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Focused review

Iron and other metals in the pathogenesis of Parkinson's disease: Toxic effects and possible detoxification

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ABSTRACT

Of the documented cases of Parkinson's disease (PD), about 10% have a genetic background. The remaining cases of PD have unknown etiology. Thus, environmental factors appear to play a pathogenic role in most of the PD cases. Several of the so far known PD inducing chemicals appear to increase the formation of mitochondrial reactive oxygen species (ROS). A suspected environmental factor is the non-proteinogenic amino acid β-methylamino-L-alanine (BMAA), which may act to carry iron species into the brain and disrupt correct biosynthesis of proteins. In addition, in epidemiological studies, it has been reported a connection between PD and metal exposures, including iron, mercury, manganese, and lead. Research has shown elevated iron levels in the *substantia nigra* of PD patients. Mitochondrial dysfunction induced by genetic or environmental factors appears to evoke cascades of biochemical events, which include non-physiological leakage of ROS and arrest of the sensitive production of dopamine. A combination of increased ROS and loosely chelated iron causes neurotransmitter dysfunction. Recent research indicates that treatment with exogenous chelators, such as deferiprone, apomorphine, and hinokitiol, can inhibit PD progression. The endogenous chelator, neuromelanin, also appears to exert protection. In the present review, the pathogenic mechanisms and genetic susceptibilities to metals in PD are explored. The paper is also focused on strategies for the therapy of PD, mainly by using chelation therapy to reduce the level of iron.

1. Introduction

Parkinson's disease (PD) is the most common neuromuscular disorder. Globally, this disease affects more than 6 million people [1]. In industrialized countries, the prevalence of PD has increased [2], which indicates that environmental factors may be crucial in the pathogenesis. PD is a neurodegenerative disease, which is characterized by neuronal cell loss in the *substantia nigra* (SN) accompanied by reduced secretion of dopamine. Although initial lesions affect basal ganglia, clinically correlated by diminished ability to coordinate movements, other regions of the brain may be involved, leading to a deterioration of cognitive functions [3]. Thus, while bradykinesia (slow movements) together with muscle rigidity and tremor are well-known characteristic traits of PD, development of dementia may also affect a substantial proportion of the patients [4].

Still, the PD etiology is virtually unknown. A minor fraction of the cases has been attributed to the use of various medications [5]. Although some of the factors that genetically increase the risk to develop PD have been identified, most are sporadic cases, and environmental factors are presumed to play an essential role in the etiology [6]. A surprisingly high incidence of a complex PD-dementia disorder observed among the original inhabitants of Guam, and New Guinea [7] was ascribed to the intake of food containing the neurotoxic amino acid BMAA (β-methylamino-L-alanine) [8]. A role of environmental exposure has been further strengthened by research about parkinsonism due to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) exposure [9]. Exposure to different pesticides (i.e., rotenone and paraquat) also has precipitated symptoms of PD [10]. Other environmental toxicants, including manganese, iron, mercury, and lead, have been suggested to raise the risk of PD development [11].

Differences in the brain metal levels, including copper and iron, of deceased PD patients compared to healthy controls have been shown in previous studies [6]. Research also indicates that iron accumulation, and exposure or dysmetabolism of manganese and copper, may be

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involved in PD development [6,12].

The present article aims at further exploring the possible relationship between metals and PD, and future strategies for PD treatment, in particular by the use of chelating therapy.

2. Mitochondrial dysfunction in Parkinson's disease

There is evidence for impaired activity of mitochondrial complex I in PD, particularly in neurons from the *substantia nigra* region, but also of mitochondria from other brain regions including frontal and temporal cortex [13,14]. Furthermore, mutations in genes associated with familial PD are involved in mitochondrial dysfunction, such as the α-synuclein gene, Parkin, and the gene for LRRK2 (*leucine-rich repeat kinase 2*) [15–17].

Further evidence for mitochondrial impairment in the etiology of PD comes from the selective sensitivity of *substantia nigra* to mitochondrial toxins, (MPTP), rotenone, and paraquat [18]. These toxins are inhibitors of mitochondrial complex I, and administration in experimental models causes neuronal death and gives rise to parkinsonism. In general, exposure to environmental/mitochondrial toxins causes an increased risk to develop PD [19].

The presence of elevated iron levels in the susceptible neurons with the simultaneous occurrence of L-dopa or dopamine is presumed to contribute to the deterioration of *substantia nigra* neurons. In the attendance of iron, dopamine, and molecular oxygen can interact directly, yielding quinones and free oxygen radicals (ROS) as products [20]. Quinones, together with ROS, appear cytotoxic, particularly in the pars compacta of the *substantia nigra* [21]. Dopamine can also be oxidized and polymerized into neuromelanin [22], giving rise to the characteristic black color of the tissue. In the case of elevated Fe(III) levels, multiple toxic species can be created from dopamine, including its metabolites [12,23,24].

It is conceivable that neurons in regions that are especially sensitive in PD, in particular pars compacta cells in the *substantia nigra*, are under high baseline concentrations of oxidative stress and are vulnerable to mitochondrial impairment. Among biochemical features characterizing these deteriorating neurons are metal accumulation and glutathione depletion [25].

3. Iron, oxidative stress, and Parkinson's disease

The total iron concentrations increase with aging due to various factors, including elevated permeability of the blood-brain barrier, iron redistribution in the brain, inflammation, as well as changes in the iron homeostasis [26,27]. With aging, the concentrations of iron increase in the *substantia nigra*, globus pallidus, putamen, and caudate nucleus [23,28]. However, it is unclear why this increase is selective for some parts of the brain. In relation to PD severity, iron accumulates especially in pars compacta and pars reticulata, portions of the *substantia nigra* [29,30]. Studies done on post-mortem tissue have detected strikingly raised iron levels in the *substantia nigra* from PD patients, in comparison to subjects without this disease [31–33]. Measurements using transcranial sonography demonstrated in vivo that iron is selectively increased in the *substantia nigra* in various forms of PD [34,35].

It is thought that the high iron concentrations in the *substantia nigra* initiate neurotoxic effects, in particular, due to toxic products from iron-dopamine interactions [21]. Local availability of endogenous iron-complexing ligands such as neuromelanin may modify, however, the harmful effects. By use of the X-ray fluorescence method, significant amounts of iron have been identified as neuromelanin-bound in *substantia nigra* neurons. Thus, neuromelanin-bound iron may be a critical neuronal protector and storage form of this metal [36,37].

