Association of Parkinson's Disease and Exposure to Aluminium and Other Heavy Metals

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Abstract:

Parkinson's disease (PD) is a prevalent neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, accompanied by motor symptoms such as bradykinesia, rigidity, and tremors. While its etiology is multifactorial, recent research highlights the role of heavy metal exposure, including aluminium, mercury, manganese, and lead, in the pathogenesis of PD. These metals, through mechanisms such as oxidative stress, mitochondrial dysfunction, and disruption of the blood-brain barrier, exacerbate neurotoxicity and neuronal degeneration.

Oxidative stress emerges as a pivotal factor in PD, driven by an imbalance between reactive oxygen species (ROS) and antioxidants. Heavy metals amplify this imbalance, inducing cellular damage that parallels natural aging processes. Aluminium, in particular, has garnered attention due to its ubiquitous presence in the environment and significant neurotoxic potential. Exposure occurs through contaminated water, food, occupational hazards, and consumer products. Aluminium disrupts neuronal function by enhancing oxidative stress, impairing calcium signaling, and inhibiting DNA synthesis. It accumulates in brain regions such as the hippocampus and cortex, promoting neuroinflammation and accelerating neurodegeneration.

Epidemiological and experimental studies underscore the synergistic toxicity of metal mixtures, suggesting a compounded risk in individuals exposed to multiple sources. Chelation therapy shows promise in mitigating heavy metal-induced neurotoxicity but faces challenges in reversing chronic exposure damage. Investigations into environmental exposure reduction strategies, such as consuming silicon-rich mineral water to limit aluminium absorption, hold preventive potential.

Understanding the intricate relationship between heavy metals and PD is crucial for developing targeted interventions. Further research is needed to elucidate specific molecular pathways and refine therapeutic approaches to mitigate environmental risk factors.

Keywords: Parkinson's disease, Heavy metals, Oxidative stress, Neurodegeneration, Environmental exposure

Sažetak:

Povezanost Parkinsonove bolesti i izloženosti aluminiju i drugim teškim metalima

Parkinsonova bolest (PB) neurodegenerativni je poremećaj karakteriziran gubitkom dopaminergičkih neurona u substanciji nigri, praćen motoričkim simptomima kao što su bradikinezija, rigidnost i drhtanje. Iako je njegova etiologija multifaktorska, novija istraživanja naglašavaju ulogu izloženosti teškim metalima, uključujući aluminij, živu, mangan i olovo, u patogenezi PB-a. Ovi metali, putem mehanizama kao što su oksidativni stres, mitohondrijska disfunkcija i poremećaj krvno-moždane barijere, pogoršavaju neurotoksičnost i degeneraciju neurona.

Oksidativni stres pojavljuje se kao ključni čimbenik u PB-u, potaknut neravnotežom između reak-

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tivnih vrsta kisika i antioksidansa. Teški metali pojačavaju ovu neravnotežu, izazivajući oštećenje stanica koje je paralelno s prirodnim procesima starenja. Aluminij je posebno privukao pozornost zbog svoje sveprisutne prisutnosti u okolišu i značajnog neurotoksičnog potencijala. Do izloženosti dolazi putem kontaminirane vode, hrane, profesionalnih opasnosti i proizvoda široke potrošnje. Aluminij remeti funkciju neurona pojačavanjem oksidativnog stresa, slabljenjem signalizacije kalcija i inhibicijom sinteze DNA. Akumulira se u regijama mozga kao što su hipokampus i korteks, potičući neuroupalu i ubrzavajući neurodegeneraciju. Epidemiološke i eksperimentalne studije naglašavaju sinergijsku toksičnost mješavina metala, što ukazuje na složeni rizik kod pojedinaca izloženih više izvora. Kelacijska terapija obećava u ublažavanju neurotoksičnosti izazvane teškim metalima, ali se suočava s izazovima u poništavanju oštećenja od kronične izloženosti. Istraživanja strategija smanjenja izloženosti okoliša, poput konzumiranja mineralne vode bogate silicijem kako bi se ograničila apsorpcija aluminija, imaju preventivni potencijal. Razumijevanje zamršenog odnosa između teških metala i PB-a ključno je za razvoj ciljanih intervencija. Potrebna su daljnja istraživanja kako bi se razjasnili specifični molekularni putovi i poboljšali terapijski pristupi za ublažavanje čimbenika rizika iz okoliša.

