



## "Metal elements and pesticides as risk factors for Parkinson's disease - A review"

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### ABSTRACT

Essential metals including iron (Fe) and manganese (Mn) with known physiological functions in human body play an important role in cell homeostasis. Excessive exposure to these essential as well as non-essential metals including mercury (Hg) and Aluminum (Al) may contribute to pathological conditions, including PD. Each metal could be toxic through specific pathways. Epidemiological evidences from occupational and ecological studies besides various in vivo and in vitro studies have revealed the possible pathogenic role and neurotoxicity of different metals. Pesticides are substances that aim to mitigate the harm done by pests to plants and crops, and are extensively used to boost agricultural production. This review provides an outline of our current knowledge on the possible association between metals and PD. We have discussed the potential association between these two, furthermore the chemical properties, biological and toxicological aspects as well as possible mechanisms of Fe, Mn, Cu, Zn, Al, Ca, Pb, Hg and Zn in PD pathogenesis. In addition, we review recent evidence on deregulated microRNAs upon pesticide exposure and possible role of deregulated miRNA and pesticides to PD pathogenesis.

### 1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD) [1,2]. In urbanized countries, the approximated incidence of PD is 0.3 % in the general population, 1.0 % in people older than 60 years and 3.0 % in people older than 80 years. PD incidence rates are approximated to range between 8–18 per 100,000 person per year [3,4]. Sex also plays an important role in PD pathogenesis. Several studies found that male exhibits greater prevalence and earlier onset of PD as compared to female [5,6]. During PD patients experience progressive extrapyramidal symptoms, including tremor, bradykinesia, rigidity and postural imbalance, additionally a variety of non-motor symptoms such as sleep and mood disorders. Augmentation of these symptoms occurs with the disease progression [7–9]. The pathological hallmarks of PD are the reduction of dopamine levels due to loss of dopaminergic neurons in the substantia nigra (SN) pars compacta (SNpc), and accumulation of misfolded alpha-synuclein ( $\alpha$ Syn), in abnormal intra-cytoplasmic inclusions called Lewy bodies (LBs) [10–12]. Genetic mutations such as Glucocerebrosidase 1 (GBA1), Leucine-rich repeat kinase 2 (LRRK2) and

PTEN-induced putative kinase 1 (PINK1) also play a prime role in PD pathogenesis as it exaggerates synucleopathies and ROS generation [13–18]. Other contributory factors comprises environmental toxicants such as pesticides, mitochondrial dysfunctions, oxidative stress, chronic neuroinflammation and calcium imbalance [19–21]. Medications, cerebrospinal meningitis and poisoning account for about 25 % cases of parkinsonism. The PD's 75 % cases are idiopathic [22,23]. Out of the 75 % idiopathic cases, more than 90 % are sporadic, while only 5–10 % have a genetic background. Circadian rhythm disorder is also one of the risk factors for PD development [24–26]. In PD development, circadian rhythm disorder also plays an important role, and it is estimated that 60–90 % of PD patients present sleep disturbance during early stages of disease progression [27]. In addition to the aforementioned contributory factors, metals alteration in the brain also play a pivotal role in PD pathogenesis. Owing to the significance of metals in the maintenance of cell homeostasis they play a pivotal role in the body functions maintenance. Among 23 elements with known physiological functions, 12 are metals including iron (Fe), manganese (Mn), zinc (Zn) and copper (Cu) [28]. Xenobiotic metals, including aluminum (Al), lead (Pb) and mercury (Hg) with unknown physiological functions are also present in a

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significant concentration in the human body [29]. Mounting shreds of evidence from the previous research has revealed that dyshomeostasis and exposition to these aforementioned metals are connected to increased PD risk [30–32]. A huge amount of in-vivo and in-vitro studies have been illustrated metals neurotoxicity through the generation of oxidative stress and other specific pathways [33]. Numerous metals are essential for physiological functions, and their dyshomeostasis have been associated with neurodegenerative disorders [28]. Metals produce reactive oxygen species (ROS), and due to this ROS, DNA damage occurs and leads to apoptosis [29,34]. Metals may also increase the expression of genes associated with neurodegenerative diseases [35]. In medical chemistry and neurotoxicology, the involvement of metals in PD pathogenesis is still a matter of great concern [36]. Its contribution is either through metallic toxicants or by depletion in essential metals for human health [37]. Numerous epidemiological studies have shown significant association between PD and long term exposure to metals [38,39]. The primary resources of metals exposure are medications, contaminated seafood, occupational exposure, environmental pollution and amalgam fillings in dental metals restorations [40–42]. A positive correlation was found between industrialization and PD prevalence in developed countries where environmental exposure to metals occur [43,44]. Metals exposure have an adverse effect on the health and cognition in children [45,46]. Occupational exposure to Fe, Al and Mn double the risk of PD. In contrast, those workers who are exposed for more than 20 years to Pb and Cu have shown 2–10 fold increase in PD prevalence [30, 47]. The Elevated level of Hg is associated with a high prevalence of PD [48]. Vanadium pentoxide (V<sub>2</sub>O<sub>5</sub>) inhalation in PD's rodent model is associated with the nigrostriatal dopaminergic system damage [49,50]. Metals ions usually exaggerate the aggregation properties of  $\alpha$ Syn in PD [51].

