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REVIEW

Influence of heavy metals in Parkinson's disease: an overview

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Abstract

Parkinson's disease (PD) is an ageing disorder with deterioration of dopamine neurons which leads to motor complications like tremor, stiffness, slow movement and postural disturbances. In PD, both genetics as well as environmental factors both play a major role in causing the pathogenesis. Though there are surfeit of risk factors involved in PD occurrence, till now there is lack of an exact causative agent as a risk for PD with confirmative findings. The role of heavy metals reported to be a significant factor in PD pathogenesis. Heavy metal functions in cell maintenance but growing pieces of evidences reported to cause dyshomeostasis with increased PD rate. Metals disturb the molecular processes and results in oxidative stress, DNA damage, mitochondrial dysfunction, and apoptosis. The present review elucidates the role of cobalt, nickel, mercury, chromium, thallium metals in α-synuclein aggregation and its involvement in blood brain barrier flux. Also, the review explains the plausible role of aforementioned metals with a mechanistic approach and therapeutic recommendations in PD.

Keywords Parkinson's disease (PD) · Heavy metals · Blood brain barrier · α-synuclein · Therapeutics

Introduction

Parkinson's disease (PD) is a second most progressive neurodegenerative condition categorized with motor and non-motor symptoms such as tremors, stiffness, slow movement, sleep disturbances, constipation autonomic dysfunctions, cognitive abnormalities and psychiatric symptoms [1, 2]. The main pathologic marker of PD is the progressive degeneration of dopaminergic (DA) neurons and the presence of α-synuclein (αSyn) in the brain [3–5]. The aetiology of PD is largely unknown, but studies have revealed that the environmental factors plays a majority role than genetic factor [2, 6, 7]. Among environmental factors, heavy metals are natural constituents which persistently exist and leads as one of the risk factor in disease occurrence [8]. They are categorized as essential and non-essential types. Metals like manganese (Mn), copper (Cu), zinc (Zn), nickel (Ni), and iron (Fe), acts as cofactors for many proteins. However, few heavy metals do not have a biological function which includes cadmium, lead (Pb), and mercury (Hg), but rather results in toxic nature if they are consumed [9]. Metals involvement in neurodegeneration ends up in oxidative stress, impairment in mitochondrial function, stress in endoplasmic reticulum, DNA fragmentation, protein misfolding, activation of microglia, and apoptosis [10]. These molecular pathways further result in common neurological symptoms like cognitive dysfunction, stress, learning disabilities, motor activities, etc. [11]. The core sources of heavy metals exposure are from occupations, pollution, adulterated seafood, medications, and metal dental restorations [12]. Metal-induced neurotoxicity in PD is still under research. Metals contribute either by producing metallic toxicants or by declining levels of essential metals [13]. Here in this review, we address the significance of heavy metals in neuronal function and its route of exposure focusing on neurotoxic effects of cobalt (Co), Ni, Hg, chromium (Cr), and thallium (Tl) in PD, and we have described the probable role of each metal in PD

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advancement along with therapeutic suggestions for treating metal toxicity in PD.

Heavy metals and their impact of neuronal function and ageing process

Heavy metals reported to be toxic in all organs, but the most affected region is the central nervous system (CNS) followed by other regions. Inorganic metals such as Pb, Mn, Al, Li, Tl, As, and Hg are predominantly reported to show detrimental effects on neurological and behavioural aspects [14]. It is very common for heavy metals to cause lifelong disabilities such as autism, cerebral palsy, PD, multiple sclerosis, and Alzheimer's disease due to their enduring and irretrievable effects [15]. According to a study, heavy metal exposure is one of the most common causes of neurotoxicity in various populations across the globe [16]. Heavy metals accumulate in the brain under physiological conditions and are integrated into essential metalloproteins that supports neuronal health as well as energy homeostasis. The accumulation of essential metals or exposure to toxic non-essential metals can cause several severe complications [17, 18]. This is common in PD which results in the death of dopaminergic neurons during aging [19]. Although heavy metals are reported to be toxic in humans, it is still unclear what factors are involved in few people to be more vulnerable than others. Certain metals like Cd, Pb, As, and Hg are known to display their neurotoxic potential through ROS production and diminished antioxidative activity [20]. The blood brain barrier (BBB) guards the brain cells from organic and inorganic toxic substances by complimentary pathways. However, toxic metals could circumvent the mechanisms and impose destruction to the brain parenchyma [16]. The efficiency of BBB may also be conceded either in extreme pathogenic conditions or through toxic potential of the metals that targets the blood–brain peripheries. Growing evidence has shown that the BBB acts as the protector of CNS which are subjected to toxicity of heavy metal association. Since the BBB has a distinct role in brain development, it is evident that damage in BBB might enhance to metal induced neurotoxicity [21]

Alterations to the nervous system are a part of the aging process, as they also affect other organ systems. Heavy metals have been linked to sensory function loss in adults, including vision, smell, and sensation, which is uncommon in children [22]. Ageing causes increased level of senescent cells which can release immune-related factors that declines the likelihood of surrounding cells [23]. Hence, senescence process will be more sensitive to heavy metals accumulation in neuronal cells. Ageing induces various cellular and molecular alterations which are susceptible to protein aggregation, oxidative stress, dyshomeostasis, reduction in toxin clearance, mitochondrial dysfunctions, apoptosis, and DNA damage. These alterations end into neuronal death and are intensified in particular susceptible neurons [24]. Essential metals such as calcium, Cu, Mn, and Co are thought to act as neurotoxic especially during ageing when their concentration changes from optimal level, whereas non-essential metals such as Hg, cadmium, and Ni lead to various molecular alterations and neurodegenerative disorders during ageing dysregulation [25]. During ageing, Hg exposure increases as atmospheric Hg levels elevates which induces oxidative stress, cell membrane damage, and autoimmunity process in PD [26]. However, frequent exposure to heavy metals is toxic to the brain which might aggravate brain's ageing process and accelerate the neurodegenerative condition. Therefore, more evidences need to be explored for a better understanding of heavy metal impact on ageing process which might aid in identifying pharmacological target sites to alleviate neurodegenerative conditions.

