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Coherent and Contradictory Facts, Feats and Fictions Associated with Metal Accumulation in Parkinson's Disease: Epicenter or Outcome, Yet a Demigod Question

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Abstract Unwarranted exposure due to liberal use of metals for maintaining the lavish life and to achieve the food demand for escalating population along with an incredible boost in the average human life span owing to orchestrated progress in rejuvenation therapy have gradually increased the occurrence of Parkinson's disease (PD). Etiology is albeit elusive; association of PD with metal accumulation has never been overlooked due to noteworthy similitude between metal-exposure symptoms and a few cardinal features of disease. Even though metals are entailed in the vital functions, a hysterical shift, primarily augmentation, escorts the stern nigrostriatal dopaminergic neurodegeneration. An increase in the passage of metals through the blood brain barrier and impaired metabolic activity and elimination system could lead to metal accumulation in the brain, which eventually makes dopaminergic neurons quite susceptible. In the present article, an update on implication of metal accumulation in PD/Parkinsonism has been provided. Moreover, encouraging and paradoxical facts and fictions associated with metal accumulation in PD/Parkinsonism have also been compiled. Systematic literature survey of PD is performed to describe updated information if metal accumulation is an epicenter or merely an outcome. Finally, a perspective on the association of metal accumulation with pesticide-induced Parkinsonism has been explained to unveil the likely impact of the former in the latter.

Keywords Parkinson's disease · Parkinsonism · Metals · Rodent models · Pesticides

Introduction

Metals are indispensable component of several biologically active proteins, which play decisive roles in the metabolic activity of the central nervous system [1]. Although deficiency of metals is associated with a few behavioral and phenotypic abnormalities, accumulation is highly toxic to the central nervous system. Overexpression and aggregation of α-synuclein, oxidative stress, mitochondrial dysfunction, inflammation, and impaired class I and class II programmed cell death are major wrongdoers of Parkinson's disease (PD) and metals are known to regulate such biological processes [1–6]. Accumulation of metals in the striatum and substantia nigra, two terribly affected areas of the brain in PD patients, is widely reported [1, 7]. Metals are reported to increase the defenselessness in experimental rodents and are associated with increased incidences of PD [8, 9, 20]. Imaging techniques have also demonstrated an accumulation of high level of metals in a toxin model of PD [10]. Like pesticides, natal metal exposure could exert lifelong effect in rodents owing to imprinting episode that intensifies the prevalence and severity of Parkinsonism upon adulthood [11, 12]. Oxidative stress is also contributed by metal accumulation. Naturally occurring agents encounter metal accumulation-mediated oxidative stress. Silymarin, resveratrol, melatonin, and their metabolites

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provide protection owing to their antioxidant, free radical scavenging and metal chelating properties [13–15] also showing the role of metal accumulation in PD.

Metal accumulation theory possibly came into the glare of publicity after emergence of the information showing incidences of gradual increase in the deposition of redox-reactive essential metals in the brain of PD patients [2, 11]. Perhaps, the theory got impetus after the development of rodent models employing individual, dual, or multiple metal combinations [1, 5]. Ample support to metal accumulation theory has come from adherence of inverse relationship between metal accumulation in PD brain and ameliorative strategies used to encounter it. Agents that encounter, scavenge, remediate, or reduce free radicals are found to lessen metal accumulation in the brain further strengthen the idea of metal accumulation theory [1, 8, 11, 16]. Furthermore, chelating agents and metal binding modulators, which reduce the severity of symptomatic disease features, also corroborate metal accumulation belief [17, 18].

Unforeseen metal accumulation possibly happens when people are exposed to metal-rich pollutants, diets, and therapies [2, 11, 19, 20]. Buildup in dopaminergic neurons is also feasible, if there is disturbance in the metabolism, uptake, removal, and transport of metals or nutritional deprivation [11, 19, 21]. Despite a few confounding observations, epidemiological and experimental investigations unambiguously discourse that metal accumulation leads to phenotypic anomalies mimicking a few fundamental characteristics of PD [1, 2, 8, 9, 20]. Accumulation in the brain is regulated by the blood brain barrier (BBB) depending on the nature of metals and their ability to cross it. Once a metal enters the brain through specific transporters, it regulates the functional activity of pertinent enzyme. Therefore, metal accumulation is expected to alter the metabolic fate of dopaminergic neurons that are located in the substantia nigra and projected to the striatum. While timely elimination regulates the entry and deposition, unfortunately, the elimination system is not yet explicitly understood.

The growing evidence, which proves the role of metals in sporadic and rodent models of PD, impelled to hoard and discuss updated information in the current article. Three schools of thought prevail in the scientific arena about metal accumulation and PD. The followers of the first thought firmly accept that metal accumulation is an epicenter and believe that accumulation is a prerequisite of PD onset [9, 22]. The second camp deems that PD progression leads to metal accumulation, which is an outcome, and therefore, the concept of metal accumulation leading to PD could not be true [22]. Another thought, albeit with less supporters, disapproves any positive or negative impact of metal accumulation per se in PD. In the current article, we explicitly emphasized and scrutinized the major perspectives of metal accumulation and its relevance in PD pathogenesis. Literature testimonies on evaluated metal content in PD and toxin(s)-induced Parkinsonism have been discussed to pinpoint the merits of metal accumulation theory in the primary (sporadic/idiopathic) and secondary (causative factor(s)-induced) PD. Moreover, an attempt has been made to assess, if metal accumulation theory bears a clear-cut proof or an abstemious flaw or is simply a propagated myth. Finally, a perspective is presented to show how an evaluation of metal accumulation in the nigrostriatal region of the brain of pesticides-induced Parkinsonism could help in validating or ruling out the hypothesis "metal buildup is a prerequisite for PD pathogenesis".

Iron Accumulation and PD

Iron deficiency is linked with diverse anomalies and clinical syndromes, such as anemia and respiratory problem. Unlike a few metals to be discussed in the latter part of the article, iron deficiency is not at all associated with the increased incidences of PD, but rather buildup is associated with neurodegeneration. Postmortem brain of patients and genetic and toxin models of PD have indicated noteworthy and selective accumulation of iron in the substantia nigra region suggesting a link of iron accumulation with PD risk [23–27]. Despite an age-dependent increase in the iron content in the adjacent tissues, buildup of iron in the substantia nigra is projected to be the main causative factor for the selective demise of dopaminergic neurons [24]. Multiple observations from in vivo iron imaging techniques, association studies of iron accumulation regulating genes, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, 6-hydroxydopamine (6-OHDA) and lipopolysaccharide-based models have supported the decisive role of iron in PD pathogenesis [10, 23, 25, 27–33]. Mutants of regulatory genes and their link with iron accumulation or iron supplementation and exposure-dependent animal experimentations and their association with disease susceptibility or increased vulnerability in adults, which were prior exposed to iron during critical period of development altogether narrate the magnitude of accumulation [11, 23, 28, 30–32, 34, 35]. Accumulation is also associated with non-depression-linked PD demonstrating the adverse effect of iron in all forms of this movement disorder [36].