Acknowledging the potential role of metals on PD, in this review we have discussed the potential association between metals and PD, furthermore the chemical properties, biological and toxicological aspects as well as possible mechanisms of Fe, Mn, Cu, Zn, Al, Ca, Pb, Hg and Zn in PD pathogenesis (Fig. 1).

## 2. Iron

### 2.1. Iron and its role in the PD pathogenesis

Mounting evidences indicate increased levels of Fe in specific brain regions in particular neurodegenerative diseases, especially in PD. In the brain of PD patient's SNpc and lateral Globus pallidus, an approximately two fold increased in Fe levels occurred. In neurodegenerative disorders including PD, inflammation associated with dysfunction of metals ion



**Fig. 1.** Inorganic elements i-e Fe, Cu, Mn, Zn, Al, Ca, Pb and Hg causing UPS impairment and as a result oxidative stress, mitochondrial dysfunction and protein misfolding which are possible mechanisms of PD pathogenesis.

homeostasis (Fe) accompanied by concomitant oxidative stress is the main factor in disease progression [52,53]. The role of Fe as risk factor for PD was suggested when the levels of total Fe was found 176 % increased, and that of ferric ion was increased by 225 % in SNpc of PD relative to age-matched control. Three lines of evidence indicated Fe as a risk factor in PD, including Fe levels, are increased in SN but not in other regions of the brain. Postmortem studies have shown elevated iron levels in DAergic neurons in PD. PD animal models showed neuroprotection by genetic or pharmacological chelation of Fe. Spectrophotometric method and Perl's staining, inductively coupled plasma spectroscopy, MRI, laser microprobe mass analysis, susceptibility weighted imaging (SWI) and enhanced T2 star weighted angiography (ESWAN) studies have shown elevated Fe levels in SNpc of the brain [54,55].

### 2.2. Possible mechanism of iron in PD pathogenesis

#### 2.2.1. Iron and oxidative stress

The Brain requires high concentration of Fe due to its role in energy metabolism, myelin formation and synthesis of neurotransmitters. Due to Fe strong redox ability, it participates in Fenton chemistry leading to ROS generation, which in turn induces oxidative stress causing cell dysfunction and ultimately cell death [56].

#### 2.2.2. Iron and ubiquitin-proteasome system (UPS)

In addition to Fe accumulation, UPS impairment is also implemented in PD pathogenesis. UPS impairment, which is also responsible for IRPs degradation, may also cause accumulation of IRPs and Fe [57–59].

#### 2.2.3. Iron and $\alpha$ Syn aggregation

$\alpha$ Syn aggregation is a key event in PD pathogenesis. The misfolding and aggregation of  $\alpha$ Syn, which may be resistant to ubiquitination is suggested to contribute to PD.  $\alpha$ Syn has been shown to directly bind Fe in both the Fe<sup>3+</sup> and Fe<sup>+2</sup> states, and ferric iron is able to foster its aggregation. ROS present in the cells could catalyze the oxidation of Fe toward its ferric form resulting in an exacerbation of  $\alpha$ -Syn aggregation. Therefore, increased levels of Fe could result in an increased translation of  $\alpha$ Syn protein [60,61].

#### 2.2.4. Iron and gene mutation

Parkin,  $\alpha$ Syn, LRRK2, PINK1, and DJ-1 are among several genes known to be linked to PD pathogenesis. Fe has a relationship among genes involved in monogenic PD. The Hyper echogenicity of the SN has also been found to be a typical sign in idiopathic PD and increased Fe level is responsible for this SN hyper echogenicity. By using transcranial sonography in PD patients having mutations in either of  $\alpha$ Syn, LRRK2, Parkin, PINK1, or DJ-1 genes, showed significantly larger echogenicity in the SN relative to healthy controls [62–64].

## 3. Copper (Cu)

### 3.1. Copper content distribution in the brain

Humans body contains Cu as the third most abundant essential transition metal. The main sources of copper exposure to the body, in form of dietary intake are cereals, fresh fruits and vegetables [65,66]. Following liver, the brain is the organ contains the highest Cu because this organ has a high metabolic rate and is prone to oxidative stress. Total brain Cu content in human has been approximated to be 3.1  $\mu$ g/g wet weight. However, due to physiological and anatomical heterogeneity of brain, different regions contain different Cu contents. In human, locus coeruleus and SN contains the highest Cu contents. Cerebrospinal fluid (CSF) 0.2  $\mu$ M of Cu content. While synaptic cleft contains 250  $\mu$ M of Cu [67,68]. During development, with age and in neurodegenerative diseases, brain Cu content and distribution changes. In PD, approximately 50 % reduction in Cu content reported in substantia nigra and locus coeruleus [69,70].