Source and route of heavy metal exposure in nervous system

In recent years heavy metals have become a growing source of ecological and worldwide public health concern. Moreover, human exposure to metals has increased through several metal sources present in the environment, including geogenic, industrial, agricultural, pharmaceutical, and home effluents [27]. Metal-based industries like mining, foundries and smelters are considered to be a prominent source of heavy metals [27–29]. Normally, heavy metals are found in trace concentrations in soil and plants [30, 31]. However, heavy metals are encapsulated in nanoparticles (NPs) which has a dimension of < 100 nm [32, 33]. Metallic NPs can cross the cell membranes and enter cellular organelles thereby affecting the physiological functions of the cell [34–36]. The metallic NPs in commercial products like sunscreens, cosmetics, toothpaste, plastics, paints, etc., are revealed to be a possible source of heavy metals to enter the body [37–39]. Regardless of where they come from, metals can enter the body through many routes, including ingestion, inhalation, and injection. They can then enter in various parts, after circulating in blood [40, 41]. According to a previous study, it was stated that the BBB is incapable of protecting against metals translocation [42]. Nerve cells are more vulnerable to toxins than other types of cells due to their restricted ability to regenerate [43]. Metallic NPs adhere to olfactory mucosa or enter bronchi and alveoli in the lung due to their tiny size [44–46]. NPs are carried from the nasal cavity by the olfactory epithelium and migrate to the choroid plexus [33, 45]. The olfactory nerve acts as a direct route for metallic NPs to reach the brain [47]. On the other hand, inhaled metal NPs can enter alveolar epithelial cells and then circulate through the blood and lymph system, eventually collecting in the heart, brain, lymph nodes and

spleen [48, 49]. The digestive tract is also a significant route for metallic NPs where it is absorbed by epithelial cells from which they can travel to the bloodstream and other organs. Similarly, metallic NPs can enter the cell through interacting with membrane components through endocytosis.. Hence, additional research is essential on the source and route of exposure of heavy metals in order to find and initiate further research. Table 1 depicts the list of studies on sources and routes of exposure of heavy metals and its effects.

BBB flux in metal induced neurodegeneration

The BBB is made up of an endothelial membrane that owns closed connections and is encased by mural vascular cells and perivascular astrocytes. It serves as a crucial barrier between the neural cell and circulating blood. By protecting neurons from circulating substances, the BBB maintains the highly controlled environment inside the CNS, which is vital for normal synaptic and neuronal function [57]. Failure to maintain any of these components results in specialized multicellular structure to cessation, promoting neurodegenerative characteristics [57, 58]. An inflammation can lead to the disruption of BBB which allows toxins, cells, and infections to reach the brain that can results in neurodegeneration [59–61]. It is said that transporters involve in metal distribution across the BBB apart from the metals that are absorbed mostly through the gastrointestinal system, lungs, and skin. Metal accumulation in the CNS affects BBB permeability, activates microglia and astrocytes, and alters water transport across the cells which can lead to brain swelling. Aquaporin-4 (AQP4) is the main water channel present in the astrocyte foot proceeding to brain capillaries and to the circumventricular epithelium where it plays a key role in preserving brain osmotic condition and excitability by regulating the extracellular space [62]. Few studies suggests that AQP4 plays as a neuroprotector, where its dysfunction leads to oxidative stress following brain metal toxicity by disrupting BBB [62, 63]. Deficiencies in metal ion homeostasis and toxic quantities of non-essential metals cause metabolic alterations and water permeability in the brain with increased AQP4 expression in the brain. Therefore, targeting a balanced modulation of water and solute transport using AQP4 leads to new therapeutic interventions in various neurodegenerative diseases. Figure 1 represents the BBB flux in neurodegeneration due to heavy metals.

Metal triggering protein aggregation and abnormalities

The exposure to several heavy metals resulted in significant accelerations of αSyn fibril formation in which Cu and Co were highly correlated with protein aggregation. Metal ions could alter the fibril morphology as well as the aggregation speed when they interact with disease-specific proteins. A wide range of studies have explored the association between heavy metals and αSyn [64–66]. According to the findings, low concentrations of some metals can directly encourage αSyn formation of fibrils [64]. In an animal model using *E. Coli* the, Co and Ni selectively induces the rapid formation of discrete αSyn oligomers in PD [67]. Recently, in a human case study, with hip replacement, elevated levels of serum Co and Cr metals were reported in atypical Parkinsonism [68]. αSyn activity was induced at low Hg_2 levels, while higher levels increased stress-response genes. The combination of mass spectrometry was utilized for characterizing αSyn binding with Co and Mn metals [69]. Similarly, in an animal model using *Caenorhabditis elegans*, Hg levels were reduced which increased the aggregation of αSyn [70]. Table 2 depicts the list of metals involve in αSyn aggregation. Till now, only limited studies have been focused on the metals with αSyn aggregation, and it is essential to understand the conformational changes of αSyn when specific metal binding occurs which leads to pathological and physiological outcomes.

Mechanistic insights of heavy metals in PD

Probable effect of Co in PD pathology

According to an animal study using mouse embryonic stem cells**,** the contribution of excessive Co in PD neurotoxicity has not been investigated. It is reported that Co-induced neuronal damage results in oxidative stress [71–73]. Here, we elucidate a probable mechanism of Co inactivating peptidyl-prolyl cis/trans isomerase or Pin1 which contributes to age-related neurodegeneration under certain physiological conditions, in this the excessive Co inactivates Pin1 which thereby activates glycogen synthase kinase 3 beta (GSK3β), an isoform of GSK3 which plays a pivotal role in neurodegenerative diseases [74]. GSK3β activation phosphorylates αSyn leading to aggregation which results in inflammation and oxidative stress. GSK3β induces microglial activation which increase the proinflammatory cytokines levels that leads to neuroinflammation. Simultaneously, GSK3β upregulates BAX level and promotes mitochondrial membrane permeabilization by separating Bcl-2 and releases cytochrome c which leads to cell death [75] (Fig. 2). Hence, this potential pathway of Co role in PD pathogenesis is yet to be investigated by conducting further research on toxic effect of Co in neurodegeneration.

Plausible role of Ni in PD

Studies have shown the influence of Ni in neurotoxicity by inducing ROS, inflammation, apoptosis, mitochondrial dysfunction, and epigenetic modifications in neuronal cells [76].

