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Metal Exposure and Oxidative Stress Induced Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder characterized by dopamine deficiency and loss of neurons in the SubstantiaNigra (SN) of brain. The deficiency of dopamine, thereafter, presents in the form of a number of motor and non-motor deficiencies and complications. Our understanding about PD is still evolving and treatments available for this disease are still quite basic. Therefore, better understanding of the pathological events linked with this disease may help us devise better treatment protocols of the disease.

Increased production of reactive oxygen species (ROS), oxidative stress, seems to be the centerpiece of PD pathology. Increased oxidative stress in PD is mainly the result of by-products generated from dopamine metabolism, mitochondrial dysfunction, and inadequate activity of the brain's antioxidant system. Once generated, ROS cause damage to the brain due to its high unsaturated fatty acid content, which makes it quite sensitive to oxidative injury.

In our daily life we're exposed to different metals and metals have been long linked as risk factors for PD development. Therefore, in this article we've considered three important metals (iron, aluminum, and copper), most of which we encounter time to time in domestic, occupational and environmental standpoints. This review, therefore, is concerned with discussing the role of these metals with increased oxidative stress in brain. Moreover, this review will also discuss how this increase in oxidative stress is linked to various component of PD pathology.

Introduction

The history of Parkinson's disease (PD) datesback totwo centuries from now when James Parkinson wrote "An essay on the shaking palsy", in 1817 [(1)]. More than 100 years later, dropout of cells in the substantianigra (SN) of brain was pointed out to be the key lesion in PD and 140 years after the initial mention of PD, dopamine was discovered as a putative neurotransmitter involved in the pathogenesis of this disease [(2)]. Discovery of

dopamine deficiency and success of levodopa treatment in improving PD symptoms was heralded as a huge success in PD treatment [3] [4] [5] [6]. But even today, our understanding about PD is still incomplete and the treatment options available are only symptomatic. Till date, there is no neuro-protective or neuro-regenerative interv-enetion that has proved to be effective in treating PD [7] [8]. Therefore, knowing more about the risk factors that increase neuronal breakdown in PD may improve our understanding of the disease and may help us come up with better treatment modalities.

Motor and Non-Motor Manifestations in PD

PD is a chronic neurodegenerative disorder with an array of motor and non-motor symptoms, which are believed to be the result of dopaminergic neuronal loss [8]. The motor manifestations in PD include bradykinesis[9]; rest tremors [10]; rigidity with postural deformities, postural instability, motor blocks (freezing)[11]; re-emergence of primitive reflexes[12] [13]; orofacial-larygenal rigidity and bradykinesia leading to sialorrhoea, dysarthria, dysphagia and hypophonia [10] [14]; neuro-ophthalmological deficits including decreased rate of eyelids blinking, spasm of convergence, reduced tear film, exposure keratitis, blephrospasm and impaired vision [15]; and respiratory insufficiency [16]. Non-motor manifestations of PD include autonomic dysfunction with orthostatic hypotension, dysfunction of sweating, erectile dysfunction and sphincter paralysis [17] [18] [19]; cognitive decline [20]; neurobehavioral abnormalities like apathy, depression, anxiety, and even hallucinations [21]; sleep disorders [22] and sensory abnormalities like pain[23]. There has been much clarity in our understanding of underlying causes of nigral cell damage. Among the mechanism involved, genetic mutations [7], mitochondrial dysfunction [24], denaturation and aggregation of proteins [25], inflammation [26] [27], and oxidative stress [29] seem to be the most important mechanisms involved in PD pathogenesis.

Role of Oxidative Stress in PD Pathology

Human brain consumes as much as 20% of body oxygen and a lot of this oxygen is converted into reactive oxygen species (ROS) [28]. Both neuronal and glial cells are responsible for the generation of ROS inside the brain and disequilibrium in the electron transport chain is the main contributor of oxidative stress at the cellular level [29]. As for oxidative stress in PD, both increased production and impaired clearance of ROS seem to be the culprit behind increase in oxidative stress. The prime factors contributing to increase ROS include dopamine metabolism and mitochondrial dysfunction. Whereas, reduced clearance of ROS is mainly due to the decrease in the concentration of catalase and glutathione peroxidase [30].