A pathogenic role of iron in PD is also supported by experiments in which therapeutic chelation of iron exerts a neuroprotective action. Treatment of animal models of PD with chelators such as deferiprone, clioquinol, or deferoxamine prevents loss of *substantia nigra* neurons and alleviates motor deficits [38–41].

Clinically, Devos et al. [38] investigated the effects of conventional chelation of iron with deferiprone (30 mg/kg/day) in patients with PD. Twelve months on deferiprone in this double-blind placebo-controlled trial decreased PD progression on the Unified Parkinson's Disease Rating Scale (UPDRS-III) with three points compared to the placebos [38].

The subcellular target of iron toxicity is still controversial. Mitochondria are crucial for iron metabolism. Mitochondria are the site of Fe—S cluster assembly for incorporation into mitochondrial complexes. Fe—S clusters are integral parts of many proteins such as complex I of the mitochondrial electron transport chain [42,43]. Pathological disruption of Fe—S clusters leads to aberrant mitochondrial function. In diseases such as Friedreich's ataxia [44] and other conditions involving disrupted Fe—S assembly, this leads to mitochondrial iron accumulation.

Mitochondria are also the sites for heme synthesis from the precursor protoporphyrin, and the incorporation of Fe by ferrochelatase. Raised levels of non-chelated iron may accompany disruption of hemoglobin synthesis.

Mitochondrial inhibition induced, e.g., by rotenone impairs Fe—S cluster synthesis and leads to mitochondrial iron accumulation [45]. Elevated mitochondrial iron causes oxidative stress and impairs mitochondrial function. Mitochondrial DNA appears to be a target in iron overload conditions [46].

Aberrant iron metabolism and mitochondrial dysfunction worsen each other, and both processes appear to operate in PD, and may significantly accelerate the progression of the disease [43].

In general, PD patients have increased levels of oxidative stress and upregulated ROS production [47]. Furthermore, mitochondrial functionality is impaired in these patients [48]. In patients with PD, it has been detected elevated contents of oxidized and nitrated proteins in the *substantia nigra* [49].

Moreover, the post-translational modifications of α-synuclein and other neuronal proteins, including tau, might be a result of the raised iron levels and oxidative stress [50].

4. Manganese, mercury, and other metals

Research indicates that some other metals than iron with neurotoxic effects may be linked to parkinsonism [51]. Manganese, as well as mercury, lead, and other metals are environmental pollutants with neurotoxic effects. It is well known that mercury can be released from dental restorations and other implants and transported into the brain via the blood-brain barrier (BBB) [52].

In medical biochemistry and neurotoxicology, metals associated with PD development is still a significant concern [51,53]. Also, a relationship between lead exposure and parkinsonism has been suggested [54]. Both mercury and lead ions can inhibit essential steps in the mitochondrial hemoglobin synthesis, particularly in cases with polymorphism of relevant genes [55], thereby increasing mitochondrial loads of free iron species.

The manganese-containing fungicide, Maneb, has been linked to raised PD risk [56]. Maneb is a polymeric complex of manganese with a thiocarbamate. Other compounds of manganese may also initiate or promote the development of PD. Thus, several workers were diagnosed with parkinsonism after exposure in a ferromanganese smelter with failing ventilation system [57]. After prolonged occupational exposure to manganese, a 51-year-old male worker developed parkinsonism [58]. Furthermore, there have been several cases of parkinsonism in intravenous drug abusers exposed to manganese via homemade ephedrine (methcathinone) [59]. Contamination with manganese remains in ephedrone, which is derived by oxidation from pseudoephedrine with the use of potassium permanganate as a catalyst [60].

Exposure to elevated mercury levels has been linked to PD exacerbation [61]. Several similarities have been noticed between the

neurotoxic effects of mercury exposure and the neurochemical characteristics of PD [6]. In a large study from Singapore, significantly elevated blood Hg concentrations were measured in PD patients compared to healthy controls [62].

In a chlorine factory, a male worker developed parkinsonism after 30 years with occupational mercury exposure [63]. Further, a 47-year-old female dentist was diagnosed with parkinsonism, which had started eighteen months earlier and was manifested mainly by resting tremor and cogwheel rigidity. A baseline quantitative urinary mercury value confirmed that she had been severely exposed to mercury. Mercury chelation therapy resulted in clinical improvement [64]. It has been reported that dental assistants and dentists who occupationally were exposed to mercury had increased mortality of dementia and PD [65]. However, since parkinsonism is a rather infrequent presentation of mercury as well as of lead poisonings, it is tempting to suggest that these characteristic symptoms result from a combination of the metal exposure and a relevant genetic polymorphism [55], resulting in inhibited hemoglobin synthesis accompanied by increased loads of free iron species.

5. Synergistic toxicity between metals, pesticides, and BMAA

Cell and animal studies demonstrated the synergistic effects between some pesticides and metals. Thus, when a mercury solution that killed one of 100 rats was given together with a lead solution that also killed one of 100 rats, all the exposed rats died [6]. In a study of rats, the synergistic effects occurred when lead, manganese, and mercury were combined [66]. Associations between pesticide exposure and PD development have been reported from epidemiological studies [67]. Furthermore, some metals and pesticides promote aggregation of the presynaptic protein α-synuclein, which has neurodegenerative effects, and such aggregation may be an important factor in the pathogenesis of PD [68]. Some divalent metals, like iron and manganese, bind to the C-terminus of α-synuclein, and copper interplays at the N-terminal region [69]. The loss of nigral dopaminergic neurons is age-related and accelerates synergistically when the herbicide paraquat is combined with iron [70]. In an animal experiment, exposure to paraquat alone or to the fungicide maneb alone caused minimal changes in the nigrostriatal dopamine system. However, the reduction in the levels of striatal dopamine was significant when paraquat and maneb were combined [6].

The cycad hypothesis of the so-called amyotrophic-lateral-sclerosis-parkinsonism-dementia complex (ALS/PDC) occurring in Guam in the period 1945–56 is of interest here. This hypothesis states that ALS/PDC neurodegeneration was precipitated by the intake of the non-proteinogenic amino acid beta-methylamino-L-alanine (BMAA), which the traditional diet of the local Chamorro population contained [71]. An alternative hypothesis (the mineral hypothesis) claimed that the locally high levels of iron and manganese together with low levels of calcium and magnesium in drinking water could precipitate the symptoms [72]. It is suggested that the neurotoxicity of BMAA involves activating receptors of excitatory glutamate [73]. However, when bicarbonate ions are present carbamate adducts get produced from BMAA, and divalent metals such as iron, manganese, and zinc may form chelates with BMAA and its carbamate adducts [74].