Table 1 Source and route of exposure of heavy metals and its effects

S/No	Metals	Source of Exposure	Route of Exposure	Mode of Penetrance	Effects	References
1	Metallic NPs	Vectors of drugs, sunscreens, toothpaste, cosmetics, plastic products, textiles, paints, and gasoline components	Inhalation and injection	Nose mucosa- bronchi- alveoli -lung-Nasal cavity. Olfactory bulb-olfactory nerve/trigeminal/ the blood- cerebral spinal fluid-choroid plexus lymph circulation-brain/bone marrow/ lymph nodes/ spleen or heart	Shrinkage of mitochondria, endoplasmic reticulum expansion and vacuolations in astrocytes. Induce toxicity in neurons. Apoptosis and necrosis of NSCs ↑ ROS production	[31, 37–39, 45, 50, 51]
2	Metallic NPs	Vectors of drugs, sunscreens, toothpaste, cosmetics, plastic products, textiles, paints, and gasoline components	Ingestion	Epithelial cells in the digestive system- bloodstream -secondary organs	It causes abnormalities in cytoskeleton formation, pre- and post-synaptic proteins, and mitochondrial cell death	[52]
3	Metallic NPs	Vectors of drugs, sunscreens, toothpaste, cosmetics, plastic products, textiles, paints, and gasoline components	Cellular uptake	Endocytosis	Dopamine depletion by alteration in dopaminergic genes	[53]
4	Hg	Contaminated food, water, air, industrial or agricultural waste	Gastrointestinal tract, inhalation, skin	Mercury vapours- lungs-bloodstream- kidney-brain and other body parts	Neurological complications like vascular dementia, stroke, cognitive impairment, mental retardation	[54]
5	MeHg	Contaminated food, air, water, amalgam-treated teeth, chemical factories, waste water from chemical plant	Consumption, gastrointestinal system, respiratory tract	Absorbed by lungs/absorbed by digestive tract- carotid artery. Combine with haemoglobin through portal vein- accumulate in CNS	It effects neuron delivery materials; causes oxidative stress, lipid peroxidation, and mitochondria dysfunction; and distracts synapse transmission, microtubule composition, amino acid transport, and cellular migration in growing brains. Motor disturbances such as ataxia and trembling, and dysesthesia such as impaired vision	[55]
6	Cr	Air, water, soil, industries, tannery facilities, stainless steel welding, pigment production, cigarette smoking	Inhalation, ingestion, through skin	Nose-lungs	Renal damage, allergy, asthma, cancer, reproductive issues, cardiovascular, neurological effects	[56]

Cr chromium; *NPs* nanoparticles; *Hg* mercury; *MeHg* methylmercury; *NSCs* neural stem cells; *ROS* reactive oxygen species; *CNS* central nervous system

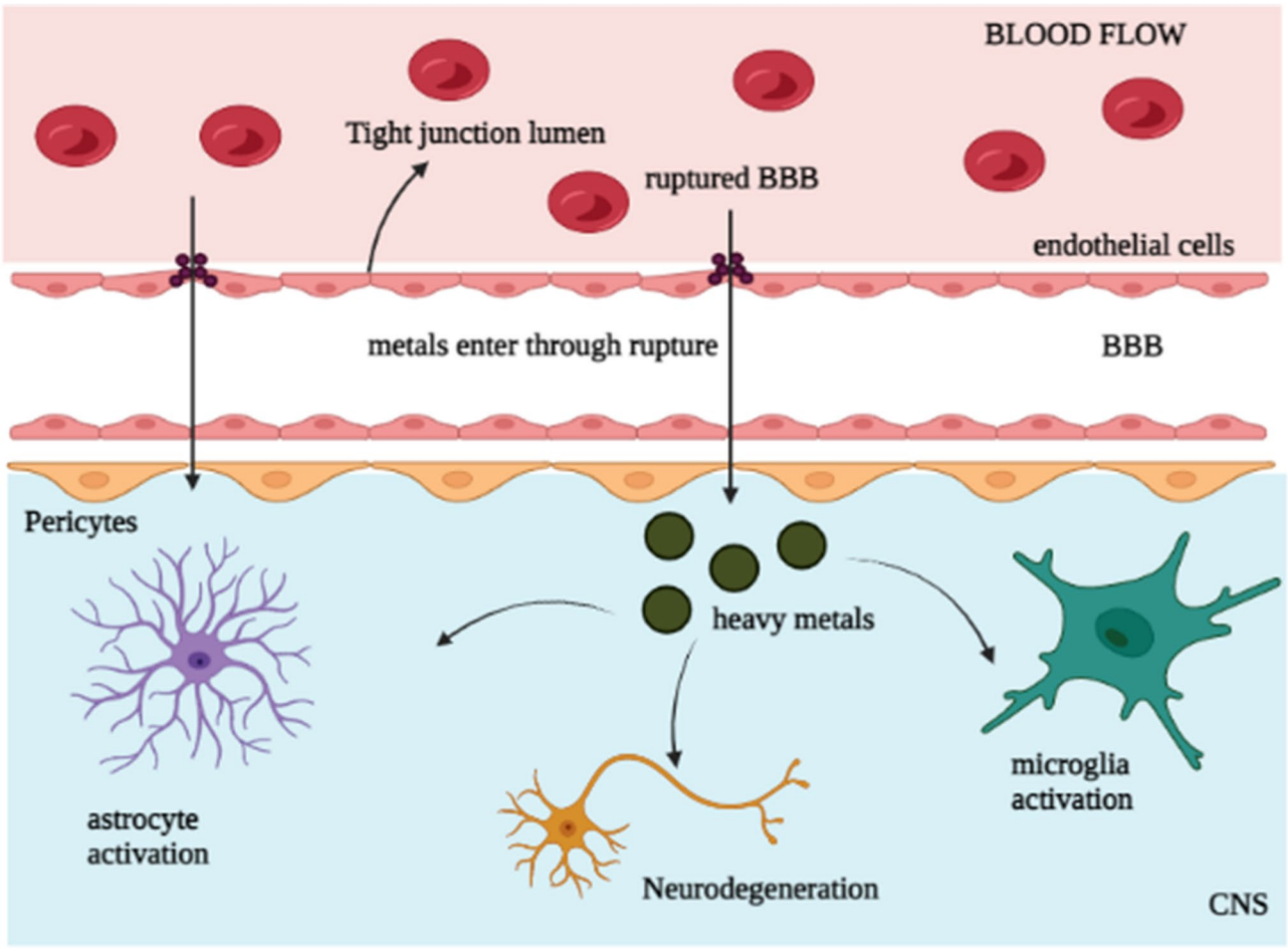

Fig. 1 BBB flux in metal induced neurodegeneration. Ruptured BBB permits the entry of toxic heavy metals thereby activates astrocytes and microglia thereby causing neurodegeneration