Role of Dopamine

Dopamine is an unstable neurotransmitter that undergoes auto-oxidation- a reaction catalyzed by metals, enzymes like tyrosinase and oxygen- to form dopamine quinones and free radicals [31]. Under normal circumstances, monoamine oxidase A (MAO-A), which is largely localized within

catecholaminergic neurons, metabolizes and regulates the levels of dopamine [32]. However, with age or neurodegenerative disease like PD, the level of MAO-B increases within glial cells and this MAO-B becomes the key enzyme metabolizing dopamine [33] [34]. The products of MAO-B metabolism include an ammonia derivate (3, 4-dihydroxyphenyl-acetaldehyde) and hydrogen peroxide (H2O2). H2O2, being highly permeable, enters the neighboring dopaminergic neurons and produces ROS like hydroxyl radicals after reacting with cellular Ferrous ions (Fe+2) [35] [36]. In addition, dopamine quinones can exacerbate neuro-degeneration too[37]. The main mechanism through which dopamine quinones trigger oxidative stress is their cyclization to aminochrome, which is a reactive molecules that depletes cellular NADPH and initiates the production of superoxide ions [38]. Finally, the concentration of free dopamine in neuronal cytoplasm can also trigger oxidative stress. Vesicular monoamine transporter 2 (VMAT2) and dopamine transporters (DAT are concerned with the sequestration of cellular dopamine within storage vesicles and reuptake of dopamine from synaptic clefts respectively. Perturbations in the functioning of these transporters can increase the concentration of free dopamine within cell cytoplasm and can cause a resultant increase in oxidative stress [39] [40].

Role of Mitochondrial Dysfunction

Mitochondrial is a dynamic organelle and controls several vital functions. As mentioned before, it has been repeatedly reported that dysfunction of electron transport chain is the main contributor of oxidative stress within cells. Several components and processes of electron transport chain like complex I, II, III, dehydrogenases in the tricarboxylic acid (TCA) and final coupling of oxygen with hydrogen ions to form water result in the generation of superoxide anions [41] [42] [43]. These anions are then turned into H2O2 by the action of manganese superoxide dismutase (MnSOD) [44]. The role of mitochondria in causing oxidative stress was first elucidated when Parkinsonism was observed in some 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) drug abusers [45]. MPTP is taken by brain astrocytes where it is converted into 1-methyl-4-phenylpyridinium (MPP+) by the action of MAO-B. MPP+ is a known inhibitor of complex I of electron transport chain. This way it inflicts damage to NS dopamine neurons by causing a drop in the level of ATP, increased oxidation of dopamine and enhanced production of ROS [46].

Role of Anti-Oxidant System

As mentioned former in the text, increased oxidative stress in PD is the result of both increased production and decreased clearance of ROS. Analysis of serum superoxide dismutase (SOD) and glutathione peroxidase (GSH) activity in controls and patients with PD showed a marked elevation in the activity of these anti-oxidant enzymes, which further proves the notion that increased oxidative stress is the centerpiece of PD pathology [47]. Moreover, postmortem analysis of brain tissues in patients with PD showed marked reduction in the level of GSHin the SN of PD

patients when compared to the control [48] [49]. The level of catalase was found to have undergone significant reduction in patients with PD [50]. Similarly, decreased level of other antioxidant like GSH peroxidase and ceruloplasmin are also observed in patients with PD [51] [52].

How ROS in PD Damage the Brain?

Human brain contains abundant polyunsaturated acids like arachidonic acid and docosahexaenoic acid. These acids are unsaturated and are highly susceptible to peroxidation induced by ROS. In fact, this is the basic mechanism of ROS induced brain injury [53]. Structural damage to the membranes caused by lipid peroxidation and exaggerated injury induced by lipid oxidation production are the further predictors of brain injury [54] [55]. One such product of lipid peroxidation is 4-Hydroxyl-2-nonenal (HNE). HNE is a highly reactive molecule that can inflict damage to the cells by denaturing proteins, causing a decrease in GSH levels, DNA fragmentation and apoptosis triggered by the activation of capsases [56] [57]. The notion that lipid peroxidation and damage inflicted by by-products of lipid peroxidation might contribute to PD progression is supported by several clinical studies as well. The results of several studies have backed the fat the level of brain unsaturated fatty acids decrease, while the level of lipid peroxidation products like HNE and malondialdehyde increase in the brain substance and cerebrospinal fluid of PD patients [58] [59] [60].

Since urbanization and industrialization, our day to day exposure to metals has increased significantly. We are subjected to metals of different sorts daily via domestic routes, industries and environmental exposure. Metal exposure is a known risk factor for PD. Therefore, the purpose of this review is to find a link between exposure to metals and increased risk of PD. Moreover, this review will also shed some light on the underlying mechanism of metal induced oxidative stress, which maybe the main event responsible for metal induced PD.

Discussion

Exposure to metals is an important risk factor for different neurological disorders. The exposure to metals can be domestic or occupational. Different metals are recognized to cause increased risk of neurological disorder by increasing the production of ROS [61]. In this review, we've discussed different metals (Iron, Aluminum and Copper) and their role in the pathogenesis of PD (Table 1). These metals are of particular interest and are discussed here because a lot of household appliance, utensils (especially cooking utensils) make use of these metals.