Consequently, it is tempting suggesting that BMAA also mediates metal dyshomeostasis with raised levels of manganese and/or iron in the vulnerable *substantia nigra* neurons. A most recent theory suggests that only animals having neuromelanin are affected by BMAA [75]. The fact that adult mice, which lack neuromelanin, are unaffected by BMAA even at high doses, whereas adult monkeys [76] and vervets [77] having neuromelanin are affected supports this theory [78]. BMAA has been shown to accumulate in high concentrations in melanin and neuromelanin producing cells, and to interact with melanin and neuromelanin pigments, thereby disrupting the anticipated protective functions of the melanins [78,79].

6. Glutathione and glutamate

Dysregulation or depletion of the intracellular tripeptide glutathione (GSH) has been associated with the etiology of several human degenerative diseases [80]. Glutathione is essential when xenobiotics get detoxified and have been linked to some PD cases. GSH depletion will increase the toxicity and retention of mercury since the heavy metal is excreted mainly as GSH-conjugates [81,82]. In the midbrain, the GSH levels decrease before the clinical symptoms in PD occur [83], which will impair the function of glutathione peroxidase and thereby promote oxidation. Among elderly patients, GSH levels are usually considerably decreased [84].

Genetic depletion of GSH and glutathione S-transferase appears to represent risk factors for movement disorders [85] including PD [86]. Thus, mercury may cause neurodegenerative changes, including movement disorders, by affecting the GSH balance [87].

GSH is a tripeptide being able to deliver one of its amino acid components, glutamate, to the neuronal network. When the glutamatergic neurotransmitters are over-active, this may cause degeneration of dopaminergic neurons [88]. By this mechanism, glutamate in excess is neurotoxic for the dopaminergic neurons in the *substantia nigra*. Bivalent metals, including lead and mercury, inhibit the glutamine synthetase that converts excessed glutamate to non-toxic glutamine [89]. Thereby these metal compounds may accentuate the toxic effects of glutamate on the dopaminergic network. The previously discussed neurotoxic agent, BMAA, can also exert a significant unphysiological glutamate-mimetic activity [90].

The dopaminergic neurons in the *substantia nigra* have long axons and contain microtubules in its entire cytoskeleton. Microtubules are composed of tubulin molecules. Each of the tubulin components has not less than 14 thiol groups (-SH), and several metal ions, including mercury, bind to these thiols with high affinity. It has been suggested that mercury could promote functional loss of tubulin [91] and thereby lead to the formation of neurofibrillary tangles.

Mercury exerts toxic actions in the brain where it is practically impossible to obtain a detoxifying effect by therapeutic chelation [92]. Even very low levels of inorganic mercury may lead to deterioration of microtubules followed by degeneration of axons [91].

7. Selenium and selenoenzymes

For humans, selenium is an essential trace element, which is an indispensable component of several enzymes, including glutathione peroxidases (GPx). In animal experiments, selenium in various forms is an antidote for mercury poisonings [93,94].

However, the intake of selenium is for a big part of the world's population less than optimal, particularly in regions in Europe [95]. In PD patients, it has been observed that reduced plasma selenium is related to decreased neurological coordination [96]. The dopaminergic neurons in the *substantia nigra* are vulnerable to oxidative stress because their content of dopamine, which is quickly oxidized to quinone derivative [21], thereby causing a cascade of harmful events, without adequate protection by GPx.

By studying brain tissue from deceased PD patients and controls, it was found that GPx4 is co-localized with neuromelanin in nigral dopaminergic neurons [97]. Interestingly, lower activity of GPx4 in the *substantia nigra* of PD patients in comparison to controls was found. Of interest here is also the loss of mitochondrial GPx4, which is dose-dependent in PC12 cells that receive dopamine [98], suggesting that reduction of mitochondrial GPx4 activity explains why the dopaminergic neurons are vulnerable in PD.

Parallel to the reduced GPx4 activity, selenoprotein P (SelP-1) expression was significantly reduced in the *substantia nigra* from PD patients compared to controls [99], indicating a role of the latter protein in the synthesis of protective selenoproteins, such as GPx4.

8. Alpha-synuclein, amyloid beta, and hyperphosphorylated tau

Intracellular insoluble Lewy bodies with aggregated α-synuclein are hallmarks of advanced PD. Stable α-synuclein is considered a causative link in the PD pathogenesis through its ability to precipitate the Lewy bodies [100]. Lewy body diseases (LBD) include uncomplicated PD, dementia with Lewy bodies, and PD dementia. Although α-synuclein appears to exert a protective action on non-dopaminergic cortical neurons, it leads to apoptosis and Lewy body formation in dopaminergic neurons [101]. Thus, soluble α-synuclein is considered a mediator of the selective loss of dopaminergic neurons [102]. The toxicity of the synuclein-dopamine couple also appears to be dependent on environmental pollutants since pesticides and metals promote aggregation of α-synuclein. Iron, as well as manganese, aluminum, and cadmium, appear to accelerate α-synuclein aggregation [68].

Another protein, amyloid-β, is considered one of the causative agents in Alzheimer's disease (AD), but amyloid-β is also considered a possible pathogenic factor in PD [103]. Interestingly, several researchers have reported pathological overlap between PD and AD with Lewy body dementia (LBD) [104,105], and environmental pollutants seem again to be a pathogenetic factor in PD [106].

The apolipoprotein E ε4 (APOEε4) allele is linked to an increased risk to develop AD, as well as PD with dementia [107]. An early occurrence of PD has been associated with the allelic expression of APOEε4 [6,107]. In addition, research indicates that APOEε4 may increase the neurotoxic sensitivity to pollutants, including lead and mercury [108].

Phosphorylated tau, found in synaptic-enriched parts of the frontal cortex, is also considered a characteristic trait in PD [109]. Tau hyperphosphorylation has been observed to occur parallel to the presence of aggregated α-synuclein [110].

Iron and aluminum, as well as mercury, have been reported to promote the formation of hyperphosphorylated tau [6,112].

9. Chelation therapy

In chelation therapy, chelating agents (i.e., chelators) are medically used to sequester or remove metals from target body sites [113–115]. While therapeutically administered chelators such as EDTA usually mobilize toxic metals from target sites, endogenous complexing agents may sequester metal excesses into a non-toxic form intra- or extracellularly, e.g., ferritin- or hemosiderin-bound iron. Adequate availability of an endogenous complexing ligand such as neuromelanin may modify the deleterious effects of iron or manganese [37]. The biosynthetic pathway leading to neuromelanin formation is complex but is presumed to occur through polymerization of 5,6-dihydroxyindole monomers formed by auto-oxidation of catecholamines [90]. Also, the biological function of neuromelanin is yet not fully known, although it is considered to protect the aging brain against toxic factors, as it efficiently binds transition metals such as iron as well as other potentially toxic molecules [24].