Table 2 Heavy metals inducing αSyn aggregation

S. no	Heavy metals	Model	Gene expression	Dose exposure	Mode of action	References
1	Co	in vivo	A53T and A30P in *SNCA*	3.5 µM	Fibril formation	[64]
2	Ni, Co	*Escherichia coli* BL21	–	45–90 nm	Oligomerization	[67]
3	Co	*Human*	*SNCA*	10 µM	Fibrillation, ECD and CAD to identify the sites of Co binding to αSyn	[69]
4	Hg	*Caenorhabditis elegans*	hsp-16.2 mtl-2 sod-4	0.002–0.02 W kg-	Hg might promote αSyn aggregation only at very low concentrations	[70]

Co cobalt; *Ni* nickel; *Hg* mercury; *SNCA* alpha synuclein; *µM* micromolar; *nm* nanometer; *W kg* weight kilogram; *ECD* electron capture dissociation; *CAD* collisional activated dissociation; *αSyn* alpha synuclein

The over-exposure of Ni has been demonstrated in several in vitro and in vivo studies but the exact mechanistic behaviour in PD is not yet understood. It has been reported that Ni crosses the BBB through the olfactory tract and primarily reaches the cerebral cortex [77]. A study has stated that on exposure to higher concentration of Ni disrupts the neurotransmitter system which subsequently alters long-term synaptic transmission [78]. However, the dose-dependent concentration of Ni suggested to show significant disturbance in dopamine, serotonin and noradrenaline function in cerebral

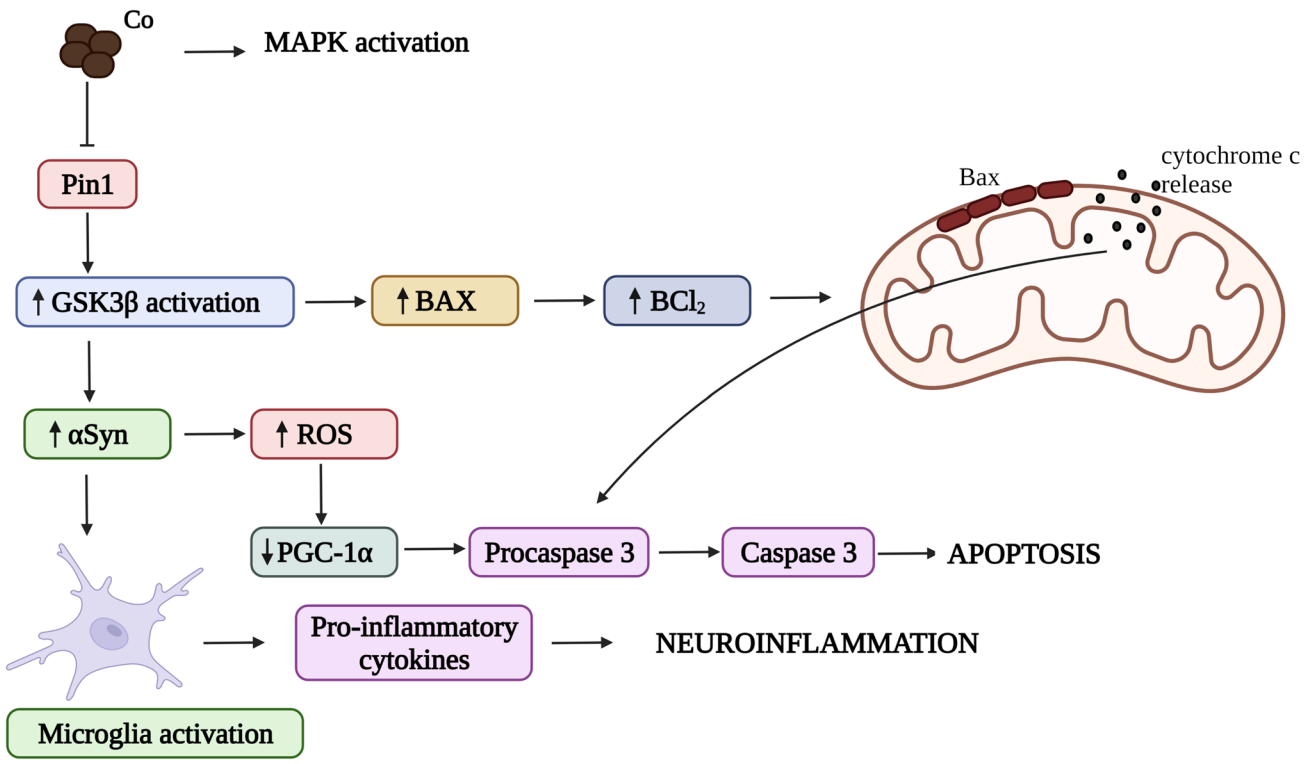

Fig. 2 Co effects in αSyn aggregation and PD initiation. Co inactivates Pin1 and activates GSK-3β which leads to phosphorylation of αSyn leading to aggregation which results in inflammation and oxidative stress. GSK-3β induces microglial activation which increase the proinflammatory cytokines levels that leads to neuroinflammation. Simultaneously, GSK-3β upregulates BAX level and promotes mitochondrial membrane permeabilization by separating Bcl-2 and releases cytochrome c which leads to cell death. *Co* cobalt; *Pin1* peptidyl-prolyl cis/trans isomerase; *GSK-3β* glycogen synthase kinase-3 beta; *αSyn* alpha synuclein; *BAX* BCl_2 associated X protein; *Bcl-2* B-cell lymphoma 2; *MAPK* mitogen-activated protein kinase

cortex and basal ganglia [79]. Earlier, it has reported that Ni alters dopamine and glutamate receptor encoding gene expression [80–82]. Though limited studies have been conducted in Ni toxicity, here we report the probable mechanistic approach of Ni influence in PD pathogenesis. Similar to other metals, Ni enters the BBB thereby causing an increase in ROS, neurotoxicity and apoptosis which leads to increased levels of αSyn aggregation which in turn hinders synaptic transmission and degeneration of dopamine leading to PD pathogenesis (Fig. 3). Therefore, the toxicity of Ni in neurodegeneration has to be elucidated in order to explore the therapeutic platform for pathological conditions in PD.