Iron

Among metals that are linked with PD, iron is the most important. Postmortem studies of the brain tissues in patients with PD showed significant increase in the iron content of SN [63] [64] [65]. In the normal brain tissues, iron is extensively distributed within different areas of basal ganglia including globuspallidus, SN and putamen [66]. However, this pattern of iron distribution changes significantly with increasing age and

neurodegenerative disease like PD. In such conditions, the levels of iron become abnormally high in SN, when compared to other areas of basal ganglia [67].

Irons seems to influence PD, both by increasing oxidative stress and decreasing anti-oxidant enzymes. Ferrous (Fe+2) and ferric (Fe+3) forms of iron can trigger a chain reaction after interacting with superoxide and hydrogen peroxide (Fenton's reaction) respectively. This chain reaction results in the formation of highly reactive hydroxyl radicals, which can trigger neurotoxicity [68] [69]. In addition, iron can increase the level of oxidative stress by causing mitochondrial dysfunction. Iron seems to increase the production of ROS by blocking the activity of complex I and complex IV of electron transport chain[70]. Moreover, excess of iron has been found to decrease the level of antioxidant enzymes-which is perhaps due to increased oxidative stress-especially glutathione [71]. Iron content and increased oxidative stress are two way process i.e. higher iron content can induce increased oxidative stress and higher oxidative stress can in turn increase iron content too. Iron is release from ferritin by the action of superoxide anions, from iron-sulfur proteins via the action of peroxynitritie and from heme compounds by the action of peroxidase [72] [73] [74].

Exposure to excess iron via different routes (oral or parenteral) can increase the risk of PD as well. Kaur et al. 2007, conducted an experiment on mice, the results of which showed that increased oral intake of iron during early stages of life made the mice more susceptible to develop PD later in their life. Such mice developed symptoms of dopamine deficiency by the time they reached 12 months and showed significant loss of nigral neurons by the time they were 24 months old. Moreover, the brain of such mice showed increased vulnerability to oxidative stress induced injury [75]. Similar results were obtained when iron was given orally or was injected within SN of mice. The higher level of iron in SN resulted in reduced levels of GSH and increased levels of hydroxyl radicals [76]. When iron chelators, like desferrioxamine, are given intramuscularly, they result in significant reduction in brain iron level and exert a neuro-protective effect against MPTP and iron in mice models [77]. All these evidences cumulatively suggest that increased iron in the SN is an important trigger for oxidative stress and resultant neuro-degeneration in PD.

Aluminum

Aluminum is a non-redox metal that is well known to have profound relation in the pathogenesis of several neurodegenerative diseases [78] [79]. The X-ray microanalysis of brains of patients with PD showed increased level of two metals in SN: one metal being iron and other being Aluminum [80].

Although, aluminum is a non-redox metal, it is believed to contribute in the pathogenesis of PD and other neurodegenerative disorder through multiple mechanisms [81]. The main mechanism through which aluminum seems to increase oxidative stress is by increasing iron induced oxidative stress. Aluminum brings alterations in membrane structure, which increases the

susceptible of membrane to undergo iron induced peroxidation [82]. However, aluminum can induce membrane oxidation through a mechanism independent of iron too[83]. Another mechanism through aluminum contributes to increased oxidative stress in brain, independent of iron, is through the increased oxidation of NADPH [84]. Not only that, but aluminum also contributes to oxidative stress in PD by increasing the production of hydroxyl oxygen species through a mechanism independent of iron [85]. In fact, in aluminum induced brain injury, nitric oxide (NO) comes into play, which interacts with superoxide anions to form peroxynitrite anions that are even more toxic than simple hydroxyl anions [86]. Like iron, another mechanism through which aluminum might induce oxidative stress mediated damage in through mitochondrial dysfunction. This maybe the result of dysfunction of mitochondrial enzymes like cytochrome c oxidase (COX) and Complex I[87]. Not only that, aluminum seems to increase oxidative stress by decreasing the level of different antioxidants as well. Anuradha et al. 2014, demonstrated that sub-acute exposure of rats to aluminum causes significant reduction in the level of GSH and activity of SOD, CAT, and glutathione peroxidase (GPx)[88].

Moreover, occupational exposure to aluminum is a risk factor for PD [89]. In fact, there have been some case reports were exposure to aluminum compounds was linked with disequilibrium of dopaminergic system [90]. Furthermore, results obtained from animal models have suggested that intra-peritoneal injections of aluminum chloride can increase oxidative stress and resultant neuronal loss in areas of brain stem [91]. All these evidence suggest that both oral and parenteral exposure to aluminum maybe a risk factor for increased oxidative stress and disequilibrium of dopaminergic system of brain.