Ključne riječi: Parkinsonova bolest, teški metali, oksidativni stres, neurodegeneracija, izloženost okolišu

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases. The prevalence of the disease has been on the rise over the past four decades and is expected to increase even further given that the main reason for that is the ageing of the population[1]. According to an article from The World Health Organization, the prevalence of PD has doubled in the past 25 years. Global estimates in 2019 showed over 8.5 million individuals with PD—a study from 2018. By Parkinson's Foundation found that more than 10 million people worldwide are living with PD. In the U.S. that number came to nearly one million, with around 90,000 people diagnosed with PD each year[2]. They also concluded that men are 1.5 times more likely to have Parkinson's disease than women. Although specific and singular causes for developing the disease are not yet known, the consequences of the disease are mostly clear. The core problem is the degeneration of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies in dopaminergic neurons. With the progression of the disease and loss of neurons in the basal ganglia, typical motor symptoms like bradykinesia, rigidity and tremor occur[3]. There are a few crucial molecular changes that lead to neuronal loss, such as misfolding and aggregation of α-synuclein, dysfunction of mitochondria and dysfunction of the proteasome system. These changes are also associated with oxidative stress and neuroinflammation and when cells are exposed to such stressors and changes for an extended period irreversible damage occurs[4]. There are a lot of potential causes for such changes and possible stressors such as genetic mutations, exogenous toxins, inflammation or a combination of all the above. The focus of this review is on the exogenous toxins, more specifically the influence of heavy metals on neurodegeneration and Parkinson's disease[5,6].

Heavy metal exposure

Heavy metals are a group of chemical elements that have a relatively high atomic number and atomic density. They are divided into essential and nonessential groups. Crucial heavy metals like iron, copper, and zinc are found in traces and are necessary for living beings as they act like cofactors for various enzymes. Nonessential heavy metals such as mercury, aluminium, and lead do not have any role in living organisms and when they find their way into the organism they have a toxic effect [7]. Heavy metals are found in traces in the soil and water but in recent decades they have become a greater problem given the increasing exposure in many different fields such as industry, agriculture, and mining[8]. Metal particles can enter the human body through various routes such as inhalation, ingestion or injection and after entering the blood circulation they can impact various organs. The brain-gut axis also has an important role in how heavy metals cause neurotoxicity through microbiome alterations[9]. Because of the small size of the particles, the brain blood barrier is not impenetrable to them and as they cross it heavy metals have a severe effect on neuronal cells as they can't regenerate. The blood-brain barrier can also be damaged by metal accumulation which opens up a way for further damage and influx of other undesirable particles[10]. Toxicity from heavy metals also comes from cellular mechanisms such as oxidative stress formation, damage to the mitochondria and DNA formation and others. Every organ is affected that way but the nervous system seems to be most sensitive to heavy metal toxicity and it is known that also the accumulation of metals can cause pathologic changes[11].

Oxidative stress mechanism in neurodegeneration

The mechanism of oxidative stress is the most known way the heavy metals cause toxicity and it is one of the crucial points in

Parkinson's pathogenesis[12]. Oxidative stress describes an imbalance between oxidative species such as reactive oxygen species (ROS) and reactive nitrogen species (NOS) and antioxidants. The balance between the two can be disrupted by the deficiency of antioxidants or by the prevalence of oxidative species. That state of imbalance is responsible for cellular damage by affecting membranes, proteins and nucleic acids all of which eventually lead to cell death[13]. Heavy metals worsen this imbalance by interfering with redox processes and thus more reactive molecules are produced [jomova]. The overall result of this accumulation of oxidative stress is reduced cell stability and their function and in the end, the overall number of cells is diminished. A similar process happens during aging where cells slowly and constantly degenerate over time. One of the key elements in the ageing process is senescence which describes a stop in the cell cycle after exposure to a significant amount of stress as a result senescence cells can not divide anymore but are not dead. Such cells produce and secrete immune-related molecules like inflammatory cytokines, growth factors, interleukins and degradable enzymes. Because of that, senescence cells significantly affect the surrounding healthy cells and cause a state of inflammation and they are more sensitive to ROS effects. On the other hand, a great amount of oxidative stress and ROS cause cellular senescence which explains how exposure to oxidative stress can cause neuronal degeneration similar to the ageing process which is a crucial factor in Alzheimer's and Parkinson's disease. Ageing, oxidative stress and senescence cells are also crucial elements in a lot of other chronic diseases such as cardiovascular, metabolic and cancer[14-16].