Previous studies on the role of Ni in mitochondrial dysfunction

Ni exposure is predominantly associated with cellular energy alterations [83]. Animal study on Wistar rats concluded that the neurotoxic potential of Ni is suggested to involve in oxidative stress and mitochondrial impairment due to the damage in mitochondrial membrane potential and mitochondrial DNA impairment which results in ATP decline [84, 85]. Diminished mitochondrial function delays mitochondrial transport chain function, ROS generation and worsens oxidative stress. In a study, cortical neurons and primary neuroblastoma noticed with dose-dependent increase in ROS during Ni deposition [82]. An animal study shows that Ni-induced neurons was reported with ROS production, elevated lipid peroxidation and destructed antioxidant function[80, 86, 87]. This lipid peroxidation generates free radicals, which precedes to structural alterations in biological membranes with impaired membrane fluidity that leads to neurodegenerative condition [80, 88]. In Ni-exposed rat model, superoxide dismutase (SOD) and catalase (CAT) activities were declined in hippocampal region signifying with an inclination in oxidative stress [80, 89]. Similarly in fish brain, CAT expression was suppressed due to Ni exposure [86, 90]. It is distinguished that SOD and CAT functions as defensive mechanism against free radical production [80]. Studies have reported with a decrease in brain antioxidant enzymes such as glutathione S-transferase (GST), SOD, glutathione (GSH), glutathione peroxides (GPx) and CAT levels in Ni-induced rats [84, 91]. Similarly, in human

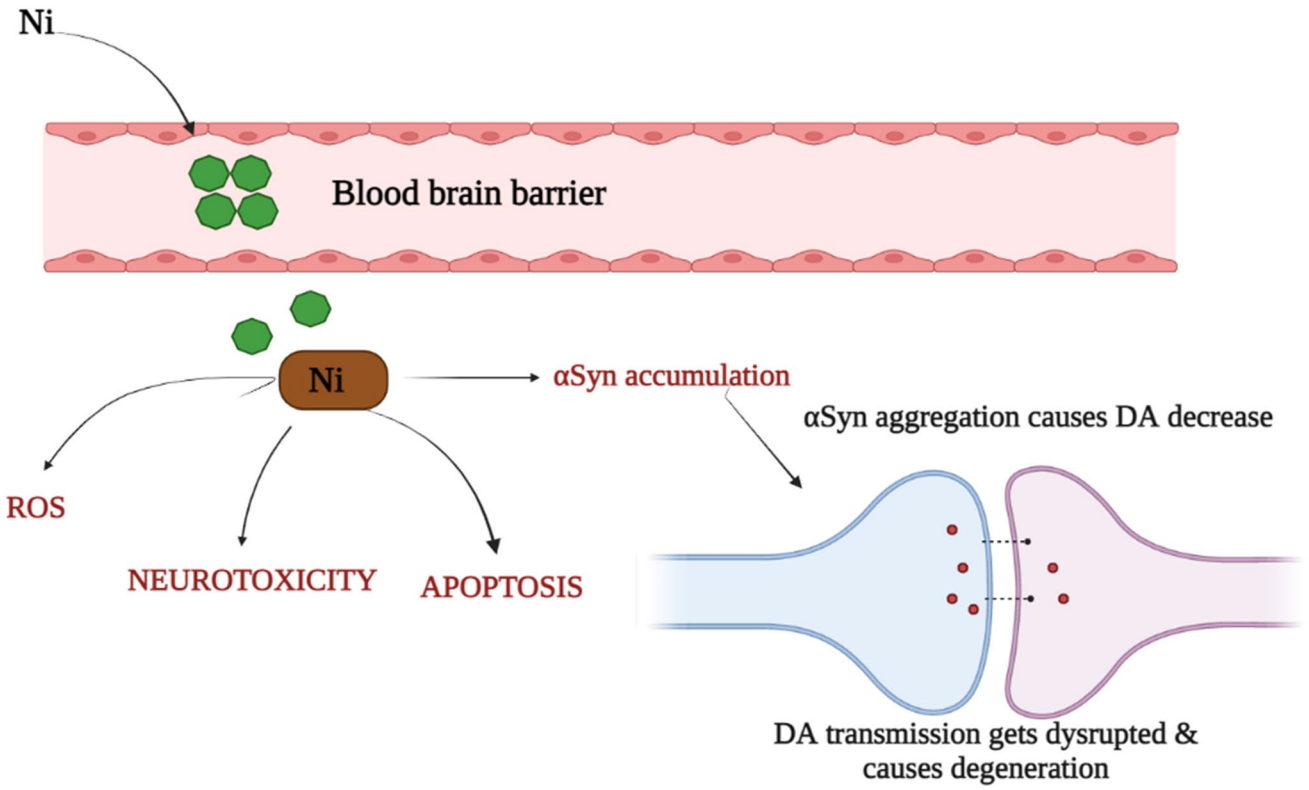

Fig. 3 Ni influence in PD. Ni crosses the blood brain barrier (BBB) and it increases ROS, neurotoxicity and apoptosis. This cellular pathology leads to increase in αSyn aggregation that hinders the synaptic transmission of DA which deteriorates as time exceeds. *Ni* nickel; *ROS* reactive oxygen species; *αSyn* alpha synuclein; *DA* dopamine

studies during hypoxia-induced stress, the hypoxia-inducible factor-1α (HIF-1α) gets distracted from degradation process due to Ni. Evidences have shown that Ni exposure can induce HIF-1α accumulation in various cells with an increase in hypoxia responses [92–94]. Iron–sulphur cluster (ISC) proteins plays a role in mitochondrial respiration and energy synthesis, where its binding site for miR-210 gets inhibited by Ni toxicity thereby causing downregulation of ISCU1/2 followed by destruction of mitochondrial electron transport mechanism and oxidative phosphorylation [89]. Taken together, these studies suggest that Ni-induced neurotoxicity alters the energy metabolism through impaired antioxidant defence system, interruption to oxidative phosphorylation and progression of anaerobic glycolysis. Though limited studies have been conducted on molecular level in Ni-induced neurotoxicity, evidences have shown the prominent role of Ni on mitochondrial function in neurotoxicity. Hence, additional research is essential to explore the molecular mechanism of Ni in mitochondrial dysfunction. Table 3 shows the list of countries with studies on Ni toxicity inducing mitochondrial dysfunction.