Copper

Copper is another metal that has been linked with PD. The link of copper with PD is particularly interesting. Unlike iron and aluminum, the concentration of copper in SN decreases significantly. It has been repeatedly demonstrated that patients with PD always have higher iron in their SN and lower level of copper [92] [93]. This apparent paradox can be explained on the basis of copper-dependent ferroxidase system activity. Ferroxidase promotes the conversion of Fe+2 into Fe+3, so that it can be moved out of the cells. The activity of ferroxidase is controlled by copper [94]. But, the activity of ferroxidase is found to diminish greatly both within the plasma and cerebrospinal fluid (CSF) of patients with PD [95] [96] [97]. Therefore, it is quite possible that decreased concentration of copper in SN is the consequence of defective function of ferroxidase [98].

As for copper induced oxidative stress, it seems to be the result of a mechanism similar to iron. Copper catalyzes the conversion of hydrogen peroxide into hydroxyl group through this reaction ($Cu^{+} + H_2O_2 \leftrightarrow Cu^{++} + OH^{-} + OH$) [99]. Alpha-Synuclein is a protein of unknown significance that is found in higher concentrations in the form of Lewy bodies within the brains of PD patients [100]. These proteins bind with copper to enhance

their redox capacity. After that, this complex produces H2O2 from ascorbic acid. This H2O2 then triggers the oxidation of dopamine and production of more neurotoxic metabolites [101]. As for lipid peroxidation, copper causes oxidative stress mediated damage to membranes through both iron dependent and independent mechanisms [102] [103]. Although copper is an essential cofactor for several mitochondrial enzymes, but its overload may cause mitochondrial dysfunction too. Copper overload has been linked with complex IV (cytochrome C oxidase, COX complex) dysfunction [104]. The Cu-Alpha-Synuclein complex also seems to decrease the level of antioxidants like GSH [101]. In addition, the malfunction ceruloplasmin (a potent antioxidant) has been reported in patients with PD [105]. Several studies have declared copper to as a risk factor for PD [106] [107]. On the other hand, there are some studies were exposure to copper and risk for PD was barely of statistical significance [108]. More research may be needed in this area.

Table 1: Summary of metal exposure and PD pathology

Metal	Brain levels (SN)	Major reaction for ROS generation	Mitochondrial dysfunction	Lipid peroxidation	Decrease/malfunction in Antioxidant activity
Iron	Increased	Fenton's reaction	Complex I and IV	Independent mechanism	GSH
Aluminum	Increased	Iron induced and peroxynitrites	Complex I and IV	Iron induced and independent mechanism	GSH, SOD, CAT, GPx
Copper	Decreased	Fenton's reaction	Complex IV	Iron induced and independent mechanism	Ceruloplasmin, GSH

GSH: Glutathione, SOD: Superoxide dismutase, CAT: Catalase, GPx: Glutathione peroxidase.

Conclusion

From this review it can be safely concluded that increased exposure to the aforementioned metals could be a marker or at least an important risk factor for the development of PD. Increase in the oxidative stress is perhaps the key mechanisms through which these metals disturb SN dopaminergic neurons and their functioning in PD. Therefore, interventions that could specifically target different mechanisms that reduce oxidative stress can be an effective tool in the fight against PD, which are still largely treated symptomatically. Moreover, devising the cut off limits to the exposure to the aforementioned metals may provide valuable results too.

However, it must also be kept in mind here is whether domestic exposure to these metals poses similar threat of developing PD as occupational or experimental exposure do is still a matter of debate. More research is needed in this area.

References

1. Parkinson J. An essay on the shaking palsy. J Neuropsychiatry ClinNeurosci 2002;14:223–36.
2. Bjorklund A, Dunnett S. Dopamine neuron systems in the brain: an update. Trends Neurosci 2007;30:194–202.
3. Hornykiewicz O. The discovery of dopamine deficiency in the parkinsonian brain. J Neural Transm 2006;70:9–15.
4. Birkmayer W, Hornykiewicz O. The L-3,4-dioxyphenylalanine (DOPA)-effect in Parkinson-akinesia. Wien KlinWochenschr 1961;73:787–8.
5. Birkmayer W, Hornykiewicz O. The effect of L-3, 4-dihydroxyphenylalanine (L-DOPA) on akinesia in parkinsonism. Parkinsonism RelatDisord 1998;4:59–60.
6. Amitabh Gupta, Valina L. Dawson, and Ted M. Dawson. What causes cell death in Parkinson's Disease?Ann Neurol. Dec 2008; 64(0 2): S3–15.
7. Dexter DT, Jenner P.Parkinson disease: from pathology to molecular disease mechanisms.Free RadicBiol Med. 2013 Sep;62:132-44.
8. Vingerhoets FJG, Schulzer M, Calne DB, et al. Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? Ann Neurol 1997;41:58–64.
9. Budzianowska A, Honczarenko K. Assessment of rest tremor in Parkinson's disease. Neurol Neurochir Pol. 08 Jan-Feb;42 (1):12-21.
10. J Jankovic. Parkinson's disease: clinical features and diagnosis. J NeurolNeurosurg Psychiatry 2008; 79:368-376.
11. Thomas RJ. Blinking and the release reflexes: are they clinically useful? J Am GeriatrSoc 1994;42:609–13.
12. Vreeling FW, Jolles J, Verhey FRJ, et al. Primitive reflexes in healthy, adult volunteers and neurological patients: methodological issues. J Neurol 1993; 240:495–504.
13. Hunker CJ, Abbs JH, Barlow SM. The relationship between parkinsonian rigidity and hypokinesia in the orofacial system: a quantitative ana. Neurology82; 32:749–54.
14. Biousse V, Skibell BC, Watts RL, et al. Ophthalmologic features of Parkinson's disease. Neurology 2004;62:177–80.
15. Sabate M, Gonzalez I, Ruperez F, et al. Obstructive and restrictive pulmonary dysfunctions in Parkinson's disease. J NeurolSci 1996;138:114–19.
16. Pursiainen V, Haapaniemi TH, Korpelainen JT, et al. Sweating in Parkinsonian patients with wearing-off. Mov Disord 2007;22:828–32.
17. Senard JM, Rai S, Lapeyre-Mestre M, et al. Prevalence of orthostatic hypotension in Parkinson's disease. J NeurolNeurosurg Psychiatry 1997;63:584–9.
18. Zesiewicz TA, Sullivan KL, Hauser RA. Nonmotor symptoms of Parkinson's disease. Exp Rev Neurother 2006;6:1811–22.
19. Aarsland D, Andersen K, Larsen JP, et al. Risk of dementia in Parkinson's disease: a