Different transport systems including copper transporter receptor (Ctr)1, copper transporter receptor (Ctr)2, DMT1, metallothioneins (MTs), glutathione (GSH), Copper-transporting P-type ATPases ATP7A and ATP7B play a pivotal role in the maintenance of mammalian cellular and systemic Cu homeostasis [71,72]. While the blood brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCB) are the main regulatory systems of the brain Cu homeostasis requiring combined action of Ctr 1 and ATP7 [73,74]

### 3.2. Role of copper in PD pathogenesis

The main pathological hallmarks in PD are protein aggregation and oxidative stress, although triggers for these events are not known, but changes in bio metals have long been suspected of playing a role in these events. Cu is an important bio metal and play a role in degenerating SNpc in PD. A Substantial decrease in tissue Cu has been reported over the decades. According to recent research, peripheral Cu dyshomeostasis occurs in PD [75]. Literature studies has proved that free Cu is more deleterious for neurodegenerative diseases due to its redox capacity and in turn, generation of free radicals as in the Fenton reaction [76].

### 3.3. Possible mechanisms of Cu toxicity in PD pathogenesis

Following are the possible mechanisms of Cu toxicity in PD

#### 3.3.1. Cu and $\alpha$ Syn interactions and their toxicity in PD

PD can arise from  $\alpha$ Syn accumulation, overexpression and aggregation as well as autosomal dominant mutations in  $\alpha$ Syn gene resulting in A53 T, H50Q, E46 K, A53E, G51D, and A30 P variants.  $\alpha$ Syn aggregation and oligomerization within the neuronal cytoplasm has a deleterious effect and linked to neurotoxicity [77,78]. Cu accumulates in the brain with aging and has the ability to bind with the  $\alpha$ Syn and initiate its aggregation. Asp and Glu residues, abundantly present at the C terminus of  $\alpha$ Syn, were identified as Cu (II) binding donors. At normal pH,  $\alpha$ Syn exhibits two binding sites for Cu (II) at M1-D2 and H50. At the same time, at pH 5.0, H50 binding site at  $\alpha$ Syn is abated replacing with D119-E123. While Cu (I) binds at M1-M5 and M116-M127. In cells both species of Cu co-exists, and transition between these species facilitates amyloid aggregates leading to ROS generation and cell damage [79]. Point mutation to major Cu (II) site H50 leads to the familial form of PD [80,81]. The Copper- $\alpha$ Syn complex is represented by post translational modifications induced by oxidative stress, and this is one of the main perspectives because synucleinopathies and neurodegenerative diseases, in general, are linked with high levels of oxidative stress in the brain [82,83]. Some studies have linked neuroinflammation with synucleinopathies [84].

#### 3.3.2. Oxidative mechanism of Cu and its role in PD pathogenesis

The ability of Cu to cycle between its oxidized state ( $\text{Cu}^{2+}$ ) and reduced state ( $\text{Cu}^{+}$ ) enables it to act as a redox catalyst and to coordinate a large variety of ligands [85]. This feature suggests its involvement in Fenton chemistry, as well as Haber-Weiss cycle, both are involved in the initiation of the generation of highly reactive hydroxyl radicals from hydrogen peroxide and results in the generation of unstable active radicals which attacks macromolecules. These radicals are the powerful oxidizing agents capable of induction of DNA strands breaks and lipid peroxidation [76]. Metals overload causes extensive genome damage, especially base modification and strand breaks demonstrated experimentally in vitro with isolated DNA [86]. Cu exerts its genotoxic effect via generation of singlet oxygen and/or hydroxyl radicals bound to or in close connection in copper-binding sites on double-stranded DNA rather than via the generation of free hydroxyl radicals [87]. The main targets of Cu induced oxidative stress is mitochondria which are accompanied by the functional impairment of mitochondrial respiratory enzymes [88, 89]. Cu induced oxidative stress, triggers apoptosis via activation of tumor suppressor proteins p53, which in turn trigger cascade of anti or

pro-apoptotic proteins or direct action at mitochondria [90]. An in-vitro study revealed that Cu assists the dopamine and related catechols such as L-Dopa and 6-OH-Dopamine oxidation. The complexes arise from these dopamine oxidations causes DNA damage [91,92].

### 3.4. Miscellaneous mechanisms associated with Cu toxicity

Although Cu toxicity is attributed to its oxidative stress, there are certain proteins to which Cu directly attached and induces its toxicity. Cu binds to X-linked inhibitor of apoptosis, induces a conformational change and decreases its half-life, thereby making the cell more susceptible to apoptotic stimuli and exerts its toxic effect [93]. Cu may bind to Cu metabolism independent protein's thiol and amino groups, thereby modifying their structure and biological functions [94]. Cu inhibits enzymatic activities of cytochrome P450, GSH transferases, and lactate dehydrogenase [95]. Cu hampers the activities of DNA glycosylases NEIL1 and NEIL2 and inhibit both phosphatase and kinase activities of polynucleotide kinase 3'-phosphatase (PNKP) that is responsible for preparation of nicked DNA for ligation. Also, Cu inhabits DNA-binding affinity of the DNA nick sensor poly(ADP-ribose) polymerase-1 (PARP-1) and H2O2-induced poly(ADP-ribose)ylation in HeLa S3 cells. Alterations in neuromodulatory functions and their effect on voltage-gated ion channels and synaptic receptors are also contributed to some extent in Cu toxicity [96,97].