Toxic effects of Cr in PD

Hexavalent (Cr(VI)) is rapidly transported to BBB than trivalent (Cr(III)) [95]. Many pathogenic mechanisms have been proposed but in PD the toxic effects of Cr are not investigated clearly. In 2011, an animal study proposed on Cr exposure depleted the levels of sulphur that resulted in Cr toxicity [96]. The study using human samples states that sulphur amino acid cysteine (Cys) and its antioxidant GSH are majorly involved in the reduction of Cr(VI) to toxic form [97, 98]. This reduction promotes ROS generation. In PD, chromate (CrO_4^{2+}) and sulphate (SO_4^{2+}) enter into the cell through CrO_4^{2+} and SO_4^{2+} transporters which readily converts Cr (VI) to Cr (III) with ROS production. Simultaneously, SO_4^{2+} level gets declined along with sulphur compound reduction. As it stated earlier, sulphur reduction causes a decline in the level of Cys and methionine (Met) amino acids which leads to mistranslation [96] thereby causing αSyn aggregation that leads to neurodegeneration. This possible mechanism shows Cr impacts sulphur decline and vice versa which might result in αSyn

Table 3 List of studies related to Ni influence on mitochondrial dysfunction

Country	Year of the study	Model	Cellular alterations	Study outcome	References
China	2010	Mouse	Oxidative damage to mitochondrial function and damage to mtDNA	↑ ROS	[82]
Morocco	2018	Rats	Neuronal degeneration and cellular death	↑ Lipid peroxide ↓ Anti-oxidant function	[80]
Turkey	2015	Fish	oxidative stress, changes in c-Fos activity, and histopathological damage	↑ Lipid peroxide ↓ Anti-oxidant function	[86]
India	2009	*Cirrhinus mrigala*	Histopathological damage	↑ Lipid peroxide ↓ Anti-oxidant function	[87]
India	2012	Human	Oxidative stress, cell death and neurodegenerative condition in central nervous system	↑ SOD, CAT, glutathione and non-enzymatic antioxidants	[88]
German	2013	Fish	Decrease in oxidative stress protein carbonyls and	↓ CAT	[90]
Nigeria	2020	Rats	Neuronal inflammation and oxidative injury	↓ GST, SOD, GSH, GPx and CAT	[91]
Nigeria	2018	Rats	Oxidative stress and mitochondrial apoptosis	↓ GST, SOD, GSH, GPx and CAT	[84]
Pennsylvania	2008	Human	HIF-1α accumulation	↑ Hypoxia-mimic	[92]
USA	2006	Human	Metal induced hypoxia or metal-induced disruption of Fe homeostasis, HIF-1α accumulation	↑ Hypoxia-mimic	[93]
Island	2011	Human	Activation of HIF-1α accumulation	↑ Hypoxia-mimic	[94]
China	2017	Human	Destruction in mitochondrial electron transport mechanism and oxidative phosphorylation	↓ ISCU1/2	[89]

ROS reactive oxygen species; *SOD* superoxide dismutase; *CAT* catalase; *GST* glutathione−S−transferase; *GSH* glutathione; *GPx* glutathione peroxidase; *HIF−1α* hypoxia−inducible factor 1−alpha; *ISCU1/2* iron−sulphur cluster 1/2

aggregation (Fig. 4). Thus, the Cr toxicity with mechanistic insight should be examined clearly in PD.

Methyl mercury (MeHg) and Tl influence in PD pathology

MeHg is an organic form of Hg which passes the BBB through amino-acid transporters. It binds with the thiol groups of Cys and GSH, where it declines the sulphur compounds that ends up in mistranslation with αSyn aggregation. Also, demethylation occurs in glial cells which ends up in catalysing hydrogen peroxide pathway to inorganic form in neuronal cells. MeHg and inorganic form increase the levels of free radicals and results in ROS production [99]. This increase in ROS and αSyn mistranslation leads to neurodegeneration of DA by intruding in the molecular mechanisms of apoptosis, autophagy, and inflammation. Similar to Hg, Tl is also toxic and the primary organelle gets affected is mitochondria. Tl interrupts the electron transport chain and depletes ATP levels. Till now, studies have reported the involvement of Tl in neurotransmission but the exact pathogenesis is yet to be identified. Tl intoxication is said to cause oxidative stress, lipid peroxidation in cell membranes and involves in antioxidant mechanisms. The correlation with these molecular pathways is widely involved in neurotoxic effects [100–102]. The above stated possible mechanisms can further be elucidated through in vivo and in vitro studies in decoding the etiological factor behind MeHg and Tl toxicity in PD pathogenesis (Fig. 5).

Metallomic biomarkers in PD

Metabolomics is an emerging field which connects biomarker discovery and pathogenicity of a disease. The study of metabolomics has provided evidences on neurodegenerative condition with the intention of investigating disease-specific pattern [103]. Table 4 depicts the study findings conducted on heavy metals associated with PD. Earlier studies resulted with an increase in Ni and Cr with an increase and decrease in Co levels in biofluids of PD patients with a consequence in oxidative stress and aggregation of αSyn. The levels of Cr, Hg and Tl reported with no change in PD patients [104–108]. Hg levels were high in CSF of PD patients leading to the death of dopaminergic neuronal death [109]. Thus, heavy metals are well-known for their effects on humans leading to PD pathogenesis. However, more studies need to be conducted on biofluids in PD research