About therapeutic chelation, interesting observations have been made in workers who developed parkinsonism after manganese exposure. Their symptoms and signs resembled those of true PD. In seven workers who had manganese depositions in their basal ganglia and symptoms of parkinsonism, Herrero Fernandez and colleagues [116] administered chelation therapy with calcium EDTA. Reduction of circulating manganese and clinical improvement was observed in four of the seven patients. EDTA has a therapeutic benefit in reducing manganese in blood in an emergency phase. However, highly water-soluble EDTA molecules pass poorly the blood-brain barrier. The FDA approved chelator para-aminosalicylic acid (PAS) is used in the treatment of tuberculosis. Mainly Chinese studies of patients have shown promising effects of PAS in the treatment of severe manganese intoxication [117]. Animal studies verified the effectiveness of PAS as a chelating agent removing manganese from the brain [118]. The salicylate structure of

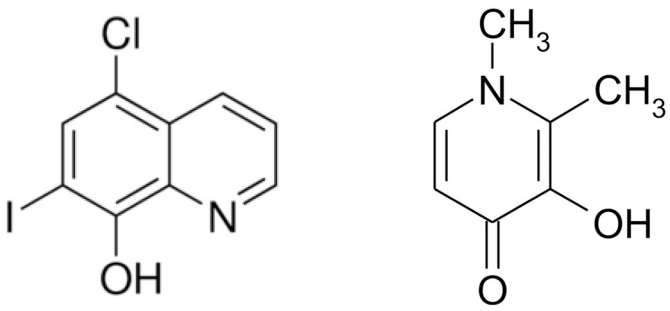

Fig. 1. Chemical structures of clioquinol (left) and deferiprone (right).

PAS has a documented anti-inflammatory effect, which may alleviate neuroinflammation. *N*-acetyl-para-aminosalicylic acid (AcPAS) is a PAS metabolite that penetrates quickly into the cerebrospinal fluid and parenchymal brain [118]. Since PAS is rapidly metabolized to the more efficient AcPAS in vivo, it is suggested that combined treatment with PAS for brain-to-blood shuttling and calcium-EDTA for blood-to-urine export is the most promising concept for therapy of manganism [119]. In some cases, mercury exposure appears to precipitate PD-mimetic symptoms, and in such cases, mercury chelation may alleviate the disease [64].

However, rather than environmental manganese or mercury exposure, the dysmetabolism of iron (Fe) with elevated cytosolic Fe in SN appears to be a crucial factor associated with neurotoxicity and neurodegeneration in PD, mainly due to the interactions of the electrophilic Fe-III-ions with dopamine [21]. Here, it is of great interest that neuroprotective effects using iron chelators like clioquinol have been observed (Fig. 1), as well as of apomorphine (Fig. 2), deferoxamine and deferiprone in mouse or rat PD models [6,38,41,120].

In addition to its chelation properties, apomorphine is an efficient dopamine agonist, which also has antioxidant activity [121]. It is a highly lipophilic compound, which rapidly penetrates BBB into the central nervous system (CNS) including into SN [122]. However, apomorphine is an acidic compound that has an emetic action when administered orally, and the most appropriate administration route in PD would be intermittent subcutaneous infusion [121]. Caffeine and nicotine tablets can also act as iron chelating drugs [12]. Postuma et al. [123] studied 61 patients, mean age 60 years, with PD in a two-month trial of caffeine. Thirty of the patients got caffeine pills, while the remaining 31 subjects received placebo capsules. In the study, the patients who received the caffeine pills improved compared to a placebo group [123]. The patients in the study who had received caffeine reported in general that motor symptoms such as movement difficulties and muscle stiffness had improved.

About nicotine, the conclusion in a meta-analysis of 41 placebo-

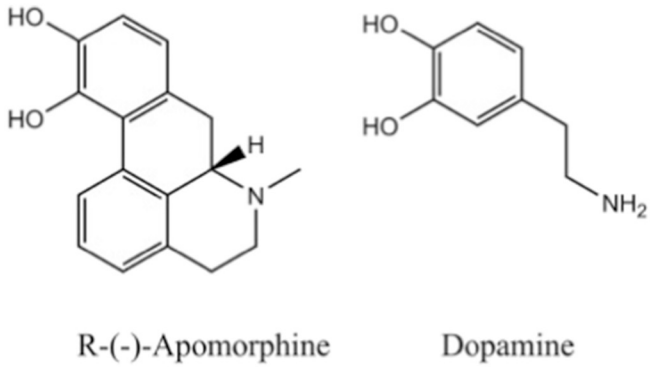

Fig. 2. The chemical structures of apomorphine and dopamine. Through their vicinal oxygen donor groups, both these compounds can bind the electrophilic iron ions.

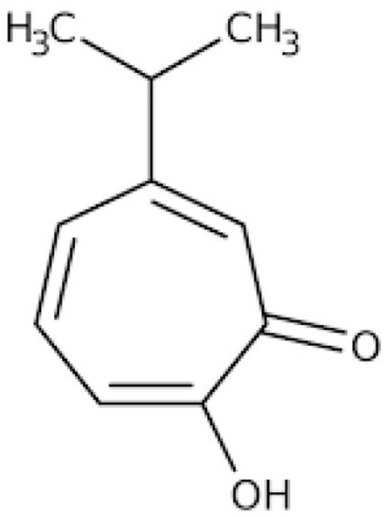

Fig. 3. Chemical structures of the chelator hinokitiol, showing the vicinal Fe-complexing oxygen groups.

controlled studies on nicotine was that it has positive effects on attention, working memory, and motor abilities [124]. Interestingly, the nicotine molecule has high affinity to Fe(III) [125]. Although a component of the cerebral effects of nicotine is related to its activation of nicotinic receptors with synergism with dopamine receptors, a significant part of its neuroprotection in PD may be due to better BBB penetration than most other chelators, and intra-neuronal chelation of iron [126].

By improving iron dysmetabolism, chelation therapy can have some advantage over L-dopa administration in PD patients [12,127,128]. The use of deferiprone as an iron chelator seems to normalize iron metabolism and reduce accumulated iron levels in the CNS, especially in PD patients with low ceruloplasmin (ferroxidase) activity [129]. Oral administration of the low-molecular-weight iron-chelator, deferiprone, is about to be widely investigated in PD and PD models [38].