community-based, prospective study. Neurology 2001;56:730–6.

20. Aarsland D, Bronnick K, Ehrt U, et al. Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. J NeurolNeurosurg Psychiatry 2007;78:36–42.
21. Ondo WG, DatVuong K, Khan H, et al. Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology 2001;57:1392–6.
22. Tinazzi M, Del Vesco C, Fincati E, et al. Pain and motor complications in Parkinson's disease. J NeurolNeurosurg Psychiatry 2006;77:822–5.
23. Zhu J1, Chu CT.Mitochondrial dysfunction in Parkinson's disease.J Alzheimers Dis. 2010;20Suppl 2:S325-34.
24. Meredith SC.Protein denaturation and aggregation: Cellular responses to denatured and aggregated proteins.Ann N Y Acad Sci. 2005 Dec;1066:181-221.
25. Tufekci KU, Meuwissen R, Genc S, Genc K.Inflammation in Parkinson's disease. Adv Protein Chem Struct Biol. 2012;88:69-132.
26. Wersinger C, Sidhu A.Inflammation and Parkinson's disease.Curr Drug Targets Inflamm Allergy. 2002 Sep;1(3):221-42.
27. Hwang O. Role of oxidative stress in Parkinson's disease.ExpNeurobiol. 2013 Mar;22(1):11-7.
28. Yan MH, Wang X, Zhu X. Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease. Free RadicBiol Med. 2011;62:90–101
29. Chun Zhou, Yong Huang, And Serge Przedborski. Oxidative Stress in Parkinson's Disease: A Mechanism of Pathogenic and Therapeutic Significance. Ann N Y Acad Sci. Dec 28; 1147: 93–104.
30. Munoz P, Huenchuguala S, Paris I, Segura-Aguilar J. Dopamine oxidation and autophagy. Parkinsons Di.2012;2012: 920953
31. Riederer P, Konradi C, Schay V, et al. Localization of MAO-A and MAO-B in human brain: A step in understanding the therapeutic action of L-deprenyl. Adv Neurol. 1987;45:111–118.
32. Saura J, Andrès N, Andrade C, et al. Biphasic and region-specific MAO-B response to aging in normal human brain. Neurobiol Aging. 1997;18:497–507
33. Youdim MB, Edmondson D, Tipton KF. The therapeutic potential of monoamine oxidase inhibitors. Nat Rev Neurosci. 2006;7:295–309.
34. Nagatsu T, Sawada M. Molecular mechanism of the relation of monoamine oxidaes inhibitors to Parkinson's disease: Possible implications of glial cells. J Neural Transm. 2006;71:53–65.
35. Kumar MJ, Andersen JK. Perspectives on MAO-B in aging and neurological disease - where do we go from here? Mol Neurobiol. 2004;30:77–89.
36. Hastings TG. The role of dopamine oxidation in Mitochondrial dysfunction:

Implications for Parkinson's disease. J BioenergBiomembr. 2009;41:469–472.

