in diabetic humans. In patients with T1D, oral administration of sodium metavanadate and vanadyl sulfate at 50–125 mg/day for 2 to 4 weeks improved fasting plasma glucose levels and daily insulin requirements. Similar amounts were administered to T2D patients, ameliorating insulin sensitivity and reducing fasting plasma glucose and HbA1c levels (Ahmadi-Eslamloo et al., 2018). Other investigations demonstrated that administration of vanadyl sulfate at a dose of 150 mg/day for six weeks increased the fractional rate of glycogen synthase by 1.5 times. However, it does not alter basal or insulin-stimulated glycogen synthase activity. The evidence suggests that V could activate the kinases involved in glycogen synthesis without insulin stimulation. Besides that, treatment with V reduced the overexpression of the main gluconeogenic enzymes, PEPCK and glucose-6-phosphatase (Oliveri et al., 2012).

Therefore, in animal models and diabetic humans, the V mechanism on glucose regulation seems to be associated with the recovery of glycogen synthesis and improving glucose uptake and metabolism (Treviño et al., 2019). Additionally, it has been proposed that the hypoglycemic effect of V could be due to the inhibition of tyrosine phosphatase enzymes. This would allow insulin signaling pathways to activate and translocate glucose transporters to the plasma membrane (Gonzalez-Villalba et al., 2016; Fontaine et al., 2020).

On the other hand, hyperglycemia has been associated with an increase in oxidative stress and LPO mediated by free radicals in patients with T2D (Likidlilid et al., 2010), which leads to a deterioration in their quality of life. Various studies have shown that V species contribute to the improvement of the activity of antioxidant enzymes and the regulation of increased levels of LPO markers (Aureliano et al., 2023). This suggests that treatment with V compounds could decrease oxidative stress in diabetic patients as well as improve metabolic function.

It is important to point out that the inorganic salts of V present very low oral bioavailability compared to the V complexes, which extend their half-life in the body. Therefore, it has allowed the study of a great structural diversity of V species, resulting in different biological and bioprocessing actions (Treviño and Díaz, 2020). In this sense, using the so-called polyoxidovanadates, such as decavanadate and chimeric derivates, in treating diabetes has been evaluated.

Antidiabetic Application of the Decavanadates

Decavanadate $[V_{10}O_{28}]^{-6}$ is a relatively stable complex in an acidic pH range (Gumerova and Rompel, 2020). Structurally, it contains ten V atoms compactly assembled with unit cell dimensions of 8.3 Å × 7.7 Å × 5.4 Å, where V^{5+} ions occupy the octahedral interstices in the ten units $[VO_6]$ (Aureliano et al., 2022). Decavanadate presents a particular absorption between 600 and 400 nm, which gives it a bright yellow or orange color that can be detected by means of UV/Vis spectroscopy (Aureliano and Ohlin, 2014). Decavanadate has a serum half-life (pH = 7, NaCl 0.9%) of 15 hours at room temperature (Ramos et al., 2006). However, at 37°C and pH 7.4 in mitochondrial respiration buffer (sucrose, 0.2 M; KH_2PO_4, 5 mM; KCl, 10 mM; $MgCl_2$, 5 mM; Tris-HCl, 10 mM; pyruvate, 5 mM; malate, 0.5 mM), a 5 mM solution of decavanadate exhibits a half-life of only 3 hours (Crans, 1994).

Also, decavanadate interacts with several biologically important proteins, including NTPDases, tyrosine kinases, phosphatases, myosin, actin, TRPM4 channel, albumin, transferrin, and glycosidases, to name a few examples (Fraqueza et al., 2019; Aureliano et al., 2022). The interaction of decavanadate with certain proteins has been shown to modify its stability. For example, the presence of actin and Ca^{2+}-ATPase significantly improves (5 and 3 times) the stability of decavanadate (Ramos et al., 2006). Likewise, the decomposition half-life of decavanadate increases from 5–27 hours in the presence of G-actin (monomeric form of actin) for 5–18 hours in the presence of sarcoplasmic reticulum vesicles at 22°C and pH 7.5 (Tris, 2 mM; $CaCl_2$, 0.2 mM; KCl, 100 mM; $MgCl_2$, 2 mM). On the other hand, the addition of ATP to the medium decreases the half-life of decavanadate from 27 to 10 hours, while in the presence of phosphatidylcholine or myosin liposomes, stability does not show changes (Gumerova and Rompel, 2020; Sciortino et al., 2021).

Therefore, it is of utmost importance to consider the different biological environments to attribute the effects that decavanadate can exert. For this, the stability and speciation of the compounds V in the presence of factors such as pH, ionic strength, countercations, buffer composition, aging time, temperature, and the presence of biomolecules and specific enzymatic substrates, will constitute a fundamental tool (Gumerova and Rompel, 2020; Aureliano et al., 2022, 2023).