Heavy metals in Parkinson's disease

Heavy metals lead to neuronal damage by several mechanisms as previously mentioned, those are accumulation of metal particles by passing through the BBB and damaging it and induction of the oxidative stress effects. Heavy metals are considered one of the most common causes of neurotoxicity and some metals like Fe, Hg, Mn, Pb and Al are often reported to cause neurological and behavioural changes and high levels of those metals can induce injuries of dopaminergic neurons and parkinsonism[17]. Iron can cause damage in two different ways, one is by accumulation in the substantia nigra which causes neurotoxicity and the other is by increasing the levels of ROS through the Fenton reaction so excess levels of iron can lead to neurotoxicity and Parkinson's disease [18]. Another reason why iron can be connected to pd is the aggregation of alfa-synuclein given that iron can bind with alfa-synuclein in both ion states so high levels of iron can induce the aggregation which is a key element of PD. In the analysis of brain tissue affected with Parkinson's disease elevated levels of iron were found along with other heavy metals like aluminium and zinc, but iron levels in substantia nigra were twice higher than control levels[19]. Mercury is a heavy metal which enters the CNS with protein carriers which makes the brain specifically vulnerable to mercury and it has been connected with the incidence of Parkinson's, moreover, the symptoms and consequences of mercury poisoning are very similar to Parkinson's. High levels of mercury in the blood of the patients with Parkinson's were found. Dental amalgams and the consumption of tuna fish are significant sources of mercury and after a comparison of the incidence of Parkinson's disease, a connection between the two was evident. Symptoms.[20-22]

Manganese poisoning also has Parkinson-like symptoms and Mg exposure has been linked to Parkinsonism in several studies[17,19]. Oxidative stress is one of the crucial points in the etiopathogenesis of Parkinson's disease and the loss of the antioxidant glutathione, increased lipid peroxidation and nitrated and oxidised proteins found in dopaminergic parts of the brain prove the effect of oxidative stress in that area[12]. One study has also found decreased levels of serum lipid hydroperoxide and nitric oxide in patients with Parkinson's, which can indicate that an oxidative process is happening[23]. Most heavy metals can be associated with Parkinson's disease because cause an imbalance of oxidants and antioxidants leading to the accumulation of oxidative stress which damages dopaminergic neurons[24].

People are more often exposed to mixtures of metals than individual metals, such exposure happens daily through food contamination and occupational hazards which is why it is useful to observe the connection between Parkinson's disease and exposure to metal mixtures. Metal mixtures can be even more toxic than individual metals because of the synergistic actions of metals[12,24]. One epidemiological study even proved a positive correlation between acid rain and Parkinson's disease because acid rain mobilises the metals from soil and pipes into drinking water[16]. The study continued to investigate lead service lines which connect households to water sources and they found a correlation between the number of installed lead service lines and the incidence of Parkinson's in the US, indicating the role of lead in Parkinson's disease[25]. Chelation therapy is a standard course of treatment for many metal intoxications, it uses a chelating agent which binds the toxic metal and removes it from the body. Chelation therapy can therefore represent a valuable course of research for treating metal-induced Parkinson's disease[26]. When chelation therapy was used for mercury and manganese-induced parkinsonism it led to significant improvements (bjorklund). One of the problems in using this method is after chronic exposure to metals because of the accumulation throughout the body and it is a challenge to find a stable and non-toxic chelating agent[26].

Aluminium

Aluminum is the third most abundant metal on Earth. It is a common element found in large amounts in the earth's crust, thus its primary natural sources are rocks such as bauxite, silicates, and cryolite. Aluminum is rather unreactive as it is quickly

oxidized in air[27]. Aluminum is widely distributed throughout the environment and eluted from soils by acid rain[28]. The growing incidence of acidic rain has led to greater solubilization of aluminium salts from their insoluble form in rocks. This has led to an elevated Aluminum content in many water reserves used for residential supply. Thus, human exposure to more soluble forms of Aluminum in water and foodstuffs has grown[29]. In addition to significant amounts in soil and water, it is often associated with oxygen molecules (Aluminum oxides) or silicon[30].