Unquestionably, iron gets accumulated in the substantia nigra and other target tissues; its role is said to be elusive owing to lack of entire mechanism of disease pathogenesis [26]. However, iron buildup in the substantia nigra induces oxidative stress, formation of intracellular α-synuclein aggregates, motor impairment, disturbed iron homeostasis, cellular disintegration, intrinsic apoptosis, microglial activation, and neuronal death [27, 33, 35, 37]. Iron chelator reduces the extent of anomalies along with reduction in the nigral iron content confirming its role in PD pathogenesis [25, 37].

Moreover, iron chelator also shrinks the cellular iron pool and offers protection from 6-OHDA, MPTP, and rotenone-induced Parkinsonism, which are exemplified with iron accumulation [29, 33]. Involvement of ceruloplasmin in iron accumulation has come from a knockout study in which ferric ammonium citrate administration-mediated iron deposition in the brain of MPTP-treated rodents and its reversal by deferoxamine, a metal chelator, were found [27]. Iron accumulation is seen, if ceruloplasmin along with ferroportin 1, which helps in iron export, is reduced in 6-OHDA-induced degeneration showing that accumulation starts immediately after toxicant exposure [32]. Oxidation of ceruloplasmin in PD patients changes its chemical nature from basic to acidic and reduces ferroxidase activity that subsequently augments intracellular iron retention [30]. Elevated level of iron and overexpression of divalent metal transporter 1(DMT1) in affected tissue of Parkinsonian rats have shown the value of latter in the former process [34]. Moreover, reduction in Nedd4 family-interacting protein 1 (Ndfip1) is found to contribute to 6-OHDA-induced iron deposition through DMT1 degradation-dependent pathway [34]. P-type ATPase/ATP13A2 causes an enlargement of lysosome and late endosome and reduces iron-induced membrane permeabilization and thereby protects from iron-induced cell damage. However, defects in ATP13A2 gene leads to PD, which is characterized with the brain iron accumulation [31]. It indicates the role of iron in the regulation of clearance mechanism of defective proteins and organelles as well as its own through the action of a few selected proteins. Combination of a naturally occurring antioxidant and an iron-chelator is found be to rescued from impaired antioxidant defense system, α-synuclein accumulation, and aggregation, inhibits monoamine oxidase, and activates hypoxia-inducible factor-1 signaling pathway along with its downstream mediators viewing that iron buildup leads to oxidative stress and thereby PD [37]. Overexpression of human α-synuclein increases the intracellular iron content and its redistribution from the cytoplasm to the perinuclear region within α-synuclein-rich inclusions further indicate the role of iron in PD [38]. Microglial activation releases inflammatory cytokines under iron overload that subsequently leads to its accumulation by increasing the level of regulatory protein 1 and hepcidin through free radical production, which shows that microglia aggravates iron-induced PD pathogenesis [35].

Despite all supportive evidences, iron alone is not a culprit of sporadic PD. This is evident from a study in which patients were found to atypically possess iron accumulation with neurodegeneration along with dystonia and orofacial stereotypes. The study shows that symptoms of iron alone-induced Parkinsonism are different from sporadic PD [28]. Moreover, a link between age and iron accumulation in different brain regions is reported; heterogeneity of phase value of accumulation and overstressed propensity in the nigra indicate the need of further assessment for commenting upon the relationship between iron accumulation and PD [24].

Manganese Accumulation and PD

Manganism was diagnosed approximately two hundred years ago; epidemiological studies correlating manganese exposure with PD came into limelight during the last few decades [7]. Like other micronutrients, it is required for catalytic activity of a few enzymes and biological function of some proteins but excessive accumulation is reported to be extremely toxic [39]. Age, gender, genetics, environmental/endogenous exposure, and ethnicity altogether determine the fate of manganese-induced toxicity. In general, manganese exposure is less than the toxic level in the general population; but mostly, its accumulation is reported in PD patients of Chinese population [40, 41]. Augmented exposure or reduced excretion leads to its accumulation in the basal ganglion that could induce Parkinsonian symptom or manganism [42]. Manganese accumulation leads to aberrant dopaminergic neurotransmission by increasing oxidative stress, mitochondrial dysfunction, inflammation, and synaptodendritic degeneration, which are reduced by the specific remedial agents (such as antioxidants, anti-inflammatory agents, mitochondrial function regulators, neuroprotective agents, etc.) further showing its role in eliciting PD-like symptoms [43].

Manganese is accumulated in the Golgi apparatus where it gets detoxified. Moreover, manganese accumulation reduces total iron content that adds to neuronal injury [44]. Manganese activates the nuclear factor erythroid-2 related factor 2 and heme oxygenase-1 pathways through free radicals and ubiquitin-proteasome pathway-dependent mechanisms [45]. Sub-acute low-level manganese exposure disrupts the release and function of dopamine, gamma amino butyric acid, and glutamate neurotransmitter, which subsequently lead to neurobehavioral anomaly [46]. Rampant exposure to manganese has long-term impact on the regulation of extracellular dopamine release in the striatum [47]. Continuing exposure to manganese during critical periods of development causes oxidative stress and impaired motor coordination [48].