A recently studied iron chelator, hinokitiol, may protect against neuronal loss in neurodegenerative disorders [130] (Fig. 3).

Other iron chelators, including lipophilic agent VK-28 (5-[4-(2-hydroxyethyl) piperazine-1-ylmethyl]-quinoline-8-ol) and desferal, effectively mobilize iron deposits. However, desferal that do not cross the blood-brain barrier appeared to be less efficient than VK-28 in detoxification of SN iron excesses [131].

In summary, the iron chelators deferiprone, apomorphine, hinokitiol, and VK-28 show efficacy in chelating iron from susceptible cerebral regions. Administration of erythropoietin by injections might also reduce pathological iron deposits, increase hemoglobin values, and thereby alleviate iron dysmetabolism and clinical symptoms in PD [132]. Taken together, the positive observations of iron mobilization on symptoms of parkinsonism consistently observed in minor experimental and clinical studies in different parts of the World may point to a new strategy in the pharmacological approach to this disease.

10. Conclusions

Numerous studies have demonstrated associations between PD progression and increased levels of iron in *substantia nigra* together with mitochondrial dysfunction. Exposure to pesticides such as rotenone and paraquat as well as exposure to mercury and some other metals appear to promote these characteristic pathological traits in the vulnerable cells. Exposure to mercury and local iron excesses may be of importance in the development of PD. It is noticed that there are many similar effects between the neurodegenerative changes of PD and the neurotoxicity of mercury [6]. The metals lead and iron have a synergistic effect when they are present together with mercury. Different metals, including mercury, and several pesticides and other environmental pollutants, may be factors in PD development.

Chelation of iron excesses and support of the detoxification mechanisms in PD with antioxidants and glutathione precursors may restore mitochondrial functions. Large clinical trials that are adequately controlled are highly requested to investigate these issues further, in particular, the hypothesized therapeutic role of iron mobilization from *substantia nigra* for arresting the progression of PD.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

References

[1] GBD, 2015 Disease and Injury Incidence and Prevalence Collaborators, Lancet 388 (10053) (2016) 1545–1602.
[2] L.M. De Lau, M.M. Breteler, Lancet Neurol. 5 (6) (2006) 525–535.
[3] J.O. Rinne, R. Portin, H. Ruottinen, E. Nurmi, J. Bergman, M. Haaparanta, O. Solin, Arch. Neurol. 57 (4) (2000) 470–475.
[4] J. Gratwicke, M. Jahanshahi, T. Foltynie, Brain 138 (6) (2015) 1454–1476.
[5] H. Sawada, T. Oeda, K. Yamamoto, A. Umemura, S. Tomita, R. Hayashi, M. Kohsaka, T. Kawamura, BMC Neurol. 13 (1) (2013) 145.
[6] G. Bjørklund, V. Stejskal, M.A. Urbina, M. Dadar, S. Chirumbolo, J. Mutter, Curr. Med. Chem. 25 (2018) 1–17, https://doi.org/10.2174/0929867325666171129124616.
[7] P.A. Cox, O.W. Sacks, Neurology 58 (6) (2002) 956–959.
[8] K.D. Hill, Aust. Syst. Bot. 7 (6) (1994) 543–567.
[9] J.W. Langston, P. Ballard, J.W. Tetrud, I. Irwin, Science 219 (4587) (1983) 979–980.
[10] Z. Qi, G.W. Miller, E.O. Voit, Toxicology 315 (2014) 92–101.
[11] S. Goldman, Annual Rev. Pharmacol. Toxicol. 54 (2014) 141–164.
[12] J. Aaseth, P. Dusek, P.M. Roos, BioMetals 31 (5) (2018) 737–747.
[13] W.D. Parker Jr., J.K. Parks, R.H. Swerdlow, Brain Res. 1189 (2008) 215–218.
[14] A.H.V. Schapira, J.M. Cooper, D. Dexter, J.B. Clark, P. Jenner, C.D. Marsden, J. Neurochem. 54 (3) (1990) 823–827.
[15] T. Nakamura, S. Tu, M.W. Akhtar, C.R. Sunico, S.I. Okamoto, S.A. Lipton, Neuron 78 (4) (2013) 596–614.
[16] A.R. Esteves, R.H. Swerdlow, S.M. Cardoso, Exp. Neurol. 261 (2014) 206–216.
[17] D. Truban, X. Hou, T.R. Caulfield, F.C. Fiesel, W. Springer, J. Park. Dis. 7 (1) (2017) 13–29.
[18] M.P. Giannoccaro, C. La Morgia, G. Rizzo, V. Carelli, Mov. Disord. 32 (3) (2017) 346–363.
[19] C.M. Tanner, F. Kamel, G.W. Ross, J.A. Hoppin, S.M. Goldman, M. Korell, C. Marras, G.S. Bhudhikanok, M. Kasten, A.R. Chade, K. Comyns, M.B. Richards, C. Meng, B. Priestley, H.H. Fernandez, F. Cambi, D.M. Umbach, A. Blair, D.P. Sandler, J.W. Langston, Environ. Health Perspect. 119 (6) (2011) 866–872.
[20] I. Miyazaki, M. Asanuma, Acta Med. Okayama 62 (3) (2008) 141–150.
[21] D.J. Hare, K.L. Double, Brain 139 (4) (2016) 1026–1035.
[22] F.A. Zucca, E. Basso, F.A. Cupaioli, E. Ferrari, D. Sulzer, L. Casella, L. Zecca, Neurotox. Res. 25 (1) (2014) 13–23.
[23] R.J. Ward, F.A. Zucca, J.H. Duyn, R.R. Crichton, L. Zecca, Lancet Neurol. 13 (10) (2014) 1045–1060.
[24] F.A. Zucca, J. Segura-Aguilar, E. Ferrari, P. Muñoz, I. Paris, D. Sulzer, L. Zecca, Prog. Neurobiol. 155 (2017) 96–119.
[25] S. Bharath, M. Hsu, D. Kaur, S. Rajagopalan, J.K. Andersen, Biochem. Pharmacol. 64 (5–6) (2002) 1037–1048.
[26] J.R. Conde, W.J. Streit, J. Neuropathol. Exp. Neurol. 65 (2006) 199–203.
[27] A.J. Farrall, J.M. Wardlaw, Neurobiol. Aging 30 (2009) 337–352.
[28] L. Zecca, A. Stroppolo, A. Gatti, D. Tampellini, M. Toscani, M. Gallorini, G. Giaveri, P. Arosio, P. Santambrogio, R.G. Fariello, E. Karatekin, M.H. Kleinman, N. Turro, O. Hornykiewicz, F.A. Zucca, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 9843–9848.
[29] D.T. Dexter, F.R. Wells, A.J. Lees, F. Agid, Y. Agid, P. Jenner, C.D. Marsden, J. Neurochem. 52 (1989) 1830–1836.
[30] E.C. Hirsch, J.P. Brandel, P. Galle, F. Javoy-Agid, Y. Agid, J. Neurochem. 56 (1991) 446–451.
[31] D.T. Dexter, A. Carayon, F. Javoy-Agid, Y. Agid, F.R. Wells, S.E. Daniel, A.J. Lees, P. Jenner, C.D. Marsden, Brain 114 (4) (1991) 1953–1975.
[32] E. Sofic, W. Paulus, K. Jellinger, P. Riederer, M.B.H. Youdim, J. Neurochem. 56 (3) (1991) 978–982.
[33] P.D. Griffiths, B.R. Dobson, G.R. Jones, D.T. Clarke, Brain 122 (4) (1999) 667–673.
[34] K.J. Schweitzer, T. Brüssel, P. Leitner, R. Krüger, P. Bauer, D. Woitalla, D. Berg, J. of Neurol. 254 (5) (2007) 613–616.
[35] S. Ayton, P. Lei, Biomed. Res. Int. 2014 (2014) 581256.
[36] A.E. Oakley, J.F. Collingwood, J. Dobson, G. Love, H.R. Perrott, J.A. Edwardson, M. Elstner, C.M. Morris, Neurology 68 (21) (2007) 1820–1825.
[37] L. Zecca, M. Gallorini, V. Schünemann, A.X. Trautwein, M. Gerlach, P. Riederer,