## 4. Manganese (Mn)

### 4.1. Mn adequacy

Even though its necessity, excessive and prolonged inhalation of Mn particulates in mining, welding and industries results in its accumulation in selected brain regions that causes CNS dysfunctions and neurological consequences. One of the prominent hazards is in the form of manganese an extra pyramidal syndrome related to PD. Mn can block dopamine synthesis at the level of tyrosine hydroxylation and can also induce the release of dopamine from intracellular stores. Positron emission tomography imaging of nonhuman primate brains has revealed impaired DA transmission, a feature of PD, in the striatum of Mn-exposed animals. The link in the clinical features and pathophysiology has been established between Mn-induced parkinsonism and PD [98–101].

### 4.2. Mn distribution in the central nervous system

Human's brain Mn concentration in ordinary physiological conditions is approximately 5.32–14.03 ng Mn/mg protein (20.0–52.8 Mm Mn), whereas in pathological conditions it reaches to 15.96–42.09 ng Mn/mg protein (60.1–158.4 Mm Mn). Mn accumulation and distribution is affected by various groups of factors which results in its dyshomeostasis and toxicity [102]. Highest Mn concentrations is found in human's brain putamen, caudate nucleus and Globus pallidus, while lowest in pons and medulla. These highest levels of Mn are correlated with age. In PD highest level were found, especially in putamen while lowest in superior and middle temporal gyrus and Globus pallidus [103–105]. Mn has acquired an importance in the brain physiology and biology due to its role as a cofactor in several enzymatic processes. Following are some of the Mn-dependent and Mn-activated enzymes that play a crucial role in brain physiology and maintenance and function such as arginase with its two isoforms ARG1 and ARG2. Glutamine synthetase (GS), superoxide dismutase (Mn-SOD1/SOD2), pyruvate carboxylase and protein serine/threonine phosphatase-1 (PP1) [106–108].

Mn is toxic at high levels. In order to maintain its homeostasis in the CNS, the outflow mechanism play a pivotal role. Recently four main proteins facilitate this outflow including Ferroportin (Fpn), Solute carrier family 30 member 10 (SLC30A10), Secretory pathway  $\text{Ca}^{2+}$ -

ATPase 1 (SPCA1) and ATPase 13A2 (ATP13A2 or PARK9). Fpn and SLC30A10 directly export cytosolic Mn out of neurons, while SPCA1 indirectly control Mn efflux through the Golgi apparatus and ATP13A2 via lysosome. In the presence of Mn, mice, and human embryonic kidney cells display more Fpn levels. People with mutations in the SLC30A10 suffer from hypermanganesemia. ATP13A2 has been associated with early-onset parkinsonism and Kufor-Rakeb syndrome [109,110].

#### 4.3. Mn possible pathogenic mechanisms in PD

Mn pathogenic mechanism is still not been completely understood, but evidence from different studies imply that Mn shows its toxicity through several mechanisms.

Reduction in dopamine levels in SNpc by 80 % is the hallmark of idiopathic PD. It is hypothesized that the locus coeruleus degeneration potentially exceeds dopaminergic degeneration in SNpc. Mn exposure affects brain tissue and extracellular NE concentrations as well as its intake. Mn effect on NE biology results in locus coeruleus disturbance and in turn, the nigrostriatal dopaminergic pathway. Mn causes a two-fold reduction in both protein and mRNA levels of  $\alpha_2$ -adrenergic receptors in locus coeruleus and SNpc [111,112].

Mn exposure elevates the extracellular concentration of  $\gamma$ -aminobutyric Acid (GABA) its nigrostriatal pathway intake, and alteration in its receptors and transport, which results in an alteration in locomotor effects such as hyperkinesia and ataxia. As GABA neurons receives dopaminergic terminals from the SNpc, so its perturbation results in dysregulation of nigrostriatal pathways [113,114].

Mitochondria are one of the most important targets for Mn-induced cellular dysfunction. It contributes to mitochondrial dysfunction by inhibiting mitochondrial complexes I and II of the electron transport chain. In addition, it decreases mitochondrial membrane potential and increases intracellular ROS levels [115,116].

Mn can trigger glial activation and neuro inflammation involving microglia and astrocytes and indirectly damage neurons [117].

Association between environmental exposure and genetic factors play a pivotal role in PD pathogenesis. Mn and genetic mutations associated with PD alters biochemical pathways and as a result, augment PD pathology. In a genome-wide study on cultured human astrocytes, Mn-induced expression changes were observed in genes associated with inflammation and DNA repair [118]. Non-human primates study revealed that Mn-induced changes in the brain gene, involved in apoptosis and inflammation [119].

Mn and  $\alpha$ Syn combination have a deleterious effect on cells survival. Mn can accelerate the in-vitro fibrillation of  $\alpha$ Syn. Moreover, a mutation in genes such as G2019S LRRK2, ATP13A2 and Parkin (PARK2) play a crucial role in Mn-induced neuronal toxicity [120–122].