Hydrogen peroxide is the main culprit of oxidative stress in manganese-induced toxicity that is produced by the mitochondrial complex II [49]. Owing to distinct distribution in transportable state as compared with the rest of metals, it affects the mitochondrial electron transport chain of neurons located in the nigra and adjacent tissues [7]. Activity of the central histaminergic system is increased in PD and 6-OHDA-lesioned rats that is further increased by manganese exposure showing its contribution in sporadic as well as toxin(s)-induced PD [50]. While periodic/regular exposure to welding fume induces permanent change in dopaminergic neurons, it is ambiguous to establish whether exposure to manganese from

welding electrodes, ferroalloy, and other means produces behavioral anomalies leading to manganism or not [41, 51, 52]. Exposure induces a few symptomatic features mimicking disease and some that are not at all associated with PD leading to the hypothesis that manganism is not identical to PD [46, 53]. Influence of manganese is reported to be quite high in the individuals possessing genetic predisposition as well [54]. Both manganism and sporadic PD are regulated by PARK genes in the similar way and oxidative stress, impaired mitochondrial function, α-synuclein aggregation, and aberrant ubiquitin proteasome system direct the nigrostriatal dopaminergic neurodegeneration in both the conditions [55]. Even very low concentration of manganese induces α-synuclein fibril formation [56]. Accumulation of welding fumes/manganese chloride impairs the mitochondrial function, degenerates tyrosine hydroxylase (TH) containing neurons, and alters the expression of PARK proteins showing that PARK genes play important role in manganism similar to sporadic PD [57]. Motor alterations and selective degeneration in the nigra induced by the inhalation of manganese mixtures are significantly reversed by levodopa indicating that manganism is similar to PD and manganese can be used to develop an appropriate disease model [58, 59]. Moreover, behavioral alterations and inflammation persist even after manganese gets cleared off from the cortical brain compartment [60] showing that the changes are irreversible similar to PD. Though the highest concentration of manganese is achieved in the basal ganglia, manganese-induced Parkinsonism is differentiated from sporadic PD owing to noticeable inhibition of dopamine release even in the absence of the loss of terminals of the nigrostriatal dopaminergic neurons [53]. Manganese-induced Parkinsonism does not involve the demise of midbrain dopaminergic neurons and levodopa is also not found to be effective according to a study [61], which further shows that manganism is different from PD. Dynamic mode of transport and detection and pharmacokinetic modeling of trafficking also indicate variability between manganese-induced Parkinsonism and sporadic PD [42]. Level of manganese is not altered in the substantia nigra but 20 % reduction in the striatum of PD patients is seen as compared with controls pointing out that accumulation of manganese is not associated with sporadic PD [62].

Copper Accumulation and PD

Long-term exposure or excessive accumulation increases disease occurrence owing to its free radical-generating property [63–65]. Contrary to this, copper rescues from PD symptoms in a study, which exhibited 34–45 % reduction in the substantia nigra of PD patients [62, 66, 67]. Moreover, no specific and straightforward relationship between copper intake and PD risk/protection has been observed in another study [68]. Despite conflicting reports, an increased level of copper-bound biologically active proteins has been consistently reported to be protective. It is supported by the verity that its supplementation increases the activity of copper bound proteins and ameliorates disease symptoms. Chelation reduces availability of copper to bound proteins and aggravates PD symptoms [69].

Neuroprotective properties of copper are partially contributed by its cofactor nature in antioxidant protein, superoxide dismutase (SOD). SOD scavenges superoxide radical and regulates electron transport chain [69]. A study performed in the cerebrospinal fluid of PD patients also indicated that free copper is toxic, while protein bound copper is protective in nature [70]. Neuroprotection is also mediated by its action against toxic effects of iron deposits [71]. Copper also prevents toxin-induced protein nitration and reduction in TH activity and its inactivation [72, 73]. Copper regulates the function of metallothioneins, ceruloplasmin, DJ-1, copper transporter 1, and P-type ATPase B proteins. Reduced expression of ceruloplasmin in the nigrostriatal pathway also shows that reduction of copper bound proteins is associated with PD [69, 74].

Copper induces the formation of oxidation products of catecholamine, which are regulated by chloride concentration and lead to DNA damage [75, 76]. Copper plays imperative role in oxidation kinetics responsible for dopaminergic neurodegeneration [76]. Copper ion directly regulates α-synuclein fibril formation and oligomerization [56, 77]. Copper-induced dopamine oxidation increases mitophagy and caspase-3-independent apoptotic degeneration [78]. While autophagy does not play any role in metal elimination, removal of damaged organelles and proteins could eliminate some metals. Nigral α-synuclein aggregation augments neuronal cell death if copper-dependent defense mechanism is impaired since its interaction with α-synuclein triggers modification and aggregation owing to the formation of reactive oxygen species [79, 80]. Although α-synuclein stimulates copper-mediated toxicity even without aggregation, aggregated forms are found to be more pathogenic [79, 81].

α-Synuclein increases the cellular sensitivity to copper showing that pathological role of α-synuclein aggregates depends on copper-binding capacity [82]. Copper also regulates an interaction of herbicide with α-synuclein [83]. Depending on pH, copper, and α-synuclein ratio, variable copper species have been reported. Binding affinity of copper (1+) with N-terminal and C-terminal regions of α-synuclein is found to be uneven and interaction leads to site-specific oxidation of the latter [84, 85]. Imbalance in the cellular copper homeostasis preferentially targets oxidation of N-terminal region while function and aggregation are regulated by C-terminal domain [86, 87]. Physiological form of α-synuclein that interacts with copper (1+) is found to be N-terminally acetylated, which subsequently abolishes binding of copper at high affinity [84, 88, 89]. Aggregation propensity and folding are regulated

by remote histidine residue that regulates its binding with copper (2+) [84]. Copper also binds to histidine residue at position 50 of the carboxy terminal sequence that finally determines the fate of α-synuclein [69]. High-affinity form of α-synuclein undergoes fibrillation and partially folded conformation [69, 90]. Although α-synuclein exists in soluble and membrane-bound forms, copper exerts its effect mainly on the soluble form [63]. Reduced cellular copper clears off larger aggregates and oligomers that are intensely localized to the plasma membrane [82]. Copper (2+) regulates protein/vesicle coordination and extent of α-helix for the membrane-associated area [91]. Deletion of any terminal results in a loss of aggregation whereas deletion of C-terminal results in a loss of membrane association [82]. Both copper and dopamine interacts with both terminus and induce folding [87, 90]. Dopamine or dopamine/copper induces α-synuclein oligomerization and cross-linking more than that of free radical-mediated covalent modification [92].

DJ-1 interacts with copper and is regulated and/or stabilized by zinc [93]. DJ-1 changes the coordination geometry of copper leading to failure of metal transfer to SOD [94]. DJ-1 requires stable homodimer for mutation that weakens its formation and compromises competency [95]. DJ-1 enhances the cellular defense and mutations reduce its protective property [96]. Even a small genetic change or concomitant addition of dopamine sensitizes copper-induced cytotoxicity [96]. Aberrant expression of Parkin also substantiates the role of copper in PD [97].