37. Asanuma M, Miyazaki I, Diaz-Corrales FJ, Ogawa N.Quinone formation as dopaminergic neuron-specific oxidative stress in the pathogenesis of sporadic Parkinson's disease and neurotoxin-induced parkinsonism.Acta Med Okayama. 2004 Oct;58(5):221-33.
38. Uhl GR, Li S, Takahashi N, et al. The VMAT2 gene in mice and humans: Amphetamine responses, locomotion, cardiac arrhythmias, aging, and vulnerability to dopaminergic toxins. FASEB J. 2000;14:2459–2465
39. Graham D. Pathways for catecholamines in the genesis of neuromelanin and cytotoxic quinones. MolPharmacol. 1978;14:633–643
40. Turrens JF. Mitochondrial formation of reactive oxygen species. J Physiol. 2003;552:335–344.
41. Barja G, Herrero A. Localization at complex i and mechanism of the higher free radical production of brain nonsynaptic mitochondria in the short-lived rat than in the longevous pigeon. J BioenergBiomembr. 1998;30:235–243
42. Murphy MP. How mitochondria produce reactive oxygen species. Biochem J. 2009;417:1–13.
43. Fridovich I. Superoxide dismutases. An adaptation to a paramagnetic gas. J Biol Chem. 1989;264:7761–7764.
44. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. Science. 1983;219:979–98
45. Ali SF, David SN, Newport GD, et al. MPTP-induced oxidative stress and neurotoxicity are age-dependent: evidence from measures of reactive oxygen species and striatal dopamine levels.Synapse. 1994 Sep;18(1):27-34
46. Kalra J, Rajput AH, Mantha SV, Prasad K.Serum antioxidant enzyme activity in Parkinson's disease.Mol Cell Biochem. 1992 Mar 25;110(2):165-8
47. Pearce RK, Owen A, Daniel S, Jenner P, Marsden CD. Alterations in the distribution of glutathione in the substantianigra in Parkinson's disease. J Neural Transm. 1997;104:661–677.
48. Perry TL, Godin DV, Hansen S. Parkinson's disease: A disorder due to nigral glutathione deficiency? NeurosciLett. 1982;33:305–310.
49. AMBANI LM, VAN WOERT MH, MURPHY S. Brain peroxidase and catalase in Parkinson's disease. Arch. Neurol. 1975;32:114–118
50. Kunikowska G, Jenner P. Alterations in m-RNA expression for Cu,Zn-superoxide dismutase and glutathione peroxidase in the basal ganglia of MPTP-treated
51. marmosets and patients with Parkinson's disease. Brain Res. 2003;968(2):206–218.
52. Ayton S, Lei P, Duce JA, et al. Ceruloplasmin dysfunction and therapeutic

potential for parkinson disease. Ann Neurol. 2012

53. Montine TJ, Neely MD, Quinn JF, et al. Lipid peroxidation in aging brain and Alzheimer's disease. Free RadicBiol Med. 2002;33:620–626.
54. Mattson MP. Modification of ion homeostasis by lipid peroxidation: Roles in neuronal degeneration and adaptive plasticity. Trends Neurosci1998;20:53–57.
55. Montine KS, Quinn JF, Zhang J, Fessel JP, Roberts LJ, 2nd, Morrow JD, Montine TJ. Isoprostanes and related products of lipid peroxidation in neurodegenerative diseases. ChemPhys Lipids. 04;128:117–124.
56. Liu W, Kato M, Akhand AA, Hayakawa A, etaI. 4-hydroxynonenal induces a cellular redox status-related activation of the caspase cascade for apoptotic cell death. Journal Cell Science. 2000; 113:635–641
57. Schmidt H, Grune T, Müller R, et al. Increased levels of lipid peroxidation products malondialdehyde and 4-hydroxynonenal after perinatal hypoxia. Pedriatric Research. 1996;40:15–20.
58. Montine KS, Quinn JF, Zhang J, et al.Isoprostanes and related products of lipid peroxidation in neurodegenerative diseases. ChemPhys Lipids. 2004; 128:117–124.
59. Picklo MJ, Amarnath V, McIntyre JO, et al 4-hydroxy-2(E)-nonenal inhibits cns mitochondrial respiration at multiple sites. J Neurochem. 1999;72:1617–1624
60. Yoritaka A, Hattori N, Uchida K, et al. Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson disease. ProcNatlAcadSci U S A. 1996;93:2696–2701.
61. Montgomery EB Jr. Heavy metals and the etiology of Parkinson's disease and other movement disorders. Toxicology. 1995 Mar 31;97(1-3):3-9.
62. Sian-Hulsmann J, Mandel S, Youdim MB, Riederer P. The relevance of iron in the pathogenesis of Parkinson's disease. J Neurochem. 2011;118:939–957
63. Double KL, Ben-Shachar D, Youdin MB, Zecca L, et al Influence of neuromelanin on oxidative pathways within the human substantianigra. NeurotoxTeratol. 2002; 24:621–628.
64. Dexter DT, Carayon A, Javoy-Agid F, et al, Marsden CD. Alter-ations in the levels of iron, ferritin and other trace metals in Parkinson's disease and other neurodegenerative diseases affecting the basal ganglia. Brain. 1991;114:1953–1975.
65. Kosta P, Argyropoulou MI, Markoula S, Konitsiotis S. MRI evaluation of the basal ganglia size and iron content in patients with Parkinson's disease. J Neurol. 2006;253:26–32.
66. Saffari Y, Sadrzadeh SMH. Iron and brain disorders. Pathology Patterns Reviews. 2004;121:65–70.
67. Sian-Hulsmann J, Mandel S, Youdim MB, Riederer P. The relevance of iron in the

pathogenesis of Parkinson's disease. J Neurochem. 2011;118:939–957.