P. Vezzoni, D. Tampellini, J. Neurochem. 76 (6) (2001) 1766–1773.
[38] D. Devos, C. Moreau, J.C. Devedjian, J. Kluza, M. Petrault, C. Laloux, A. Jonneaux, G. Ryckewaert, G. Garçon, N. Rouaix, A. Duhamel, P. Jissendi, K. Dujardin, F. Auger, L. Ravasi, L. Hopes, G. Grolez, W. Firdaus, B. Sablonnière, I. Strubi-Vuillaume, N. Zahr, A. Destée, J.C. Corvol, D. Pöltl, M. Leist, C. Rose, L. Defebvre, P. Marchetti, Z.I. Cabantchik, R. Bordet, Antioxid. Redox Signal. 21 (2) (2014) 195–210.
[39] D.T. Dexter, S.A. Statton, C. Whitmore, W. Freinbichler, P. Weinberger, K.F. Tipton, L. Della Corte, R.J. Ward, R.R. Crichton, J. Neural Transmiss. 118 (2) (2011) 223–231.
[40] D. Kaur, F. Yantiri, S. Rajagopalan, J. Kumar, J.Q. Mo, R. Boonplueang, V. Viswanath, R. Jacobs, L. Yang, M.F. Beal, D. DiMonte, I. Volitakis, L. Ellerby, R.A. Cherny, A.I. Bush, J.K. Andersen, Neuron 37 (6) (2003) 899–909.
[41] N.P. Mena, O. García-Beltrán, F. Lourido, P.J. Urrutia, R. Mena, V. Castro-Castillo, B.K. Cassels, M.T. Núñez, Biochem. Biophys. Res. Comm. 463 (4) (2015) 787–792.
[42] J.R. Liddell, Neurodegener. Dis. Manag. 5 (4) (2015) 345–364.
[43] J.R. Liddell, A.R. White, Neurochem. Int. 117 (2018) 126–138.
[44] A. Rötig, P. de Lonlay, D. Chretien, F. Foury, M. Koenig, D. Sidi, A. Munnich, P. Rustin, Nat. Genet. 17 (2) (1997) 215–217.
[45] O. Stehling, C. Wilbrecht, R. Lill, Biochimie 100 (2014) 61–77.
[46] X. Gao, J.L. Campian, M. Qian, X.F. Sun, J.W. Eaton, J. Biol. Chem. 284 (8) (2009) 4767–4775.
[47] V. Dias, E. Junn, M.M. Mouradian, J. Park. Dis. 3 (4) (2013) 461–491.
[48] H. Büeler, Exper. Neurol. 218 (2) (2009) 235–246.
[49] P.F. Good, A. Hsu, P. Werner, D.P. Perl, C.W. Olanow, J. Neuropathol. & Exp. Neurol. 57 (4) (1998) 338–342.
[50] L. Casella, L. Bubacco, D. Valensin, M. Tegoni, Impact 2017 (6) (2017) 9–11.
[51] R. Lucchini, E. Albini, L. Benedetti, S. Zoni, A. Caruso, E. Nan, P. Pasqualetti, P.M. Rossini, G. Binetti, L. Benussi, G. Parrinello, R. Gasparotti, A. Padovani, F. Draicchio, L. Alessio, G. Ital. Med. Lav. Ergon. 29 (3 Suppl) (2007) 280–281.
[52] A. Jokstad, Y. Thomassen, E. Bye, J. Clench-Aas, J. Aaseth, Pharmacol. & Toxicol. 70 (4) (1992) 308–313.
[53] E.J. McAllum, D.I. Finkelstein, J. Mol. Neurosci. 60 (3) (2016) 279–288.
[54] M.G. Weisskopf, J. Weuve, H. Nie, M.H. Saint-Hilaire, L. Sudarsky, D.K. Simon, B. Hersh, J. Schwartz, R.O. Wright, H. Hu, Environ. Health Perspect. 118 (11) (2010) 1609–1613.
[55] D. Echeverria, J.S. Woods, N.J. Heyer, D. Rohlman, F.M. Farin, T. Li, C.E. Garabedian, Neurotoxicol. Teratol. 28 (2006) 39–48.
[56] S. Costello, M. Cockburn, J. Bronstein, X. Zhang, B. Ritz, Am. J. Epidemiol. 169 (8) (2009) 919–926.
[57] J.D. Wang, C.C. Huang, Y.H. Hwang, J.R. Chiang, J.M. Lin, J.S. Chen, Br. J. Ind. Med. 46 (1989) 856–859.
[58] J.W. Kim, Y. Kim, H.K. Cheong, K. Ito, J. Korean Med. Sci. 13 (1998) 437–439.
[59] A. Stepens, I. Logina, V. Liguts, P. Aldiņš, I. Ekšteina, A. Platkājis, I. Mārtinsone, E. Tērauds, B. Rozentāle, M. Donaghy, New Engl. J. Med. 358 (10) (2008) 1009–1017.
[60] Y. Sanotsky, R. Lesyk, L. Fedoryshyn, I. Komnatska, Y. Matviyenko, S. Fahn, Movement disorders: official journal of the Movement Disorder Society 22 (9) (2007) 1337–1343.
[61] C.G. Ohlson, C. Hogstedt, Scand. J. Work Environ. Health 7 (4) (1981) 252–256.
[62] C.H. Ngim, G. Devathasan, Neuroepidemiology 8 (3) (1989) 128–141.
[63] K. Miller, S. Ochudło, G. Opala, W. Smolicha, J. Siuda, Neurol. Neurochir. Pol. 37 (2003) 31–38.
[64] Y. Finkelstein, J. Vardi, M.M. Kesten, I. Hod, Neurotoxicol 17 (1) (1996) 291–295.
[65] P.A. Schulte, C.A. Burnett, M.F. Boeniger, J. Johnson, Am. J. Pub. Health 86 (9) (1996) 1281–1288.