Zinc Accumulation and PD

Maintenance of homeostatic relationship among essential metals is required for the normal functioning of the brain [98]. Zinc controls synaptic transmission along with iron and copper and regulates elevation in an impaired compartmentalization leading to deregulation of homeostasis [99]. Zinc acts as an antioxidant at the desired cellular concentration; depletion or excess induces free radical generation [65]. Antioxidant nature of zinc is not because of metal per se, but is rather due to zinc-containing proteins [100]. Alteration in the intracellular zinc content is associated with functional anomaly in neurons. Deficiency is implicated in growth problem, mental retardation, emotional disturbance, and physical and immunological aberrations in children while it is not associated with any specific problem in adults [101]. Deficiency also leads to excessive consumption of iron and copper, accumulation of manganese, ingestion difference of vitamin E/copper, and decreased consumption of vitamin B12 [102].

Higher concentration is even more toxic since metals oxidize macromolecules and reduce the cellular antioxidant defense system [103]. Zinc is profusely present in the hippocampus, cerebral cortex, thalamus, and olfactory cortex [104] and its accumulation in the nigrostriatal region leads to PD [62]. Although concentration of zinc in other brain regions of PD patients remains the same, it increases by 50–54 % in the substantia nigra and 18–35 % in the striatum indicating the role of its accumulation in neurodegeneration [62]. Presence of zinc-dependent matrix metalloproteinase-2 (MMP-2) in α-synuclein inclusions and selective augmentation in expression of MMP-2 in the striatum also indicate the same notion [105]. Since zinc is required for normal functioning of MMP-2, its accumulation increases the susceptibility of degenerative diseases that are characterized with α-synuclein aggregate formation, inflammation, BBB dysfunction, and myelin deterioration [105]. Zinc also increases an interaction of herbicide with α-synuclein [83]. Accumulation of zinc is associated with stern dopaminergic neuronal cell loss as evident from the overexpression of metallothionein, an indicator of metal homeostasis disturbance [74, 106]. A decrease in zinc-dependent SOD and ferroxidase activity in the cerebrospinal fluid of PD patients also indicates its relevance in the regulation of antioxidant defense system [70]. A chelator that crosses the BBB reduces the level of essential metals, such as zinc, and reduces neurotoxicity [18] confirming the role of zinc accumulation in PD.

Parkinsonian toxins that inhibit the mitochondrial complex I, such as N-methyl-4-phenylpyridinium (MPP^+) and 6-OHDA, induce zinc accumulation in the substantia nigra pars compacta showing that cytosolic labile zinc accumulation could be an indicator of degenerating dopaminergic neurons [107, 108]. Similarly, 3-morpholinosydnonimine mediates the mitochondrial accumulation of metals, including zinc, and the induction of metallothionein gene protects from it; this further highlights the role of zinc in neurodegeneration [74, 109]. Zinc induces nicotinamide adenine dinucleotide phosphate-oxidase-dependent free radical generation, dopamine and glutathione depletion, apoptotic loss of TH-positive neurons, reduction in the expression of monoamine transporters, and microglial activation after long-term exposure to high doses showing its role in Parkinsonism [8]. Apocyanin, an antioxidant, and/or N-acetyl cysteine, an anti-inflammatory agent, are found to reduce zinc-induced alterations that validate the role of zinc in oxidative stress-induced PD in experimental models [16].

Zinc induces PD even in manganese-exposed population since manganese is competently and effectively transported by zinc transporters [110]. Two types of transporters are found to be responsible for manganese transport and/or storage in the brain; one is iron and another is zinc. But a stable relationship between manganese and zinc at the tissue and cellular levels suggests that zinc transport/storage is associated with manganese transport and accumulation [111]. Since zinc is known to induce its own transporters, little excess in its concentration could promote uncontrolled passage of manganese in the brain leading to PD-like symptoms in manganese exposed

individuals. Moreover, zinc along with iron influences the effect of lead and affects dopaminergic neurons [112]. It is also supported by a study that has shown an increased expression of transporters and transferrin receptors owing to concurrent and altered level of metals [98].

Accumulation of zinc produces adverse effect on the BBB as elevated level is found to be associated with barrier dysfunction [35]. Defective BBB could allow an entry of unwanted molecules and radicals in the brain. Moreover, disturbance in zinc homeostasis leads to the lysosomal impairment, α-synuclein accumulation, and mitochondrial dysfunction through PARK 9-dependent mechanism [113]. Interestingly, higher intake of zinc is also reported to be protective against PD in a study [68]. The interaction of DJ-1, a neuroprotective and antioxidant protein, with copper is regulated and/or stabilized by zinc showing that zinc regulates neurodegeneration/protection even in familial PD [93].

Mercury Accumulation and PD

History of a possible association of mercury exposure with PD is quite old as dental amalgam fillings have been used from the ancient era and is projected to be associated with disease pathogenesis [114]. J.M. Charcot, who is appropriately referred to as the father of modern neurobiology, primarily emphasized the hereditary etiology of PD. But he never ruled out the possibility of mercury exposure as an etiological factor even in the absence of a clear cut association [115]. Mercury absorption occurs through the lungs; afterwards, it reaches to the bloodstream and subsequently enters and accumulates in the central nervous system [116]. Mercury exposure induces adverse effect on dopamine transporters leading to a dose-dependent depletion of the striatal dopamine [117]. Although an obvious monotonic dose–response association between PD and blood mercury is seen, scalp hair mercury is not found to be the first-rate disease predictor [118]. While no significant association between occupational mercury exposure and PD is seen in an epidemiological study, confidence interval of odds ratio did not ignore the likelihood [119]. In another epidemiological study, a rare clinical variant of mercury intoxication was found to be associated with Parkinsonism even in the absence of chronic exposure specific neuropsychiatric signs [120]. PD subjects are found to be associated with detectable blood mercury level, but barely a few controls are found to have the same, which substantiate that it plays a role in disease etiology [121]. High urinary excretion, which could be extrapolated as high mercury exposure, is also found to be linked with increased average tremor intensity (a hallmark of PD) within high-frequency window [122]. Higher mercury exposure is also related to abnormal facial expression [123] that is often reported to be a secondary characteristic of PD. However, inadequate longitudinal exposure assessment, negative confounding by better access to dental care in the elite groups, inadequate epidemiological studies, insufficient number of cases and controls for power statistics, and lack of animal experimentations have been the major limitations. Therefore, better designed studies are still needed to confirm its association with PD [114].