MicroRNAs (miRNAs) are single stranded RNAs that regulate gene expression post-transcriptionally via binding to the 3'-untranslated region (UTR) of mRNAs. Additionally, mir-7 and mir-433 play a pivotal role in the regulation of the SNCA gene in normal and PD brain. Mn exposure leads to dysregulation of several miRNAs' which regulate apoptosis and synaptic transmission. Dysregulation of miRNA expression was recently identified as contributing to a higher risk of neurodegeneration [123–125].

## 5. Zinc (Zn)

### 5.1. The brain function and Zn importance

The Brain contains the average Zn concentrations between 10–15  $\mu$ g/g of wet tissue. Different regions of the brain have different Zn levels with highest in hippocampus, amygdala and cerebellum. Zn is transported through BBB in the form of complexes with amino acids L-histidine and cysteine. Zn is present in the brain in three forms, first pool: in metals bound form which constitutes 90 %, second pool: in ions form and constitutes about 10 % and stores in presynaptic vesicles of

glutamatergic neurons. Third pool: consists of free ions and present in non-precise form and constitutes 1%. Zn acts as a second messenger. It inhibits NMDA receptors and GABA receptors-mediated response which leads to the reduction of neuronal excitability. Zn enhances AMPA receptors in postsynaptic cells and regulates cell excitation. Therefore sustainable Zn homeostasis is required for proper brain functioning [126–128].

### 5.2. Zn neurotoxicity and possible mechanisms concerned with PD pathogenesis

Zn is important for proper brain functioning. Zn dyshomeostasis in the brain leads to the pathogenesis of numerous neurodegenerative disorders, including PD. Evidence from recent research revealed that Zn ions are capable of directly binding to PARK9. High Zn concentrations are a possible cause of PD as elevated Zn levels were found in SNpc of post mortal brain of PD patients [129–131]. Taking into consideration the aforementioned studies, it is revealed that Zn may play an important role in PD pathogenesis by following possible mechanisms

Until now, three main hypotheses are devised by which Zn may possibly cause cells damage and death, including excessive Zn causes excitotoxicity, induces oxidative stress and impairs the production of cellular energy. These all may act synergistically and cause cell death [132,133]. In addition, oxidative stress due to ROS production contributes significantly to PD pathogenesis. Zn is involved in this process because its dyshomeostasis causes free ROS generation, decrease superoxide dismutase (SOD) activity as well as expression levels of metallothioneins, which in turn induces oxidative stress. ROS generation in the mitochondria disrupts metabolic enzymatic activities and in turn, activates apoptotic processes [134]. In PD pathogenesis proteins misfolding and aggregation plays an important role. Protein aggregation results in Lewy bodies (LB) formation in dopaminergic neurons.  $\alpha$ Syn is the main constituents of LB. Under normal conditions, UPS is responsible for its degradation. The malfunctioning of UPS is responsible for aberrant protein aggregation and protein death. Ubiquitin-conjugated proteins serve as a marker for impaired UPS. Numerous studies revealed that Zn dyshomeostasis causes induction of UPS impairment which in turn causes  $\alpha$ Syn aggregation and increased expression of ubiquitin-conjugated proteins in the dopaminergic neurons and augment PD pathogenesis [135–139].

## 6. Aluminum (Al)

### 6.1. Al neurotoxicity

Al neurotoxicity is well-established fact now both in human and rodents. Al distributes in various brain regions and in human, its content increases with aging. Epidemiological and molecular studies have been linked the long-term exposure to Al along with its cellular concentrations, with multiple neurological disorders including PD. Elevated levels of Al have been found in dopamine-related brain regions in PD patients. The mechanism involving Al neurotoxicity is poorly understood. But the following mechanisms are considering as possible key contributors in Al-induced neurodegenerative diseases.

Oxidative stress is one of the major mechanisms behind metal induced neurotoxicity. It is a biochemical process resulting from the generation of ROS in the electron transport chain. Several studies have shown the presence of oxidative products of lipids, proteins and DNA in PD postmortem tissues. Even though Al is not a transition metal, but it reacts with other metals to generate ROS. Numerous researchers have shown the involvement of Al induced ROS and oxidative stress in Al neurotoxicity [140,141]. Numerous studies have revealed that in PD, Al affect tyrosine hydroxylase (TH) activity and inhibits DNA synthesis. Presence of Al is associated with increased aggregation of  $\alpha$ -synuclein proteins. Mitochondria are important organelles serve as the power house of cells. It helps in the maintenance of cell functions. Several

studies have revealed the involvement of Al induced oxidative stress in mitochondrial dysfunction [142,143]. Al induced oxidative stress results in proteins misfolding, reduced microtubule transport of neuronal vesicles, lipid peroxidation and eventually results in apoptosis. In addition to the aforementioned mechanisms, Al may create pro-inflammatory signals, innate immune disruption, altering NF- $\kappa$ B, p53 and JNK pathways and play a pivotal role in PD pathogenesis [144–146].