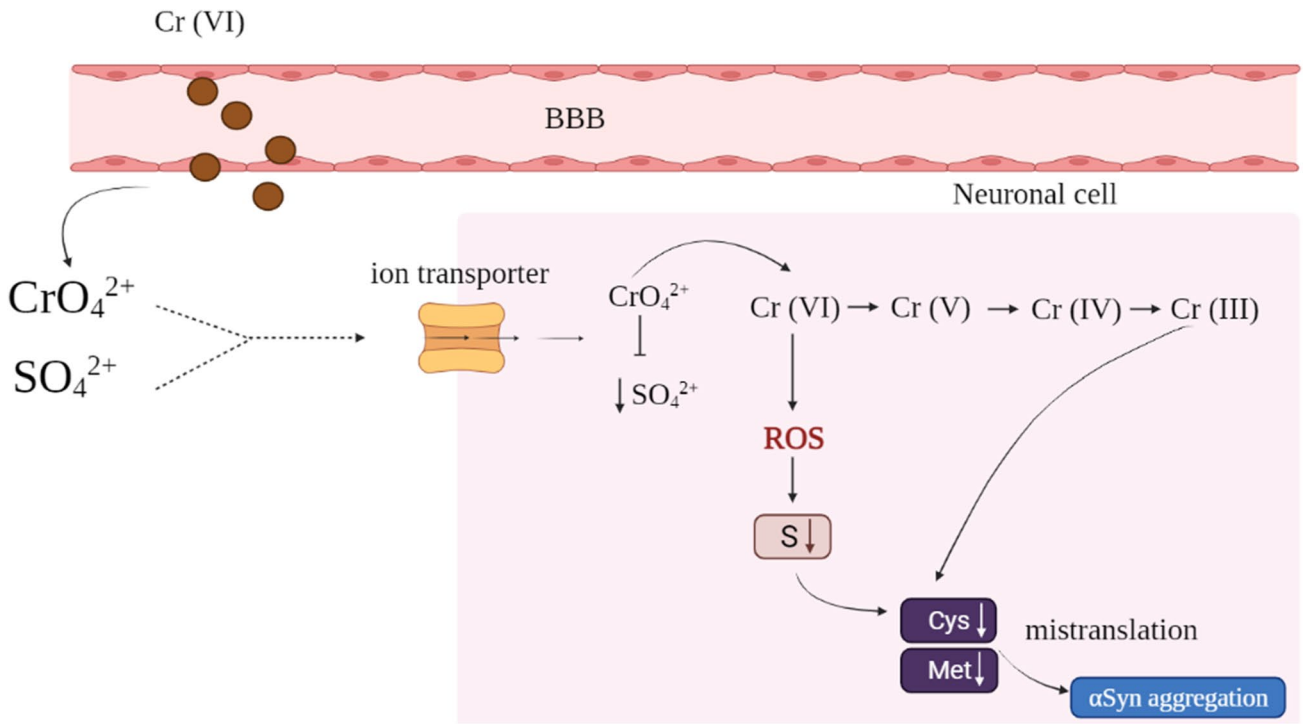

Fig. 4 Cr toxicity in neurodegeneration. Cr(VI) crosses BBB where the ions chromate (CrO_4^{2+}) and sulphate (SO_4^{2+}) enter into the cell through CrO_4^{2+} and SO_4^{2+} transporters which readily converts Cr (VI) to Cr (III) with ROS production. SO_4^{2+} level and S level declines. S reduction causes a decline in the level of Cys and Met amino acids which leads to mistranslation thereby causing αSyn aggregation that leads to neurodegeneration. *Cr(VI)* hexavalent chromium; BBB: blood brain barrier; *CrO_4^{2+}* chromate; *SO_4^{2+}* sulphate; *Cr (VI)* tetravalent; *Cr (III)* trivalent; *ROS* reactive oxygen species; *Met* methionine; *Cys* cysteine; *αSyn* alpha synuclein

which would enhance to unravel a detailed mechanism of PD behavioural and neurological effects.

Therapeutic recommendations for heavy metals treatment

Though therapeutic strategies are progressing in PD, the therapeutic implications for metal-induced PD is the chelation therapy which is a common therapeutic approach used to treat heavy metals intoxication in many diseases. Metal chelation treatment uses a chelating agent (CA), which is a chemical that creates stable coordination complexes with the target metal ion. When the CA is supplied to the patient, it acts as a scavenger, extracting the metal from its stores and promoting its decorporation from the body [110]. Some common chelating agents are dimercaprol, 2,3-Dimercapto-Propanesulphonate (DMPS), sodium-calcium EDTA (CaNa2-EDTA), deferoxamine (DFO), penicillamine, dimercaptosuccinic acid (DMSA), DMSA analog, monoisoamly dimercaptosuccinic acid (MiADMSA), mono-cyclohexyl dimercaptosuccinic acid (MchDMSA), and monomethyl dimercaptosuccinic acid (MmDMSA) [111]. Chelating drugs like DMSA and DMPS can be used orally and have lower toxicity than dimercaprol. Furthermore, DMSA appears to be more effective in removing MeHg, including from the brain. DMPS cannot repair MeHg levels in the brain, but it can effectively remove it from the kidney [112]. Still many clinical studies are in process to examine the Hg chelating agents in treating neurological disorders [113]. N-acetylcysteine, CaEDTA, and dimercaprol is known to be effective in decreasing the circulating Cr levels through urine excretion [114]. Ni hyperactivity was treated by disulfiram chelating agent in a case of 49-year-old women [115]. Similarly in Tl, the chelating agent diethyldithiocarbamate has cleared higher levels of Tl in urine [116]. This was suggested to be used for any patient suffering from high levels of Tl. For Co toxicity, EDTA was recommended in lowering the levels of Co in blood [117]. Hence, Table 5 suggest the therapeutic ways for treating heavy metals toxicity. However, extensive research is required on chelating agents of toxic metals in order to understand the mode of actions and to inspect the economical and safe therapeutic compound to overcome heavy metals toxic effects. Therefore, heavy metal toxicity treatment in PD should be investigated since there are no much studies focused till now.