Magnesium Accumulation and PD

Magnesium is the second most abundant divalent intracellular metal cation involved in the intracellular processes [124]. Association of magnesium accumulation/dietary intake with PD is hard to define since both accumulation and low level are found to be associated with risk as well as protection in animal and epidemiological investigations. A multicenter hospital-based case–control study performed in Japan did not observe any relationship between magnesium intake and disease risk rather high intake was found to be neuroprotective [68]. Low amount owing to decreased function of dopaminergic neurons leads to catalepsy, which shows that low intake could be a contributory factor in PD [125]. On the other hand, magnesium (2+) acts as a calcium (2+) channel antagonist and reduces the damaging consequence of calcium (2+)-induced neuronal inflammation showing its protective efficacy [126]. Magnesium inhibits iron-induced α-synuclein aggregation that further confirms the notion [127]. Cytosolic content is regulated in the brain to equilibrate changes in rapidly available free energy and magnesium and to moderate cadmium/aluminum-mediated effects illustrating that low magnesium level could lead to neurodegeneration [128–130]. While magnesium prevents the length of dopaminergic neuritis, it can exacerbate MPTP-induced striatal dopamine depletion [131, 132]. Furthermore, low dose increases motor activity and latency to heat stimuli, but medium and high doses decrease the same and increase pole climbing time in MPTP-treated mice [132]. Magnesium exerts imprinting effect since low magnesium intake (1/5th of desired value) over generations is found to be associated with significant death of dopaminergic neurons in the substantia nigra [133].

Regardless of the fact that the mitochondria maintain magnesium homeostasis, its high level leads to dysfunction and formation of protein aggregates in the brain mitochondria [134]. Rotenone reduces magnesium-dependent block of N-methyl-D-aspartate current in dopaminergic neurons of the substantia nigra signifying that magnesium-mediated excitotoxic mechanism participates in rotenone-induced Parkinsonism [135]. Contrary to it, an increase in magnesium content is found to inhibit the cellular free radical generation, maintains energy production, and rescues from toxin-induced Parkinsonism [136]. A gradual decrease in the magnesium (2+) concentration in the mitochondria is seen in response to a neurotoxin in differentiated PC12 cells viewing that its

specific concentration is needed to maintain the normal neuronal functions [137].

Association of magnesium deficiency or accumulation is also reflected from the studies, which have shown the presence/absence of association of ion channel protein variants with PD risk. Human solute carrier family 41 (magnesium transporter), member 1 (SLC41A1) gene encodes for sodium (1+)/magnesium (2+) exchanger, which is involved in magnesium (2+) efflux system [124]. SLC41A1 is found to be dysfunctional when magnesium (2+) efflux is impaired. Moreover, long-term and chronic intracellular magnesium (2+) deficiencies in PD patients are found to increase magnesium (2+) efflux by SLC41A1 variant p.A350 V [138, 139]. PD is also associated with reduced expression of transient receptor potential cation channel, subfamily M, member 2 and 7 channel proteins [140].

Studies available have shown no significant association of magnesium with PD or neuroprotection. Although low magnesium in the diet is associated with olfaction, magnesium along with calcium, iron, silicon, and zinc are not correlated with duration or severity of PD or anti-PD drugs [141, 142]. Mystifying observations across studies indicate that magnesium is associated with PD risk. Despite contradictory reports, it is believed that measurement of brain magnesium (2+) could help in differential disease diagnosis [128]. Overall, association of PD with magnesium accumulation/deficiency has been elusive and studies are still required to spell it out.

Lead Accumulation and PD

During recent years, chronic exposure to lead has been minimized owing to complete ban on gasoline, but it remains to be a major public health concern [143]. Limited studies are available showing an association between lead exposure and PD [144]. PD risk gets elevated by >2-fold in people in the highest quartile for lifetime lead exposure indicating that chronic exposure could be a risk factor [145]. While lead alone is not found to be associated with PD in a study, dual combination of lead, iron, or copper increases the risk [64]. An increase in the plasma lead level in urban PD subjects is found in a study [146] pointing out the accumulation of lead in the brain. A 10-fold increase in radioactive lead in the lipid fraction is also seen indicating that lead is primarily accumulated in the lipid fraction [147]. An increase in bone lead content is not found to be associated with risk but cumulative exposure augments PD risk in the typical patients [148]. Similarly, the tibia bone lead unlike the patella lead is seen to be associated with cognition deficit and cumulative exposure aggravates the condition [149]. Association of lead with PD is also evident from a study where a case was exposed to lead for 17 years in a car battery industry and was diagnosed with high level of lead in the blood. The person was initially characterized with the primary disease symptoms, followed by the secondary symptoms and later by the late stage disease symptoms. Moreover, the patient was also found to be levodopa responsive [150]. Lead exposure increases α-synuclein aggregation and aggresome formation and inhibits degradation and thereby supports the lead accumulation theory of PD [151]. Although studies have shown an association of lead accumulation/exposure, lead level is not found to be altered in the substantia nigra and striatum of patients as compared with other regions of the brain, which simply contradicts its adverse association with PD [62].

Aluminum Accumulation and PD

Except a few scattered contradictory observations, reports have shown an association of aluminum accumulation in the central nervous system and exposure to aluminum-containing antacids with increased incidence of neurodegenerative diseases [152–154]. Aluminum gets accumulated in the substantia nigra and/or striatum, particularly in the gray matter, and is linked with PD pathogenesis [130, 155]. Presence of aluminum in the Lewy bodies of the nigra of PD patients also indicates its significance [156]. Aluminum increases monoamine oxidase-B (MAO-B) enzyme activity and is associated with dopamine degradation and depletion thereby indicating its etiological worth in PD [157]. Augmentation in aluminum content in neuromelanin granules shows that it promotes oxidant formation, which accounts for the selective degeneration of neuromelanin-positive neurons [158, 159]. Accumulation of aluminum in hair and increase in urinary 8-hydroxy-2′-deoxyguanosine, an indicator of oxidative stress, in Mongolian patients further support the negative role of this metal in PD [160]. Aluminum enhances 6-OHDA-induced oxidative stress, reduces endogenous antioxidant defense enzymes, and increases nigrostriatal dopaminergic neurodegeneration, which additionally support the notion that this metal adds on PD hallmarks induced by a Parkinsonian toxin [161].

Aluminum increases interaction between pesticides and α-synuclein [83]. Exposure reduces TH-immunoreactivity, neurotransmitter content, and motor functions and induces fibril formation from aggregated α-synuclein leading to conformational change attributed to the development of a partially folded intermediate [56, 155]. While aggregation and structural changes are reported, newer and specific tools are expected to help in understanding the mechanism of aggregation [162]. It triggers phosphorus leading to homeostatic imbalance in the serum of patients showing that aluminum indirectly regulates PD pathogenesis [163]. Albeit most of the studies have shown an association of aluminum accumulation with PD, it is found to reduce lipid peroxidation and 6-OHDA-induced dopaminergic lesion in the striatum [100].