## 7. Calcium (Ca)

### 7.1. Calcium dyshomeostasis and its role in PD pathogenesis

Brain  $\text{Ca}^{2+}$  dyshomeostasis has been associated with PD and other neurodegenerative disorders. The peculiar dependence of SNpc DA neurons on voltage-dependent L-type  $\text{Ca}^{2+}$  channels make it more vulnerable for damage. The demands of sustained  $\text{Ca}^{2+}$  entry enhance the aging process and make SNpc DA neurons more vulnerable to genetic and environmental challenges [147–149].  $\text{Ca}^{2+}$  dyshomeostasis is associated with PD pathology through various mechanisms.  $\text{Ca}^{2+}$  promotes  $\alpha$ Syn toxicity through  $\text{Ca}^{2+}$ -dependent protein phosphatase calcineurin. In addition, some studies have proven that  $\alpha$ Syn interacts with membrane to cause  $\text{Ca}^{2+}$  dyshomeostasis. Aggregates of  $\alpha$ Syn activate calcium pumps SERCA, which in turn causes  $\text{Ca}^{2+}$  dyshomeostasis [150–152]. Genetic mutations such as mutations in genes sequence of  $\alpha$ Syn, Parkin, and DJ-1 play an important role in  $\text{Ca}^{2+}$  dyshomeostasis and PD [153]. Cysteine proteases such as calpains and caspases, are activated by  $\text{Ca}^{2+}$  that degrade various substrates, including cytoskeleton proteins, metabolic enzymes and membrane receptors. It triggers apoptosis, through activation of pro-apoptotic proteins such as Bax, Par-4 and p53 [154]. Mitochondria are responsible for the “fine tuning” of  $\text{Ca}^{2+}$ . Impairment of mitochondrial influx/efflux leads to  $\text{Ca}^{2+}$  dyshomeostasis and  $\text{Ca}^{2+}$  overload. This overload causes opening of permeability transition membrane pore (PTP). This mitochondrial  $\text{Ca}^{2+}$  dyshomeostasis is a key factor in PD pathogenesis.  $\text{Ca}^{2+}$  induces oxidative stress through various mechanisms, including activation of oxygenase such as arachidonic acid metabolism, mitochondrial  $\text{Ca}^{2+}$  perturbation, energy metabolism [155–157].

### 7.2. Lead (Pb)

Pb leads to alterations and decreases in dopamine, serotonin and other metabolites in the cerebral cortex, the basal and medial hypothalamus and hippocampus. In addition, it may affect the functional capacity of noradrenergic, dopaminergic, cholinergic, and GABAergic systems. In PD, Pb damages morphology of DA neurons that alters DAT. The DAT alteration causes extracellular DA levels and as a consequence causes neurotoxicity in CNS. Evidence from previous work have shown that Pb causes an alteration in  $\text{Ca}^{2+}$ -mediated cellular processes and mimics  $\text{Ca}^{2+}$  binding to regulatory proteins. Also, it affects the release and reuptake of several neurotransmitters controlled by voltage gated  $\text{Ca}^{2+}$  channels. In the hippocampus, Pb causes  $\alpha$ Syn accumulation, resulting in apoptosis and autophagy. It also activates protein kinase C (PKC) leading to ROS generation. Pb also induces ER stress. Pb is involved in epigenetic changes. Glial cells reactivity in response to brain injury is one of the pathological hallmarks of neurotoxicity because reactive microglia and astrocytes release numerous neurotoxic products including ROS, nitric oxide, proinflammatory cytokines and excitatory amino acids. Pb is involved in the induction of glial reactivity. Pb toxicity can be ameliorated by Pb chelating therapy [158–162].

### 7.3. Mercury (Hg)

In developing countries, Hg toxicity accounts for 8-fold increase in PD incidence [163,164]. Hg is associated with nervous tissues damage in mammalian species as well as young and adult humans as high levels of Hg is found in deceased brain tissues of patients suffering from

neurodegenerative diseases. Epidemiological, in-vivo and in-vitro studies have revealed that Hg toxicity depends upon its chemical forms, times and doses of exposure. MeHg toxicity and its involvement in neurological dysfunction have been proven by two epidemics. First epidemics; The Minamata bay disaster in Japan (1953) by ingestion of MeHg fish and shell fish and second epidemic; in Iraq (1971–1972) by ingestion of bread contaminated by organomercury fungicide. Both took 1043 and 452 lives, respectively [165]. Hg can disrupt neurobiological processes such as synaptic transmission through over activation of NMDA receptors [166]. As Hg toxicity depends upon its form, different forms of Hg exert different toxicity levels through different mechanisms.  $\text{Hg}^{2+}$  form is very toxic for the brain because of its long half-life. It can cause brain damage due to its ability to bind irreversibly to thiol sulfhydryl (–SH) group altering protein structure and inhibiting enzymatic functions, binding with cysteine residue and glutathione causes inactivation of hormones and Sulphur cofactor. It can cause tubule disruption by binding to the thiol group of  $\alpha$ - and  $\beta$ -tubulin. It can impair Ca-ATP pumps alter Ca homeostasis. It has the ability to inhibits glutamate uptake, promoting its release in extra cellular space. MeHg can cross the BBB as well as its take up by neuronal cells through MeHg-L-cysteine complex where it targets CNS. Epidemiological studies have shown that MeHg can transfer from pregnant mother to fetus, and causes neuronal deficits in their offspring. MeHg interacts with, and oxidized nucleophilic groups of biomolecules, sulfhydryl groups (thiol/thiolate; –SH/–S) are the main targets in biological system. MeHg interaction with sulfhydryl-containing proteins such as neurotransmitter receptors, transporters, antioxidant enzymes and non-proteins thiols such as glutathione and cysteine are main neurotoxicity mediators. MeHg direct exposure causes depletion in GSH levels. Its interaction with selenohydryl (selenol/selenolate; –SeH/–Se) is important target of neurotoxicity [167–170].