[66] A. Papp, L. Pecze, A. Szabó, T. Vezér, J. Appl. Toxicol.: Intern. J. 26 (4) (2006) 374–380.
[67] A. Ascherio, H. Chen, M.G. Weisskopf, E. O'Reilly, M.L. McCullough, E.E. Calle, M.A. Schwarzschild, M.J. Thun, Ann. Neurol. 60 (2) (2006) 197–203.
[68] V.N. Uversky, J. Li, A.L. Fink, J. Biol.l Chem. 276 (47) (2001) 44284–44296.
[69] A. Binolfi, L. Quintanar, C.W. Bertoncini, C. Griesinger, C.O. Fernández, Coord. Chem. Rev. 256 (19–20) (2012) 2188–2201.
[70] J. Peng, L. Peng, F.F. Stevenson, S.R. Doctrow, J.K. Andersen, J.Neurosci. 27 (26) (2007) 6914–6922.
[71] G.E. Kisby, M. Ellison, P.S. Spencer, Neurol 42 (7) (1992) 1336–1340.
[72] G.R. Denton, H.G. Siegrist, J.P. Jano-Edwards, J. Toxicol. Environ. Health, Part A 72 (9) (2009) 574–576.
[73] R. Van Onselen, L. Venables, M. Van De Venter, T.G. Downing, Neurotox. Res. 33 (1) (2018) 15–23.
[74] P. Diaz-Parga, J.J. Goto, V.V. Krishnan, Neurotox. Res. 33 (1) (2018) 76–86.
[75] N. Delcourt, T. Claudepierre, T. Maignien, N. Arnich, C. Mattei, Toxicologie Analytique et Clinique 30 (3) (2018) 176–177.
[76] P.S. Spencer, P.B. Nunn, J. Hugon, A.C. Ludolph, S.M. Ross, D.N. Roy, R.C. Robertson, Science 237 (4814) (1987) 517–522.
[77] P.A. Cox, D.A. Davis, D.C. Mash, J.S. Metcalf, S.A. Banack, Neurotoxicol 57 (2016) 310–311.
[78] O. Myhre, D.M. Eide, S. Kleiven, H.C. Utkilen, T. Hofer, Sci. Rep. 8 (1) (2018) 2308, https://doi.org/10.1038/s41598-018-20327-y (https://www.nature.com/articles/s41598-018-20327-y).
[79] O. Karlsson, N.G. Lindquist, E.B. Brittebo, E. Roman, Toxicol. Sci. 109 (2) (2009) 286–295.
[80] N. Ballatori, S.M. Krance, S. Notenboom, S. Shi, K. Tieu, C.L. Hammond, Biol. Chem. 390 (3) (2009) 91–214 1.
[81] N. Ballatori, T.W. Clarkson, Biochem. Pharmacol. 33 (7) (1984) 1093–1098.
[82] J. Alexander, J. Aaseth, Biochem. Pharmacol. 31 (5) (1982) 685–690.
[83] T.L. Perry, D.V. Godin, S. Hansen, Neurosci. Lett. 33 (3) (1982) 305–310.
[84] V. Serru, B. Baudin, F. Ziegler, J.P. David, M.J. Cals, M. Vaubourdolle, N. Mario, Clin. Chem. 47 (7) (2001) 1321–1324.
[85] K. Skullerud, S. Marstein, H. Schrader, P.J. Brundelet, E. Jellum, Acta Neuropathol. 52 (3) (1980) 235–238.
[86] M. Hsu, B. Srinivas, J. Kumar, R. Subramanian, J. Andersen, J. Neurochem. 92 (5) (2005) 1091–1103.
[87] S. Nabi, Methylmercury and Alzheimer's disease, in: S. Nabi (Ed.), Toxic Effects of Mercury, Springer India, New Delhi, 2014, pp. 201–209.
[88] H. Sawada, T. Kawamura, S. Shimohama, A. Akaike, J. Kimura, J. Neurosci. Res. 43 (4) (1996) 503–510.
[89] E.M. Sierra, E. Tiffany-Castiglioni, Toxicol 65 (3) (1991) 295–304.
[90] N. Delcourt, T. Claudepierre, T. Maignien, N. Arnich, C. Mattei, Toxins 10 (1) (2017) 6.
[91] T. Syversen, P. Kaur, J. Trace Elem. Med. Biol. 26 (4) (2012) 215–226.
[92] T.W. Clarkson, Environ. Health Perspect. 100 (1992) 31–38.
[93] G. Bjørklund, J. Aaseth, O.P. Ajsuvakova, A.A. Nikonorov, A.V. Skalny, M.G. Skalnaya, A.A. Tinkov, Coord. Chem. Rev. 332 (2017) 30–37.
[94] G. Bjørklund, BioMetals 28 (4) (2015) 605–614.
[95] M.P. Rayman, Lancet 379 (9822) (2012) 1256–1268.
[96] A. Shahar, K.V. Patel, R.D. Semba, S. Bandinelli, D.R. Shahar, L. Ferrucci, J.M. Guralnik, Mov. Disord. 25 (12) (2010) 1909–1915.
[97] F.P. Bellinger, M.T. Bellinger, L.A. Seale, A.S. Takemoto, A.V. Raman, T. Miki, A.B. Manning-Boğ, M.J. Berry, L.R. White, G.W. Ross, Mol. Neurodegener. 6 (1) (2011) 8.
[98] D.N. Hauser, A.A. Dukes, A.D. Mortimer, T.G. Hastings, Free Rad. Biol. Med. 65 (2013) 419–427.
[99] F.P. Bellinger, A.V. Raman, R.H. Rueli, M.T. Bellinger, A.S. Dewing, L.A. Seale, M.A. Andres, J.H. Uyehara-Lock, L.R. White, G.W. Ross, M.J. Berry, J. Park. Dis. 2 (2) (2012) 115–126.