Notably, among vanadate oligomers, decavanadate has the highest biological impact. Due to its stability under physiological conditions, it is thought to not completely disintegrate into other vanadate oligomers without first ameliorating, *in vivo*, oxidative stress markers, lipid peroxidation, and enzymatic activity (Aureliano and Ohlin, 2014). Therefore, decavanadate has a more significant therapeutic impact than vanadate salts by influencing different biological processes, such as; the regulation of the muscle

contraction/relaxation mechanism, after modulating the activity of actin and myosin, as well as pumps, ion channels, metabotropic receptors, and signaling cascades (Aureliano, 2017; Aureliano et al., 2022, 2023).

In several tissues, decavanadate improves antioxidative defense mainly via NRF2, increasing catalase activity and glutathione content (Aureliano, 2017, 2022; Treviño and González-Vergara, 2019). Likewise, *in vivo*, decavanadate administration has shown effects on mitochondrial activity and mitochondrial antioxidant enzymes (Aureliano et al., 2022). Recently, the biological role of decavanadate as an insulin mimetic or insulin enhancer has been discussed in STZ-induced diabetic rat models (Pereira et al., 2009) and in diabetic murine models induced by hypercaloric diets or with alloxan (Treviño et al., 2015, 2016, 2018). Decavanadate administration showed improvements in serum glucose levels and glucose tolerance (Bâlici et al., 2015; Treviño et al., 2016). Decavanadate also presented greater efficacy in inducing glucose uptake in rat adipocytes (Pereira et al., 2009). These results suggest that decavanadate not only potentiates the effect of insulin but also promotes insulin synthesis (Treviño et al., 2019; Ścibior et al., 2021). Although the precise mechanism of V compounds has not yet been elucidated for T1D and T2D, it is believed that the insulin-enhancing effect could be due to protein tyrosinase phosphatase inhibition. This protein promotes dephosphorylation of the insulin receptor, thereby turning off insulin signaling (Aureliano et al., 2022).

However, due to its high anionic charge, it is necessary to stabilize decavanadate employing counterions (Aureliano et al., 2022). In particular, one of the biologically important molecules that have been successfully combined with decavanadate for the treatment of diabetes is metformin.

Metformin is a molecule that can form salts and coordination compounds, acting as a monocation, dication, neutral, or anion (Zhu et al., 2002). It has been informed that hypoglycemic drugs such as metformin, indicated for controlling diabetes, can be prescribed to regulate the neurodegenerative metabolic process (Moran et al., 2019b; Muñoz-Arenas et al., 2020; Naseri et al., 2022). The improvement in physiological functioning could be due to AMPK activation, the master energetic sensor, and the mitochondria biogenesis modulator (Markowicz-Piasecka et al., 2017). In hepatocytes, metformin activates AMPK, thereby decreasing acetyl-CoA carboxylase activity and increasing fatty acid oxidation, regulating lipogenesis and gluconeogenesis (Zhou et al., 2015). Likewise, it is known that metformin is capable of rapidly crossing the blood-brain barrier after its oral administration (Labuzek et al., 2010), which would allow it to act as a neuroprotective agent in the CNS (Ou et al., 2018). Furthermore, research indicates that metformin triggers autophagy, prevents oxidative stress, reduces neuroinflammation, and plays a role in neural repair in a wide range of CNS diseases (Du et al., 2022). Metformin ameliorates AD-associated neuropathological changes and decreases cognitive impairment in differentiated N2A cells in the brains of db/db diabetic mice and individuals with TD2 (Zhou et al., 2015). These findings promote metformin as an optimal candidate for neurodegeneration and AD risk reduction.

However, the neuroprotective activity of metformin is still not fully known since it is prescribed based on the level of hypoglycemia and IR without considering the neurodegenerative process or its mechanisms of action (Li et al., 2019). Recent investigations have shown that the combination of hypoglycemic drugs such as metformin and decavanadate (metformin decavanadate [MetfDeca]) recover biochemical metabolism, serum lipid, and glucose levels (Treviño et al., 2015). Glycemia restoration augments insulin sensitivity in tissues and normalizes serum lipids in animal models with T1D, T2D, and MS (Treviño et al., 2018). Besides, a study carried out by Yanardag et al. (2006) demonstrated that oxidative stress in the liver and muscle tissues of diabetic rats induced by alloxane presented a significant improvement after treatment with MetfDeca. Similarly, increased levels of LPO markers in diabetic animals were restored after MetfDeca treatment. Thus, MetfDeca has been proposed as a potential drug for treating diabetes and related disorders.