Calcium Accumulation and PD

Several direct and indirect studies have highlighted that calcium (2+) homeostasis in the endoplasmic reticulum is a decisive factor of neurodegeneration [164, 165]. Reticular calcium (2+) and activation of calcium–calmodulin–calcineurin cascade is regulated by α-synuclein showing that calcium homeostatic disturbance could be associated with disease pathogenesis [166]. Maintenance of calcium homeostasis owing to an accumulation of lactoferrin (an iron-binding protein) is required for protection against MPTP-induced neurodegeneration demonstrating its importance in the normal function of dopaminergic neurons [167]. Excessive concentration, deposition, or even slight changes in calcium content of dopaminergic neurons could lead to the onset of PD symptoms [154, 168]. Mitochondrial dysfunction and defective autophagy, two critical events of degeneration, are also regulated by the mitochondrial calcium influx [169, 170]. Attenuation in the mitochondrial calcium capacity or augmentation in oxidative stress lowers the threshold for opening of the mitochondrial permeability transition pore [171]. Moreover, dopamine transporter-1 receptor signal transduction pathway depends on L-type calcium (2+) channel in order to mediate cyclic adenosine monophosphate response element-binding protein phosphorylation [172]. The impaired mitochondrial calcium (2+) accumulation during agonist stimulation is a major consequence of human complex I deficiency [173]. Calcium-binding domain, which is located in the 15 amino acids at the acidic C-terminal end of α-synuclein, induces filament formation that continues through intermediate or protofibrillar species leading to PD [174].

Cadmium Accumulation and PD

Indisputably, the central nervous system disorders are the second most health risk associated with metal exposure [175]. Although cadmium accumulation is less studied as compared with iron, manganese, and copper, a trend of increased disease risk with its exposure is reported [176]. High cadmium level along with manganese, iron, lead, and aluminum are also seen in Mongolian PD subjects as compared with Japanese [160]. An old person, who was acutely exposed to cadmium, was found to possess PD-like features showing that cadmium exposure damages the basal ganglion, the most affected site in PD [177]. Effects of cadmium on cognition, behavior, learning deficits, and altered dopaminergic function are also reported [112] showing that cadmium accumulation could lead to PD. Cadmium alters the interaction of Parkinsonian toxins with α-synuclein that further shows its role in disease pathogenesis [83]. Cadmium exposure also modulates ubiquitin proteasome pathway, antioxidant enzymes, phase II enzymes, and cell cycle regulators implicated in PD pathogenesis [178]. Besides, an auto-transplantation study has shown lack of any change in cadmium along with a few other metals after operation showing that cadmium accumulation is significantly associated with PD pathogenesis [179]. Even though an association between PD risk among nurses and exposure to cadmium is reported, no explicit and unambiguous association between adulthood ambient exposure to cadmium and PD risk is seen [144].

Arsenic Accumulation and PD

It is not yet clear if arsenic accumulation induces the nigrostriatal dopaminergic neurodegeneration or not. Undeniably, arsenic (3+) induces oxidative stress leading to the activation of early transcription factors [180]. Clear cut evidence is still not available that could have explicitly explained its role in PD. Arsenic (3+) synergistically enhances dopamine toxicity in differentiated dopaminergic neurons in culture [181] indicating that it aggravates dopaminergic neuronal cell death. Moreover, glutathione transferase-ω E155 deletion linked with abnormal arsenic excretion and age-at-onset of PD, which further indicates that arsenic could be a critical player [182]. Despite a few supports, arsenic accumulation theory of PD gets jolted owing to the presence of its low concentration in PD patients in comparison with controls [183].

Cobalt Accumulation and PD

Association of cobalt accumulation is appraised; however, no study has yet confirmed its substantial association with PD [106]. While cobalt (2+) induces rapid formation of discrete annular α-synuclein oligomeric species, cobalt (3+) causes significant acceleration in α-synuclein fibril formation [56, 174]. Since fibril and oligomer formation are very much associated with PD, therefore, the role of cobalt in PD pathogenesis needs to be explored further.

Is Metal Accumulation an Epicenter or Outcome of PD?

Metals get accumulated owing to lack of fully operational excretion machinery irrespective of their route of entry [184–186]. Accumulation in the brain also happens due to metal-mediated increase in the BBB permeability. Accumulation leads to oxidative damage, metal–metal interaction, estrogen-like effects, and epigenetic modifications [187]. Metal accumulation is contributed by both innate and acquired factors, which are evident from the studies that have shown accumulation of a specific metal in a fussy population

[184–186]. For instance, iron gets accumulated in the brain of the people of Irish, Scottish, British and Scandinavian ancestry much more in comparison with the people of rest of the world. It shows that hereditary/innate factors regulate metal accumulation process [186]. Presence of higher accumulation in males as compared with females indicates implicit role of acquired factors in metal buildup [186].

Exposure to manganese, copper, lead, iron, mercury, aluminum, zinc, and cadmium appears to be the main environmental risk factors (Table 1) along with pesticides [22, 100, 188, 189]. However, it is still a Demigod subject if metal accumulation is an epicenter or merely an outcome [9] (Table 2). Although a trend of increase in disease risk with metal exposure at work place is reported, limited studies exist in this direction [144, 176]. One school of thought believes that metal accumulation is neither an epicenter nor an outcome, but rather it is an indispensable process, which has zilch contribution to PD rather to keep healthy. The notion is reliant on the plethora of information that demonstrate the protective effect of metals or their essentiality for the catalytic activity of a few enzymes opposite to metal accumulation theory that deems accumulation as a causative or contributory factor. For example, metal supplementation is needed to maintain the normal physiology of dopaminergic neurons of the substantia nigra, one of the most badly affected tissues, during metal deficiency [22]. Furthermore, with the best of our knowledge, no scientific evidence is available in the literature that could have explicitly demonstrated an increased prevalence of PD in populations, which are more prone to metal accumulation [186] as compared with populations in which accumulation is found to be less. Such proofs validate the hypothesis that metal accumulation is not associated with PD or at least it

Table 1 Contribution of metals in PD pathogenesis based on epidemiological studies and animal experimentations: name of the metals, their association with disease, and disease features are mentioned along with appropriate citations