Due to the induction of neuronal toxicity, Hg represents itself as one of the etiological factors for PD. Hg ingestion causes loss of DA neurons and glutathione depletion in SNpc, glutamate increase and mitochondrial dysfunction. Occupational exposure to Hg causes parkinsonism. Many scientists have investigated and proved the correlation of PD with Hg levels [171]. Blood Hg levels in PD patients have six folds higher as compared with control group. Another study conducted in Taiwan has proved the correlation of PD with the presence of dental amalgam. Among several professionals’ dentist were most common in PD patients [172]. Another study investigated the correlation between PD and airborne metals in female nurses and found that among other metals, only Hg is associated with highest PD risk [173]. Numerous in vitro and in vivo experimental studies have proved the Hg toxicity and its possible mechanisms in the etiology of PD, Such as oxidative stress and ROS generation,  $\text{Ca}^{2+}$  dyshomeostasis, mitochondrial dysfunction, apoptosis and neuroinflammation [174–180].

### 7.4. Possible role of pesticides and deregulated miRNA to PD

In spite of their beneficial role in agriculture, they have been associated with severe side effects on human health, such as acute poisoning and chronic consequences, even neurodegenerative diseases. PD is also strongly associated with environmental exposures to numerous substances and pollutants, amongst them several pesticides [181–183]. Glutathione-S-transferase (GST) and total antioxidant capacity are greatly influenced by pesticides. Oxidative stress (OS) has been proven to play a major role in the manifestation of neurodegenerative diseases such as PD. Pesticides may lead to these neurotoxic processes via OS [184,185]. A meta-analysis concluded that prolonged pesticide exposure was associated with a higher risk for PD of up to 11 % [186]. Another meta-analysis of case-control studies concluded that pesticides are associated with a higher risk for PD and alterations in genes related to PD. Moreover, in France, PD has even considered a professional disease of farmers applying pesticides [187,188]. In another case-control study Paraquat and rotenone were closely associated with higher risk

of developing PD [189,190].

MicroRNAs (miRNAs) are small non-coding RNA molecules, that control the expression of genes in several cellular processes and the translation of mRNAs following the transcription [191,192]. miRNAs are considered to modify more than half of protein-coding genes [193]. Several studies have validated the involvement of numerous miRNAs in the disease's manifestation. In view of the wide interest of the scientific community on PD and miRNAs, many studies have been published [194, 195].

#### 7.5. Some key deregulated miRNAs involvement in pesticide-related neuronal death and PD pathogenesis are as following

Paraquat (PQ) is one of the most widely distributed herbicides. Since 1882, before the discovery of its herbicidal activities, it was known as a redox agent. Its redox potential, that produces reactive oxygen species (ROS) and consumes NADPH is toxic to plants and mammals [196]. PQ has been linked with a significantly higher risk of developing PD. Possible mechanisms underlying its links to PD have been proposed, employing a multi-faceted theory [197]. It has been shown that it can enter dopaminergic neurons via dopamine transporters (DAT), and mutations in the DAT gene also confer susceptibility to PD upon exposure to PQ [198]. A study on PQ-exposed SHSY5Y dopaminergic neurons revealed an upregulation of the highly brain-specific miRNA-153, which was linked to the researchers' previous finding, that PQ leads to cellular death via oxidative stress [199,200]. Concerning PD, miR-153 has increased in CSF samples from late onset of PD (LOPD) patients [201]. The in-vitro studies of pesticide exposure and the PD CSF results both show an upregulation, a common finding that could hint towards PQ being involved in PD pathogenesis [202]. A recent study on neuro-2a cells exposed to PQ indicated a significant downregulation of miR-17-5p, a molecule which promotes cell proliferation and suppresses apoptosis, alongside -210-3p, -503-5p and -374-5p. The researchers proposed that these molecules are involved in PD-pathogenesis via cellular death through endocytosis, ubiquitin-mediated proteolysis, cell cycle changes and the MAPK signaling pathway, especially the -17-5p molecule [203]. Numerous human sample investigations and in-vitro studies evident the fact that PD seems to be a derivative of environmental and genetic interactions in the individuals. We cannot deny the possibility that the miRNA deregulation noted in the cell lines could be due a global response against the neurotoxicant applied. The PQ study found the miRNA let-7 family downregulated, which is in line with the studies with CSF and plasma samples from PD patients, hinting towards another common feature between PD and PQ. miR-29, which has been implicated in epithelial-mesenchymal transition (EMT), skeletal muscle cell and osteoblast differentiation, as well as in cardiac fibrosis and systemic sclerosis which was found downregulated in human neural progenitor cells exposed to PQ [204]. It was also reported to decrease in CSF samples from PD patients [205]. It also possibly represents a common link between PQ and PD. miR-181, with -181b downregulated in the PQ study. Two studies have shown decreased levels of miR-181a in serum and brain tissue of late onset PD patients [206].