MetfDeca as a Treatment for Neurodegenerative Diseases

In neurodegenerative diseases, the percentage of brain neurons decreases, and synaptic signaling is disrupted. Senescent and aged neurons cannot maintain proteins in their correct folded state. Consequently, a series of events is triggered, such as disturbance of protein homeostasis, DNA methylation, oxidative stress, mitochondrial and endoplasmic reticular injury, inflammation, and hormonal signal transduction dysfunction. Together, these favor the development of neurodegenerative diseases (Zhang et al., 2022). Diabetes and metabolic diseases develop many of these risk factors for neurodegenerative diseases. The pathophysiological mechanisms in these conditions are complex and possibly overlap, primarily through vascular, neurodegenerative pathways, or both (Moran et al., 2019b). In addition, obesity, a sedentary lifestyle, and aging, associated with impaired insulin signaling and IR, accelerate neurodegenerative conditions (Vieira et al., 2018).

Insulin regulates the brain's nutrient balance and cognitive, neuroregulatory, neurotrophic, and neuroprotective processes. As neurodegenerative diseases progress, the insulin gene and the expression of IRS decrease significantly, establishing brain IR (Rivera et al., 2005; Sędzikowska and Szablewski, 2021). Therefore, it has been suggested that IR could be linked to the development of neurodegenerative disorders. Due to the little progress in the development of effective treatments for neurodegenerative diseases, currently, research has focused not only on novel therapies but also on exploring the use of commonly used drugs that are prescribed for other conditions to reduce the incidence and prevalence of neurodegenerative pathologies (Moran et al., 2019a). In that sense, polyoxidovanadates, particularly MetfDeca, a chimeric compound, are viable options.

Recent investigations have reported that the administration of MetfDeca in rats with MS improved object recognition memory and decreased brain senescence biomarkers such as oxidative stress and neuroinflammation in the hippocampus. Besides, MetfDeca increased the density and length of the dendritic spines of the hippocampus of rats with MS (Díaz et al., 2021). These results demonstrate that MetfDeca exhibits a potential therapeutic effect in MS by inducing neuronal and cognitive restoration mechanisms. Likewise, in aging rats (20 months), MetfDeca treatment improved short-term and long-term recognition memory and reactive astrogliosis. Even redox balance and pro-inflammatory cytokines (interleukin-1β and tumor necrosis factor-α) decreased at similar concentrations to young adult control (Díaz et al., 2023). However, little has been reported in the research framework on the effect of MetfDeca on neurodegenerative diseases and aging, but MetfDeca could be a pharmacological option for treating these issues.

Conclusion and Future Perspectives

Aging is a physiological and progressive phenomenon in the life cycle of all living beings. It is characterized by a series of alterations in molecular pathways that result in the loss of organism functionality and trigger degenerative processes. The brain is one of the particularly affected organs and has been linked to an increased risk of neurodegenerative diseases, including AD. In particular, it has been observed that the metabolic stress and neuroinflammation that causes neurodegeneration in AD are similar to the processes observed in the peripheral tissues of diabetic models and patients. In this sense, it is understandable to consider the use of drugs with antidiabetic potential to treat neurodegenerative disorders and aging.

Recent studies and clinical trials *in vivo* and *in vitro* show that POVs and V compounds benefit metabolic and cellular processes related to the progression of pathologies associated with aging and the development of neurodegenerative diseases. Animal models have shown positive results in lowering blood glucose and exerting anti-inflammatory and antioxidant properties. In addition, the combination of POVs with hypoglycemic drugs, such as metformin, results in MetfDeca, which is an effective option to modulate or minimize the negative effect of brain aging and neurodegenerative diseases.

However, the neuroprotective role of this compound has not yet been fully addressed. Therefore, a larger number of studies are required to evaluate the mechanisms of action through which MetfDeca exerts its neuroprotective activity with minimal adverse effects. Speciation studies of V compounds should be included to elucidate direct and indirect effects that might exist during the study, anticipating early alterations in cell metabolism induced by POVs, including MetfDeca. Likewise, information related to the interaction of these compounds with other biological systems is relevant to these considerations, as well as their clinical application in the treatment of neurodegenerative diseases and aging.

Therefore, interdisciplinary studies and a greater amount of preclinical work will be required to establish MetfDeca as an effective and safe pharmacological option to reduce neuronal damage caused by metabolic alterations associated with the development of neurodegenerative disorders and aging, which affect a large part of the world population. Despite this, the results observed *in vivo* and *in vitro* demonstrate the potential of MetfDeca as a therapeutic alternative, promoting interest in the development of a greater number of investigations and a deeper understanding of its role in various pathologies.

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