S. no.	Name of metal	Association	Parkinsonian features	References
1	Iron	Accumulation is associated with sporadic PD and toxin-induced Parkinsonism	Aggregate formation, behavioral deficits, selective degeneration, and levodopa responsiveness	[23–27]
2	Manganese	Accumulation is associated with the onset of manganism, slightly similar to PD as observed in epidemiological and experimental studies	Aggregate formation, behavioral anomalies, and degeneration of dopaminergic neurons but divisive levodopa responsiveness	[39–41, 51, 57–59, 61]
3	Copper	Accumulation of free form leads to Parkinsonism while protein bound form leads to protection as observed in the limited epidemiological studies	Aggregate formation, selective neuronal loss, and mitochondrial dysfunction	[62, 63, 65–69, 80]
4	Zinc	Accumulation leads to Parkinsonism as inferred from the limited epidemiological studies and protective effect is also reported	α-Synuclein aggregation, microglial activation, behavioral deficits, neurodegeneration, and mitochondrial dysfunction	[8, 16, 62, 68, 104, 105, 107, 108]
4	Mercury	Accumulation is associated with some minor features of Parkinsonism but not yet explicitly accepted as Parkinsonian metal	Dysfunction of dopamine transporters, tremor, and abnormal facial expression	[115, 117, 119, 121–123]
5	Magnesium	Accumulation also leads to a few minor changes associated with Parkinsonism but often found to be protective in nature	Loss of dopaminergic neurons	[68, 125, 127, 131–133]
6	Lead	Accumulation leads to a few selected Parkinsonian features	Neuronal loss and levodopa responsiveness	[64, 145, 146, 148, 150]
7	Aluminum	Buildup in the brain induces neurotoxicity but epidemiological evidences are rare	MAO-B activity augmentation	[130, 152–155, 157]
8	Calcium	Accumulation leads to secondary features of PD/Parkinsonism	Mitochondrial permeability transition pore opening, complex I deficiency and α-synuclein filament formation	[154, 168, 171, 174]
9	Cadmium	Accumulation induces a few features but epidemiological and experimental studies are limited	Basal ganglion affected, learning deficits, and altered dopaminergic function	[112, 177]
10	Arsenic	Accumulation leads to some changes, but still lacks proofs to ascertain its definite contribution in PD/Parkinsonism	Higher dopamine toxicity	[181–183]
11	Cobalt	Buildup leads to a disease feature but inadequate data to support its association with PD/Parkinsonism	α-Synuclein fibril formation	[56, 102]

Table 2 Controversies over metal accumulation in PD pathogenesis: summary of clues, which support or contradict the contribution of metals in PD pathogenesis

S. no.	Clues to support epicenter theory	Verities that contradict	Clues that support outcome theory	Verities that contradict	References
1	Metal accumulation leads to some behavioral impairments resembling PD	It also reduces toxin-induced behavioral anomalies	PD occurs even without metal accumulation and metal-induced behavioral anomalies do not truly mimic sporadic PD	Toxin(s)-induced Parkinsonism induce metal accumulation only after neurodegeneration begins	[10, 20, 24, 26, 40, 41, 48, 66, 67]
2	Metal accumulation is associated with the selective cell loss, dopamine depletion, mitochondrial dysfunction and α-synuclein aggregation, and levodopa responsiveness	Degeneration is often vague and non-selective and studies have repeatedly shown lack of levodopa responsiveness	Accumulation happens after significant neurodegeneration and metals also reduce aggregation and neurodegeneration in a few studies	Changes appear after metal accumulation in toxin-induced disease showing that it is the primary cause	[32, 40–42, 53, 56, 58, 59]
3	Metal-induced biochemical and molecular features generally mimic PD	Main cardinal features of sporadic PD are usually absent in metal-induced Parkinsonism	Metals get accumulated during disease progression	No conclusive meta-analysis study have shown association or lack of it	[62, 83, 105, 110]
4	Some metals unequivocally induce a few cardinal disease features	Several metals do not induce even one cardinal feature	Specific metal accumulation is reported in a few epidemiological studies	No significant accumulation of any metal is seen in sporadic PD patients in a few other studies	[62, 117, 122, 144]

is not a causative factor. Moreover, a few population studies have also shown lack of relationship between the two [22].

Campaigners of the jingle "causative factor theory" contradict the tune of "no impact theory" or "outcome/consequence theory". Supporters of "causative factor theory" believe that protection offered by metals is not because of metal per se rather it is an antioxidant property of metal bound proteins that provides defense (Fig. 1). Elevated level of metals in the substantia nigra of patients in comparison with the rest of the brain indicates that metal accumulation is a contributory factor [104, 107, 108]. Accumulation theory explains that higher oxidation state of metals induces oxidation of macromolecules and aggregation of α-synuclein [22]. High metal conjugates lead to glutathione depletion in the substantia nigra of PD patients showing that oxidative stress occurs owing to metal accumulation and metal accumulation does not occur because of oxidative stress. Higher level of metals is seen in Mongolian PD patients (population that is not genetically prone to metal accumulation like Irish) as compared with Japanese further shows that accumulation leads to oxidative stress and could be a causative factor [160]. Excess dopamine, the main neurotransmitter, and levodopa, the main PD therapy, are also known to increase oxidative stress [188, 189] showing that stress could be a secondary event. Moreover, presence of high nitrate content in the cerebrospinal fluid in PD patients treated with levodopa or with dopamine agonist vis-à-vis their respective controls further supports it. However, nitrite (an end product of nitric oxide metabolism that is an indicator of nitrosative stress/oxidative stress) is apparently unrelated with PD risk in another study [190] showing that stress could be secondary to metal accumulation. Activated microglial cells are reported to contain high level of free metals, such as iron [22]. Since two major events in PD pathogenesis, i.e., oxidative stress and microglial activation occur in the nigrostriatal tissues owing to metal accumulation but not vice versa show that metal accounts for the initiation of neurodegeneration.