68. Jomova K, Valko M. Advances in metal-induced oxidative stress and human disease. Toxicology. 2011;283:65–87.
69. Nunez MT, Urrutia P, Mena N, Aguirre P, Tapia V, Salazar J. Iron toxicity in neurodegeneration. Biometals. 2012;25: 761–776
70. Harley A, Cooper JM, Schapira AH.Iron induced oxidative stress and mitochondrial dysfunction: relevance to Parkinson's disease.Brain Res. 1993 Nov 12;627 (2):349-53.
71. Núñez MT, Gallardo V, Muñoz P, et al. Progressive iron accumulation induces a biphasic change in the glutathione content of neuroblastoma cells.Free RadicBiol Med. 2004 Oct 1;37(7):953-60.
72. Chinta SJ, Andersen JK. Redox imbalance in Parkinson's disease. Biochim BiophysActa. 2008;1780:1362–1367.
73. Kaur D, Andersen J. Does cellular iron dysregulation play a causative role in Parkinson's disease? Ageing Res Rev. 2004;3:327–343
74. Berg D, Gerlach M, Youdim M, et al. Brain iron pathways and their relevance to Parkinson's disease. J Neurochem. 2001;79:225–236.
75. Kaur D, Peng J, Chinta SJ, Rajagopalan S, et al. Increased murine neonatal iron intake results in parkinson-like neurodegenera-tion with age. Neurobiol Aging. 2007; 28:907–913.
76. Sziráki I, Mohanakumar KP, Rauhala P, et al. Manganese: A transition metal protects nigrostatal neurons from oxidative stress in the iron-induced animal model of parkinsonisn. Neuroscience. 1998;85: 1101–1111
77. Lan J, Jiang DH. Desferrioxamine and vitamin e protect against iron and MPTP-induced neurodegeneration in mice. J Neural Transm. 1997;104:469–481.
78. Yokel R. A.The toxicology of aluminium in the brain: a review. Neurotoxicology 2000; 21, 813–828.
79. Zatta P., Lucchini R., Van Rensburg S. J. and Taylor A. The role of metals in neurodegenerative processes: aluminum, manganese, and zinc. Brain Res. Bull. 2003; 62, 15–28.
80. Hirsch EC, Brandel JP, Galle P, et al. Iron and aluminum increase in the substantian-igra of patients with Parkinson's disease: an X-ray microanalysis. J Neurochem. 1991 Feb;56(2):446-51.
81. Exley C. The pro-oxidant activity of aluminum. Free RadicBiol Med. 2004 Feb 1;36(3):380-7.
82. Gutteridge JM, Quinlan GJ, Clark I, Halliwell B.Aluminium salts accelerate peroxideation of membrane lipids stimulated by iron salts. Biochim BiophysActa. 1985 Jul 31;835(3):441-7.
83. Verstraeten SV, Oteiza PI.Effects of Al(3+) and related metals on membrane phase state and hydration: correlation with

lipid oxidation.Arch BiochemBiophys. 2000 Mar 15;375(2):340-6.