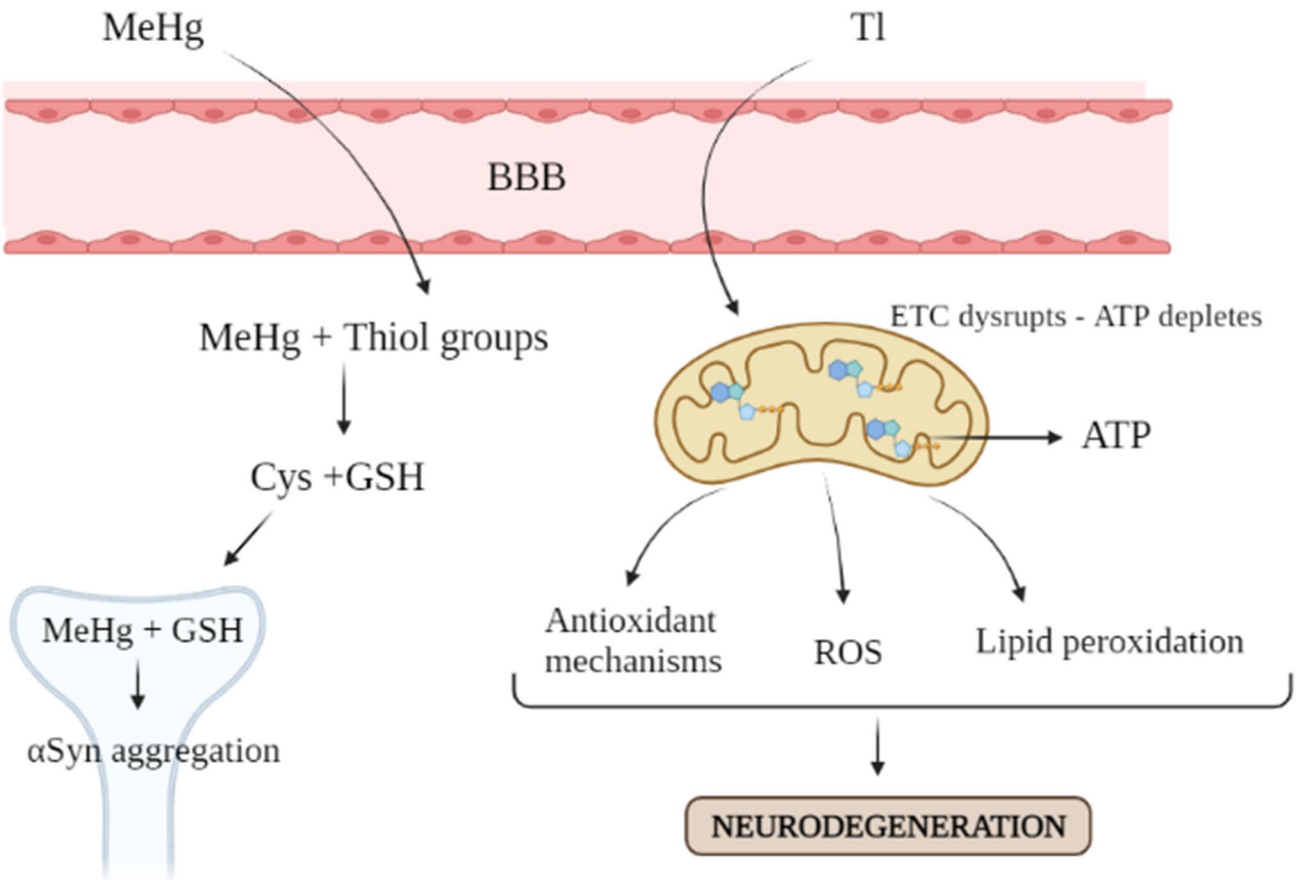

Fig. 5 MeHg and Tl role in PD pathogenesis. MeHg crosses BBB and it binds with thiol groups which reduces the levels of Cys and GSH; in neuronal cells MeHg with GSH gets activated and causes αSyn aggregation. Tl disrupts the mitochondrial function which depletes ATP levels thereby results in ROS, lipid peroxidation and interrupts antioxidant mechanism. These will lead to neurodegeneration. *MeHg* methylmercury; *Tl* thallium; *Cys* cysteine; *GSH* glutathione; *ATP* adenosine triphosphate; *ROS* reactive oxygen species

Table 4 Metallomic biomarkers studies in biofluids of PD subjects

Heavy metals	Biofluids	Model	No. of subjects	Analytical methods used	Outcome of the study	References
Cr	CSF and serum	Human	28 patients and 43 controls	Atomic absorption spectrophotometer, Electro thermal atomizer, Auto sampler	No difference	[105]
Cr, Ni, Co, Tl	Serum and blood	Human	71 patients and 44 controls	ICP-MS and ICP-AES	↑ Cr, Ni, ↑ Oxidative stress ↓ Co, Tl ↑ αSyn accumulation	[104]
Cr, Co, Hg	CSF and Serum	Human	250 patients and 280 controls	Atomic Absorption Spectrophotometry	↑ Cr, Co, Hg ↑ Oxidative stress	[106]
Ni	Serum	Human	33 patients and 99 controls	HR-ICP-MS	↑ Ni	[107]
Ni	CSF	Human	33 patients 101 controls	ICP-sf-MS SEC-ICP-DRCMS FT-ICR-MS	No significance level of Ni	[108]
Hg	CSF	Human	36 patients and 42 control	ICP-OES and ICP-sf-MS	↑ Hg ↑ DA neurons death	[109]

Cr chromium; *Ni* nickel; *Co* cobalt; *TI* thallium; *Hg* mercury; *CSF* cerebrospinal fluid; *PD* Parkinson's disease; *ICP–MS* inductively coupled plasma mass spectrometry; *ICP–AES* inductively coupled plasma atomic emission spectroscopy; *HR–ICP–MS* high–resolution inductively coupled plasma mass spectrometry; *ICP–OES* inductively coupled plasma–optical emission spectrometry; *(FT–ICR)–FT–ICR* Fourier–transform ion cyclotron resonance; *DA* dopamine

Table 5 Chelation therapy for treating heavy metals toxicity

Heavy metals	Biofluid	Model	Chelation therapy	Outcome of the study	References
Cr	Urine	Rat	NAC treatment, CaEDTA, and dimercaprol	↓ Cr in circulating blood	[114]
	Blood	Human	disulfiram	↓ Ni levels in blood	[115]
Hg	Urine, blood, serum and sweat	Human	BAL D-penicillamine Sodium diethyldithiocarbamate	↓ Hg levels	[113]
Tl	Blood and urine	Human	diethyldithiocarbamate	↓ Tl levels	[116]

Cr chromium; *Hg* mercury; *Co* cobalt; *Ni* nickel; *Tl* thallium; *NAC N*−acetylcysteine; *CaEDTA* calcium disodium ethylenediaminetetraacetate; *BAL* 2,3−dimercapto−l−propanol

Conclusion

Heavy metals get accumulated in various organs leading to toxicity. There are a number of cellular events that are disrupted by heavy metals and here the current review highlights the importance of heavy metals in PD pathogenesis. Ageing factor along with exposure to toxic metals need to be unravelled in neurodegenerative diseases. Though many studies have highlighted the toxicity of metals in PD, there are limited research focused on therapeutic aspect. As a new focus, the mechanistic behaviour of heavy metals in neurodegeneration presented in this review will be a novel approach in PD and in other neurodegenerative disorders. The mechanistic viewpoint would aid in developing therapeutic compounds in altering neurodegenerative condition in PD.

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Declarations

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