Al-containing materials have a widespread presence in the environment, and when ingested by humans, some Al salts can reach the brain. Brief exposure to high levels of Al can lead to clear evidence of neurological damage[29]. Aluminum is widely used for the production of cosmetics, food, kitchen utensils and pharmacological agents such as antacids, antiperspirants and vaccines; thus, humans can be exposed to this metal during the production and use of several products. Cases of occupational exposure such as use as a leather tanning agent, a component of hemodialysis solution and drinking water after purification with Aluminum coagulants, have also been reported. Residual Al in drinking water was demonstrated as one of the main sources of human prolonged exposure to this metal[30]. Administration of amounts of Aluminium to experimental animals in the drinking water that correspond to levels found in some residential water sources can increase inflammatory activity in the brain and are associated with neuropathological changes[29]. In 1988, in Camelford drinking water was accidentally contaminated by Al, and more than 20,000 people were exposed to high levels of Aluminium for several days. A 10-year-old follow-up study reported that residents who were exposed to Al exhibited various symptoms related to cerebral impairment (such as inability to concentrate, short-term memory loss, and poor psychomotor performance. Furthermore, an increased Al level was observed in the brains of some symptomatic residents[28]. Despite its widespread distribution throughout the environment, Aluminium is not essential for life. In contrast, it is a well-established neurotoxin. The main penetration routes for Aluminium into the human organism are oral intake and inhalation. The daily intake of Aluminium is estimated to be 10-20 mg/day. Food is considered to be a primary source of Aluminium in humans, constituting about 50% of Aluminium's Tolerable Weekly Intake (TWI), with vegetables contributing to the most Aluminium exposure. In general, the Aluminium levels in most foods are low and vary within a wide range. Contamination from food additives such as baking powder or cooking utensils accounts for a considerable part of Aluminium intake. The use of Aluminium utensils was estimated to increase the Aluminium intake by approximately 2 mg/day. Drinking water usually contributes to less than 5% of the total oral exposure to Aluminium. Aluminium content in drinking water is a sum of Aluminium present in all natural waters and the one coming from Aluminium salts used for water treatment processes[31]. The leading Aluminium absorption site for the general population is the digestive tract. The absorption rate of Aluminium by the gastrointestinal tract is low and widely varies. This amount is influenced by various factors including individual differences, age, pH, stomach contents, chemical speciation of Aluminium, and coexisting substances. The rate of Aluminium absorption is increased in older people, patients with Down's syndrome, and patients with AD.

Once it is absorbed from the GIT, Aluminium rapidly appears in the blood, and approximately 80% of it is transported by binding to transferrin, a Fe transporter protein, while the remaining Aluminium binds to albumin and citrate[28].

Respiratory absorption of Aluminium is important, although it is difficult to estimate. Aspired Aluminium, which is available mostly for occupationally exposed populations, for instance, during mining and processing of Aluminium ores, welding and cutting, could be absorbed into the bloodstream either directly through the lung tissue and respiratory epithelium of the nasal cavity or enter the gastrointestinal tract via mucociliary clearance and swallowing. The nasal cavity also contains the olfactory epithelium, which makes up the direct pathway for Al into the brain[31]. The cohort study from 2021. estimated association of aluminium dust exposure and risk of neurodegenerative diseases in mining workers from Ontario. The study found that exposure to McIntyre Powder, which is an aluminium powder formulation used for prophylaxis against silicosis in mining workers, was associated with an elevated incidence rate of PD and the rate of PD was increased with prolonged exposure. Al is excreted from the body through numerous routes, depending on whether it has been absorbed into the bloodstream or where it had been deposited in the organism. The absorbed fraction is eliminated in 95% through the kidneys. Thus, high Al levels can be observed in patients with renal failure or kidney disease. The unabsorbed Al located in the GIT is excreted via the faeces. Other possible routes of Al elimination comprise the skin, hair, sebum, nails, sweat, semen, milk, and bile. As for the remaining Al, the larger part of it accumulates in the bones, while a small, but considerable amount can cross the blood-brain barrier. The mechanism of how Al reaches the brain is not fully understood. One of the possibilities is it hijacks physiological transportation and absorption mechanisms. As mentioned before, the major fraction of Al after absorption is bound by serum transferrin (Tf). As such, by using transferrin receptor (TfR)-mediated endocytosis Al could be transported through the BBB. Most of the remaining Al circulates as Al citrate, which is much more prominent in cerebrospinal fluid (CSF). In addition, it was demonstrated that some blood vessels display a greater affinity for Al accumulation than others, such as the posterior cerebral artery that supplies the hippocampus. Besides the hippocampal area, Al is mostly deposited in the cerebellum and cortex[31]. Additionally, Al can probably reach the brain directly through the continuity of the

olfactory epithelium, the olfactory nerve, the olfactory bulb and the choroid plexuses[31]. Some factors, such as the increase of the blood-brain barrier permeability, citric acid, parathyroid hormone, and vitamin D, can promote aluminium to enter the brain. The clearance of aluminum from the brain is slower than in other organs and it has a wide range of biological effects. Al cations and their compounds can disrupt crucial cell functions and processes. Thus, the effects of exposure to Al are visible on a molecular and systemic level[31].