84. Kong S, Liochev S, Fridovich I.Aluminum (III) facilitates the oxidation of NADH by the superoxide anion.Free RadicBiol Med. 1992;13(1):79-81.
85. Méndez-Alvarez E, Soto-Otero R, Hermida-Ameijeiras A, et al. Effects of aluminum and zinc on the oxidative stress caused by 6-hydroxydopamine autoxidation: relevance for the pathogenesis of Parkinson's disease. BiochimBiophysActa. 2002 Mar 16;1586(2):155-68.
86. Szutowicz A. Aluminium NO, and nerve growth factor neurotoxicity in cholinergic neurons. J Neurosci Res. 2001;66:1009–18
87. Vučetić-Arsić S, Radonjić NV, Jovanović M,et al. Oxidative stress precedes mitochondrial dysfunction in gerbil brain after aluminum ingestion.Environ Toxicol Pharmacol. 2013 Nov;36(3):1242-52.
88. Anuradha S. Majumdar, AbhijitNirwane, and Rahul Kamble. Coenzyme Q10 Abrogated the 28 Days Aluminium Chloride Induced Oxidative Changes in Rat Cerebral Cortex. Toxicol Int. 2014 May-Aug; 21(2): 214–221.
89. Gorell JM, Rybicki BA, Cole Johnson C, Peterson EL. Occupational exposure to specific metals (manganese, copper, lead, iron, mercury, zinc, aluminum and others) appears to be a risk factor for Parkinson's disease (PD) in some, but not all, case-control studies. Neuroepidemiology. 1999;18:303–8.
90. Li H, Campbell A, Ali SF, Cong P, Bondy SC. Chronic exposure to low levels of aluminum alters cerebral cell signaling in response to acute MPTP treatment. ToxicolIndust Health. 2008;23:515–524.
91. Chia-Yi Yuan,Yih-Jing Lee, correspond-ding and Guoo-Shyng Wang Hsu. Aluminum overload increases oxidative stress in four functional brain areas of neonatal rats. J Biomed Sci. 12; 19(1): 51.
92. Dexter DT, Wells FR, Lees AJ, et al. Increased nigral iron content and alterations in other metal ions occurring in brain in Parkinson's disease. Journal of Neurochemistry. 1989;52(6):1830–1836
93. Riederer P, Sofic E, Rausch WD, et al. Transition metals, ferritin, glutathione, and ascorbic acid in Parkinsonian brains. Journal of Neurochemistry. 1989;52 (2):515–520.
94. Boll MC, Sotelo J, Otero E, Alcaraz-Zubeldia M, Rios C. Reduced ferroxidase activity in the cerebrospinal fluid from patients with Parkinson's disease. Neuro science Letters. 1999;265(3):155–158.
95. Tórsdóttir G, Kristinsson J, Sveinbjörns-dóttir S, et al. Copper, ceruloplasmin, superoxide dismutase and iron parameters in Parkinson's disease. Pharmacology and Toxicology. 1999;85(5):239–243.
96. Boll MC, Alcaraz-Zubeldia M, Montes S, Rios C. Free copper, ferroxidase and SOD1 activities, lipid peroxidation and NOx content in the CSF. A different marker profile in four neurodegenerative

diseases. Neurochemical Research. 2008;33(9):1717–1723.

97. Boll MC, Sotelo J, Otero E, Alcaraz-Zubeldia M, Rios C. Reduced ferroxidase activity in the cerebrospinal fluid from patients with Parkinson's disease. Neuro-science Letters. 1999;265(3):155–158.
98. Sergio Montes, Susana Rivera-Mancia, Araceli Diaz-Ruiz, et al. Copper and Copper Proteins in Parkinson's Disease. Oxid Med Cell Longev. 2014; 2014: 147251.
99. Wang HJ, Wang M, Wang B, et al. The distribution profile and oxidation states of biometals in APP transgenic mouse brain: dyshomeostasis with age and as a function of the development of Alzheimer's disease. Metallomics. 2012;4(3):289–296.
100. Spillantini MG, Schmidt ML, Lee VM-, Trojanowski JQ, Jakes R, Goedert M. α-synuclein in Lewy bodies. Nature. 1997;388(6645):839–840.
101. Wang C, Liu L, Zhang L, Peng Y, Zhou F. Redox reactions of the α-synuclein-Cu2+ complex and their effects on neuronal cell viability. Biochemistry. 2010;49(37):8134–8142.
102. Beckman JK, Borowitz SM, Greene HL, Burr IM. Promotion of iron-induced rat liver microsomal lipid peroxidation by copper. Lipids. 1988 Jun; 23(6):559-63.
103. Dillard CJ, Tappel AL.Lipid peroxidation and copper toxicity in rats.Drug ChemToxicol. 1984;7(5):477-87.
104. Sokol RJ1, Devereaux MW, O'Brien K, et al. Abnormal hepatic mitochondrial respiration and cytochrome C oxidase activity in rats with long-term copper overload.Gastroenterology. 1993 Jul;105(1):178-87.
105. Olivieri S, Conti A, Iannaccone S, et al. Ceruloplasmin oxidation, a feature of Parkinson's disease CSF, inhibits ferroxidase activity and promotes cellular iron retention. Journal of Neuroscience. 2011;31(50):18568–18577.
106. Gorell JM, Johnson CC, Rybicki BA, et al. Occupational exposure to manganese, copper, lead, iron, mercury & zinc and the risk of Parkinson's disease. Neuro Toxicology. 1999;20(2-3):239–247.
107. Younes-Mhenni S, Aissi M, Mokni N, et al. Serum copper, zinc and selenium levels in Tunisian patients with Parkinson's disease.Tunis Med. 2013 Jun;91(6):402-5.
108. Willis AW, Evanoff BA, Lian M, et al. Metal emissions and urban incident Parkinson disease: a community health study of Medicare beneficiaries by using geographic information systems. The American Journal of Epidemiology. 2010;172(12):1357–1363.