Campaigners of the view, which considers metal accumulation as an outcome of PD pathogenesis, provide substantial evidences in their support. They believe that low level of natural antioxidants, such as glutathione and SOD, and impaired activity of metal bound antioxidants are the major roots of disease pathogenesis. Reduced antioxidant defense system

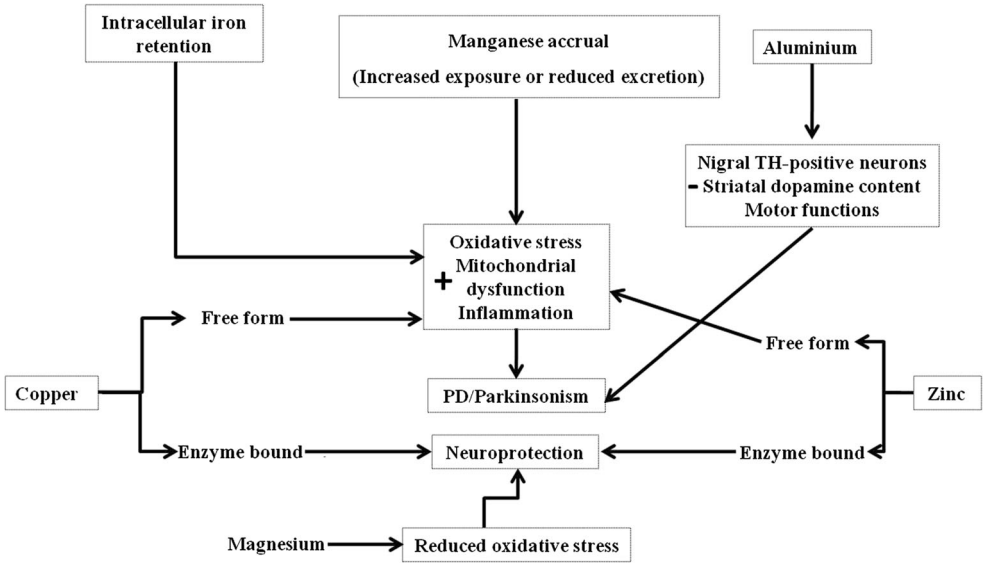

Fig. 1 Metals in PD pathogenesis: accumulation of free form of metals, such as copper, iron, or zinc, and metals per se, such as aluminum, cadmium, or arsenic, in the brain cause/protect dopaminergic neurodegeneration. Metal, if bound to an antioxidant and free form magnesium, per se rescue from PD

directs metal accumulation or availability of free metals in the substantia nigra [22] leading to the hypothesis that accumulation is an outcome and not the starting point. This theory is also supported by the fact that dopamine and levodopa form conjugates with glutathione in PD patients leading to oxidative stress that ultimately leads to PD [188, 189, 191]. Moreover, believers of this theory simply disagree with "causative factor hypothesis" with a convincing logic "if metal accumulation is the main cause why low level of a few metals is also associated with PD". Moreover, neurotoxins mainly inhibit the mitochondrial complex I and lead to oxidative stress and provoke the elimination of metals from metal bound proteins that subsequently increase free metal content [107–109]. Therefore, availability of excessive free metals could be a consequence and not a cause. However, exposure to metals could induce hydrogen peroxide production by the inhibition of the mitochondrial complex II suggesting that metal accumulation leads to oxidative stress and could be the primary event [49]. Moreover, population studies correlating metal exposure and disease pathogenesis are still limited. With inadequate studies, it is hard to pin down a hypothesis that could be near to reality. Animal experimentations performed till date is either one metal centric or one parameter centric; therefore, interpretation biasness could not be excluded. Moreover, most of the experimental animals do not develop PD naturally and disease needs to be induced by specific neurotoxin; therefore, animal results, even if positive, could not be completely extrapolated to humans and relied upon. Overall, the study seems to be inconsistent and inconclusive owing to lack of meta-analysis of genes that regulate the level of metals in the brain of exposed populations and their association with PD across the globe. Such studies need to be performed extensively along with multiple contributory factor-based investigations in order to reach up to a definite conclusion, if metal accumulation is an epicenter or an outcome or none of the above.

Does Exposure to Pesticides also Induce Metal Accumulation in the Brain?

A few direct and indirect studies have shown a possibility of metal accumulation in the substantia nigra of pesticides and non-pesticides, such as MPP^+, 6-OHDA, lipopolysaccharide, and rotenone, models of Parkinsonism [10, 23, 25, 28–33, 107, 108]. Extent of exposure time to pesticides and heavy metals has also been linked with the age at onset in non-familial PD [192]. A number of studies have shown an implication of metals and pesticides either alone or in combination of two in PD pathogenesis [1, 193]. However, in combinational exposure, the level of metals is rarely measured to counter an uncertainty "if pesticide or Parkinsonian toxin induces metal accumulation in the nigrostriatal tissues of the brain". Moreover, metal containing pesticides are also found to induce an additional degree of oxidative stress in dopaminergic system of rodents that is exposed to a non-metal containing Parkinsonian pesticide. Such observation directly indicates the existence of a possible crosstalk between metal and Parkinsonian pesticide in order to exert sternness of disease features [194]. Cypermethrin-induced changes in the non-neuronal system of lower animals are found to be induced by cadmium showing that metals could induce toxic effects of the pesticides [195]. The similar likelihood in non-human primates and rodents could not be ignored until disapproved in the pre-clinical studies. Presence of even low level of pesticide in the diet is found to induce

cadmium accumulation in the kidney irrespective of the dietary content of zinc and copper [196] showing that pesticide exposure leads to metal accumulation. All these three metals are individually known to induce the symptomatic features of Parkinsonism at some or the other concentrations. Moreover, dietary deficiency of one metal is also reported to lead an accumulation of other in the brain [20]. Such postulations indicate a possibility that during nutritional deprivation, pesticide exposure leads to metal accumulation.

Despite extensive research employing various models and research tools, it has still remained an unrequited Demigod issue "if metal accumulation is an epicenter or an outcome". Pesticides are found to induce α-synuclein aggregation and bound to metal-induced partially folded α-synuclein [83]. High iron content in the brain of toxin-induced rodent model of Parkinsonism [29] has also indicated that toxins induce metal accumulation. Parkinsonian toxins that inhibit the mitochondrial complex I also induce metal accumulation in the substantia nigra indicating that metal accumulation could be an indicator of degenerating dopaminergic neurons [107, 108]. But detailed studies are not yet performed to assess the accumulation level of all suspected metals in the substantia nigra employing all pesticide and toxin models of PD. Experimental evidences would be expected to narrate the appropriateness of suggested theories more precisely. Therefore, such studies need to be performed and a correlation between metal accumulation and pesticide exposure needs to be established. Once such correlation is established and is found to be affirmative, a clear cut wrapping up can be drawn whether metal accumulation is an epicenter or an outcome. The Demigod question that exists today in PD biology could be answered agreeably if time- and dose-dependent accumulations of all suspected metals could be measured in the target tissues of control and Parkinsonian toxin/pesticide-treated animals and subsequently correlated with behavioral and supplementary phenotypic disease symptoms.

Conclusion

Despite a strong association between metal accumulation and PD, it is not yet clear whether metal accumulation leads to PD or PD leads to metal accumulation.

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Compliance with Ethical Standards

Conflict of Interest The authors state no conflicts of interest.

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