[100] Y.K. Al-Hilaly, L. Biasetti, B.J. Blakeman, S.J. Pollack, S. Zibaee, A. Abdul-Sada, J.R. Thorpe, W.F. Xue, L.C. Serpell, Sci. Rep. 6 (2016) 39171, https://doi.org/10.1038/srep39171.
[101] J. Xu, S.Y. Kao, F.J. Lee, W. Song, L.W. Jin, B.A. Yankner, Nat. Med. 8 (6) (2002) 600–606.
[102] H.L. Roberts, D.R. Brown, Biomol. Ther. 5 (2015) 282–305.
[103] T. Lashley, J.L. Holton, E. Gray, K. Kirkham, S.S. O'Sullivan, A. Hilbig, N.W. Wood, A.J. Lees, T. Revesz, Acta Neuropathol. 115 (4) (2008) 417–425.
[104] D. Aarsland, C.G. Ballard, G. Halliday, J. Ger. Psych. Neurol. 17 (3) (2004) 137–145.
[105] D.J. Burn, Curr. Opin. Neurol. 19 (6) (2006) 572–579.
[106] M.S. Petersen, J. Halling, S. Bech, L. Wermuth, P. Weihe, F. Nielsen, P.J. Jørgensen, E.P. Budtz-Jørgensen, P. Grandjean, Neurotoxicol. 29 (4) (2008) 584–590.
[107] A.I. Tröster, J.A. Fields, A.M. Paolo, W.C. Koller, J. Neurol. Sci. 248 (1–2) (2006) 62–67.
[108] M.E. Godfrey, D.P. Wojcik, C.A. Krone, J. Alzheimers Dis. 5 (3) (2003) 189–195.
[109] G. Muntane, E. Dalfo, A. Martinez, I. Ferrer, Neurosci. 152 (4) (2008) 913–923.
[110] T. Duka, M. Rusnak, R.E. Drolet, V. Duka, C. Wersinger, J.L. Goudreau, A. Sidhu, FASEB J. 20 (13) (2006) 2302–2312.
[112] A. Yamamoto, R.W. Shin, K. Hasegawa, H. Naiki, H. Sato, F. Yoshimasu, T. Kitamoto, J. Neurochem. 82 (5) (2007) 1137–1147.
[113] J. Aaseth, M.A. Skaug, Y. Cao, O. Andersen, J. Trace Elem. Med. Biol. 31 (2015) 260–266.
[114] G. Bjørklund, Saudi J. Kidney Dis. Transpl. 26 (3) (2015) 611–612.
[115] G. Bjørklund, J. Mutter, J. Aaseth, Arch. Toxicol. 91 (12) (2017) 3787–3797.
[116] E. Herrero Hernandez, G. Discalzi, C. Valentini, F. Venturi, A. Chiò, C. Carmellino, L. Rossi, A. Sacchetti, E. Pira, Neurotoxicol. 27 (3) (2006) 333–339.
[117] F.Q. Du, X.A. Mo, Y.M. JIang, X. Fu, H.Y. Gao, F.L. Liao, China Occupat. Med. 5 (2008) 014.
[118] S.L. O'Neal, W. Zheng, Curr. Environ. Health Rep. 2 (3) (2015) 315–328.
[119] J.I. Lachowicz, V.M. Nurchi, G. Crisponi, I. Cappai, R. Cappai, M. Busato, A. Melchior, M. Tolazzi, M. Peana, E. Garribba, M.A. Zoroddu, P. Coni, G. Pichiri, J. Aaseth, New J. Chem. 42 (10) (2018) 8035–8049.
[120] F. Febbraro, K.J. Andersen, V. Sanchez-Guajardo, N. Tentillier, M. Romero-Ramos, Experim. Neurol. 247 (2013) 45–58.
[121] A. Boyle, W. Ondo, CNS drugs 29 (2) (2015) 83–89.
[122] S. Ribaric, Molecules 17 (5) (2012) 5289–5309.
[123] R.B. Postuma, A.E. Lang, R.P. Munhoz, K. Charland, A. Pelletier, M. Moscovich, L. Filla, D. Zanatta, S. Rios Romenets, R. Altman, R. Chuang, B. Shah, Neurology 79 (7) (2012) 651–658.
[124] S.J. Heishman, B.A. Kleykamp, E.G. Singleton, Psychopharmacol 210 (4) (2010) 453–469.
[125] A.E. Fazary, Metal Complexes of Nicotine: A Group of Negligible Compounds, Pelagia Research Library, 2017.
[126] J. Zhang, Q. Liu, Q. Chen, N.Q. Liu, F.L. Li, Z.B. Lu, C. Qin, H. Zhu, Y.Y. Huang, W. He, B.L. Zhao, FASEB J. 20 (8) (2006) 1212–1214.
[127] R.B. Mounsey, P. Teismann, Int. J. Cell Biol. 2012 (2012) ID 983245.
[128] R.J. Ward, D.T. Dexter, R.R. Crichton, J. Tr. Elem. Med. Biol. 31 (2015) 267–273.
[129] G. Grolez, C. Moreau, B. Sablonnière, G. Garçon, J.C. Devedjian, S. Meguig, P. Gelé, C. Delmaire, R. Bordet, L. Defebvre, I.Z. Cabantchik, D. Devos, BMC Neurol. 15 (1) (2015) 74.
[130] J.H. Moon, J.H. Lee, Y.J. Lee, S.Y. Park, Oncotarget 7 (21) (2016) 29944–29957.
[131] D.B. Shachar, N. Kahana, V. Kampel, A. Warshawsky, M.B. Youdim, Neuropharmacol 46 (2) (2004) 254–263.
[132] I. Pedroso, M. Garcia, E. Casabona, L. Morales, M.L. Bringas, L. Pérez, T. Rodríguez, I. Sosa, Y. Ricardo, A. Padrón, D. Amaro, Behav. Sci. 8 (5) (2018) 51.