Specific mechanisms of aluminium toxicity are not yet known but it is presumed that the damage happens through oxidative stress and inhibition of DNA synthesis. It can alter hippocampal calcium signal pathways that are essential for neuronal plasticity and memory, in addition to generating oxidative stress and binding to negatively charged membrane structures in neurons. Aluminium neurotoxicity, which affects the production of the neurotransmitter acetylcholine, is particularly harmful to cholinergic neurons. There had been reports of neurotoxic consequences such as disorientation, memory issues, and dementia from dialysis patients who had been exposed to aluminium salts through dialysate. Plasma and brain tissue samples from those patients showed higher levels of aluminium and it was concluded that aluminium salts were the cause of said symptoms. Several studies on animals such as zebrafish and rats offer interesting insight into aluminium neurotoxicity. In the study from 2022 adult zebrafish were exposed to aluminium and the results showed the alteration of histology of cerebral tissue, neurodegeneration and demyelination. Aluminium exposure also affected the expression of marker genes involved in Parkinsonism[33].

In the study from 2022 learning and memorization in rats were observed as they were exposed to aluminium, the results showed impairment in learning and memory which was even more evident after increasing the dose of aluminium[34]. In another study conducted on rats in 2016, the effect of aluminium on mitochondrial bioenergetics was described and the capacity of aluminium to promote oxidative stress in the brain was highlighted[35]. Another animal study investigated the effect of induced dementia due to low doses of aluminium chloride (AlCl3) in the rotenone model of Parkinson's disease. The results indicated the involvement of oxidative stress in the neurotoxicity caused by either AlCl3 or rotenone and showed that the motor, behavioural and memory deficits induced by rotenone in mice were increased by the concomitant administration of a low dose of AlCl3. This suggests that increased intake of this metal is likely to have adverse effects on motor symptomatology and possibly the response to treatment in subjects with idiopathic Parkinson's disease. Furthermore, excessive levels of aluminium were proven to cause dopaminergic injury. The simplest way of explaining much of the research on Al neurotoxicity is the idea that Al can accelerate the development of the inflammatory changes that characterize the normally ageing brain[29]. In this day and age, we are not able to completely avoid environmental exposure to aluminium. Considering there is still not any proven requirement for aluminium in any living organism there isn't a reason not to reduce our everyday exposure. This could be achieved by using nature's way of avoiding biologically available aluminium, as regular consumption of silicon-rich mineral waters both reduces gastrointestinal uptake of aluminium and facilitates our urinary excretion of systemic aluminium[36].

Conclusion:

The evidence strongly implicates heavy metals, particularly aluminium, mercury, manganese, and lead, in the pathogenesis of Parkinson's disease (PD). These metals contribute to neurodegeneration through mechanisms such as oxidative stress, disruption of mitochondrial function, and damage to the blood-brain barrier, ultimately exacerbating neuronal damage and PD progression. Aluminium, due to its widespread environmental presence and neurotoxic properties, emerges as a significant contributor to PD pathology. Its ability to accumulate in brain regions such as the hippocampus and substantia nigra underscores its role in neuroinflammation and oxidative damage. The synergistic effects of metal mixtures present an additional risk, emphasizing the importance of considering cumulative environmental exposures. Epidemiological studies linking acid rain, contaminated drinking water, and occupational hazards to increased PD incidence further substantiate these findings. Chelation therapy offers a potential avenue for treatment by reducing metal-induced toxicity; however, its efficacy in reversing chronic exposure remains limited. Preventative strategies, such as reducing exposure to environmental sources of heavy metals and utilizing methods to minimize their absorption, such as consuming silicon-rich mineral water, may help mitigate risks. Further research is essential to better understand the molecular mechanisms underlying heavy metal-induced neurodegeneration and to develop targeted interventions. Reducing environmental exposure and exploring advanced therapeutic approaches could significantly alleviate the burden of PD associated with heavy metal toxicity.[37-41]

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