As a whole, PQ seems to be the main culprit in the oxidative procedures that may link pesticides with PD. Regarding microRNAs, several of those that have been reported as deregulated in a PD context have emerged in PQ-related research as well.

#### 7.6. Organophosphates

Organophosphate (OP) pesticides are mostly insecticides, which are frequently applied in agricultural production and occasionally for industrial or residential use. OPs mechanism of action is the inhibition of acetylcholinesterase (Ache) [207]. Following acute OP poisoning, let-7 g were found downregulated, which are also downregulated in the CSF of PD patients [208]. Moreover, miR-141 was also found

downregulated (miR-141-5p) upon acute OP poisoning, was reported downregulated (miR-141-3p) in neuron samples from PD patients. MiR-126 was found upregulated in the serum of patients exposed to OP and in two studies on dopaminergic neuron samples from PD patients [209].

#### 7.7. Triazines

Triazines are herbicides. Atrazine, a widely-used triazine has been shown to be directly toxic for the dopaminergic neurons. It has been confirmed that miR-126 contributes to parkinsonism via the down-regulation of factors in IGF-1/PI3K signaling and the rendering of cells susceptible to neurotoxins [210,211].

#### 7.8. Organochlorines

Organochlorine (OC) pesticides represent another well-known insecticide class. OC substances exert their action due to their similarity to  $\gamma$ -aminobutyric acid (GABA) receptor antagonist picrotoxin, consequently blocking the inhibitory action of GABA [212]. The upregulation of the miRNA-190 family in animal models exposed to DDT, in several tissue samples, while their target gene product, Tp53inp1, was unsurprisingly decreased [213]. Tp53inp1 has involved in oxidative stress response, and its product acts as an antioxidant. Thus, miRNA's deregulation could also be involved in the OS procedure that leads to dopaminergic neuron death [214]. OCs have been shown to induce CYP polymorphisms, and thus they have been implicated in the etiology of neurodegenerative processes, such as in Alzheimer's disease and PD [207,215].

#### 7.9. Rotenone

Rotenone is the prototypical member of the rotenoid family of naturally-occurring substances with insecticidal abilities. It inhibits mitochondrial complex I, resulting in reduced ATP generation, ROS generation and oxidative stress [216]. An odds ratio of 2.5 for humans exposed to rotenone to develop PD and attributed the rotenone-induced mitochondrial dysfunction [217]. The researchers studied the concentrations of several PD-related miRNAs in the striatum of the rotenone exposed rats and found a significant increase in miR-26a and miR-34a, and a significant decrease in miR-7 and let-7a [218]. MiR-34 was found increased in PQ-exposed neural progenitor cells. Taken together, this persistent upregulation in experiments with three pesticide categories (rotenone, OCs, PQ) have been associated with PD literature, could indicate that pesticides may be indeed associated with PD. MiR-7, in the rotenone experiment shown decreased, was also found decreased in an in-vitro study of manganese exposure, which also causes a Parkinsonian syndrome, and in brain samples of LOPD patients. miR-26a, here significantly increased, was also reported upregulated in both neuronal, and CSF samples from PD patients [219].

The aforementioned studies suggest a common pattern indicating that specific miRNAs are deregulated in a PD context, and several of those are also deregulated as a result of pesticide exposure, raising the possibility of a likely link between the two.

## 8. Conclusion

Metals ions which are essential for the operation of many physiological processes in the human body have a prominent role in the sustenance of healthy life. Furthermore, the homeostasis and forms of these metals in the human body is also of great concern. Even though the fundamental molecular mechanisms of PD etiology and pathogenesis is still obscure, metals toxicity have been documented in the implication of PD pathogenesis by several epidemiological studies with several potential mechanisms. In many cases, the metals equilibrium is disturbed, which leads to deleterious effect on the entire body including the brain.

Such changes in the brain lead to impairment of neurons by different mechanisms including oxidative stress, mitochondrial dysfunctions, neuroinflammation and apoptosis. Consequently, the development of neurodegenerative diseases including PD occurs. Several metals such as Fe, Cu, Pb have a synergistic effect among themselves and with Hg, which adds to their neuronal toxicity. Among metals, Hg is the most toxic because it is neurotoxic in every chemical form. Due to high tubulin content, nigral dopaminergic neurons are most sensitive to Hg. Taken together, metals have a fundamental role in PD etiology and pathogenesis. In addition to metals, numerous studies have revealed the deregulation of specific miRNAs due to pesticides exposure, and their involvement in PD pathogenesis. The results finding from various studies suggest that in addition to standard treatment, using of chelating agents and antioxidants might contribute to the treatment of PD. Metals toxicity are still unclear; understanding the underlying mechanisms is essential for designation of novel therapeutic approaches. A Better understanding of these mechanisms will assist in the development of multifactorial approaches to delay or cure PD progression.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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