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Toxin-Induced Animal Models of Parkinson's Disease: An Update

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Abstract

Parkinson's disease (PD) has been a very common neurodegenerative disease. PD is a motor disorder and has been characterized by three cardinal symptoms i.e. tremors, bradykinesia and rigidity of muscles. Basically the features of PD are pathlogically related to the progressive degradation of production of dopamine in substantia nigra. The symptoms of Parkinson's disease can be reproduced in animals by substances that could block DA (D_2) receptors in striatum such or the agents that cause deficiency of dopamine. The Parkinson's disease models should ideally cause the loss of selective loss of neurons. The experimental animal models are aimed to reproduce the causes, the pathology, or the clinical manifestation of the disease. In the present review, we are discussing some of the classic experimental models of PD. Some examples of the most important reported toxin induced animal models for PD are the reserpine model, rotenone model, 6-OHDA induced nigrostriatal DA neurodegenerative model. These Parkinson's disease animal models have put forwarded the perception to understand the etiology, pathogenesis, disease process and molecular mechanisms of Parkinson's disease.

1. Parkinson's disease

Parkinson's disease (PD) has been a very common neurodegenerative disease and after Alzheimer's disease, it has been reported to be the second most common [1]. This neurodegenerative disorder is age related and among the people of age between 65- 69 years, its prevalence has found to be 1 to 2% percent approximately [2,3,4]. PD is a motor disorder

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and has been characterized by three cardinal symptoms i.e. tremors, bradykinesia and rigidity of muscles but in the patients of significant minority, postural instability, dementia, hypokinesia, impaired gait and non-motor manifestations including dementia, psychosis, depression and autonomic dysfunction have also reported to be involved. Basically the features of PD are pathlogically related to the progressive degradation of production of dopamine in substantia nigra [5]. Dopaminergic neurons have been found to be lost by 50-80% by the time when the symptoms start to appear [6,7].

Yet, dopaminergic neurons other than substantia nigra, to a lesser extent, have also reported to be affected in PD. Furthermore, a major limitation of current Parkinson's therapies that has been still counted is that considerable attention on non dopaminergic lesions has been focused only recently, despite the fact that around 30 years ago, the involvement of non dopaminergic neurons degeneration was reported [8].

There is broad variation in the incidence and rate of prevalence of different studies as these have been performed with different methodology on different population. In Asian countries, the incidence and rate of prevalence have found to be slightly lower and it has been found to increase progressively along with the increase in age [5].

2. Animal experimental models for PD

A number of experimentally induced animal disease models are being used currently for various neurodegenerative disorders. The neurodegenerative disease models should ideally cause the loss of selective loss of neurons [8]. The experimental animal disease models are aimed to reproduce the causes, the pathology, or the clinical manifestation of a particular disease [9]. Most of the models that are existing currently are not able to reproduce the lesions and symptoms of a given disease in full spectrum. Probably due to this reason why animal neurodegenerative disease models poorly indicate the effectiveness of neuroprotective agents in man [8].

The symptoms of Parkinson's disease can be reproduced in animals by substances that could block DA ($D_{2)}$ receptors in striatum such as haloperidol or the agents that cause deficiency of dopamine such as 6-OHDA and reserpine, according to the method of administration of putative environmental toxins in experimental animals.Based on the well

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characterized neuronal loss in PD and its pathophysiology there are two ways for the development of animal experimental models for PD :

i. Inducing PD by reproducing gene mutations in experimental animals, that have been seen in inherited forms of the disease

ii. Administration of putative environmental toxins in experimental animals causing PD [8].

In the present review, we are discussing the toxin induced experimental models of PD. Some examples of the most important reported experimental animal models for PD are the reserpine model, rotenone model, 6-OHDA induced nigrostriatal DA neurodegenerative model, neuroleptics induced catalepsy, tremor models, methamphetamine, MPTP, MPP^+, β-carbolines, iron and tetrahydroisoquinolines models [10].

Paraquat

Paraquat has been widely used as an agricultural herbicide in the 20th and early 21st centuries. Chemically, it is 1,1'-dimethyl-4,4-bipyridinium [11-13]. Paraquat is considered safe in the industry and worldwide regulations in in the United States but the long term use of paraquat include some toxic effects such as skin cancer, lung damage and PD [11,12,14]. It has structural similarity with the MPTP's active metabolite, MPP^+ [11,14-18]. MPP^+ or paraquat exposure has been considered as risk factors for for the disease [16]. Both MPTP and Paraquat have been found to cause depletion of DA neurons in SN [11,12,15,19,20]. In fact, paraquat has been reported to be more cytotoxic as compared to MPP^+ [21].

Paraquat has been found to have poor absorption from the gastrointestinal tract. In rats, only 5 to 10% (approximately) of an administered dose has been found to be absorbed. Excretion is through kidney and intestine. After 48 hours, 45% (approximately) of a single dose is found to be excreted in rats. On the basis of earlier findings and poor absorption, paraquat has been assumed to be excluded largely from the circulation of brain based on the assumption that the significant concentrations of paraquat would not able to cross the BBB (blood brain barrier). Therefore most of the concentration of paraquat reaching the brain after a single administration, is associated apparently with structures that are not associated with BBB such as the ventricles of cerebrum and the pineal gland or with the structures that are

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not having rigid BBB such as area postrema, hypothalamus and the anterior portion of the olfactory bulb.

It has been shown by the use of microdialysis technique in rats brain that after administering subcutaneously, paraquat could be present in the dialysate. The destructed BBB function by paraquat or its radical was not found to be responsible for paraquat's brain penetration but paraquat was proposed to be taken up by the transport system of neutral amino acid into the brain and after that transported to the substantia nigra [22]. The young animals however were used for this study, the possible age associated BBB changes are there which could be censorious for paraquat uptake in brain. It has now been agreed by various findings that reaching of paraquat into the brain is an age associated episode. The levels of paraquat can be found higher in the brains of neonates in comparison to the elderly and adult rat brains [23], or either in very old or very young i.e. 12 & 24 months old and 2 weeks old animals respectively in comparison to the adult (3 months old) normal rats [24,25]. Apparently, this can be said that the better sequesters of paraquat are the neonates or very young animals.

The intraperitoneal injection of paraquat has been found to end up concentrated in the SN and is connected with DA neuronal loss [11,20]. Paraquat generates ROS within neurons that leads to the fragmentation of DNA and the production of protein carbonyls and malondialdehyde [13,18,26]. In biological systems, paraquat's redox cycling comprise 2 implications: (i) ROS generation (ii) depletion of necessary reducing agents such as NADH and NADPH, and therefore disturbing different cell functions and processes. In neurons, an electron donor is required by paraquat to be reduced. Some of the cellular enzymes have been examined which could donate electrons to paraquat such as NOS [27], thioredoxin reductase [28] and mitochondrial complex-I [29].

Administration of paraquat has been reported to activate generation of superoxides mediated by NADPH oxidase in microglial and neuronal cells [30,31] that has been involved as a responsible mechanism for increased degeneration of DA neurons mediated by paraquat. In addition, NOX 1 activation mediated by paraquat resulting in increased aggregation and expression of α-synuclein [32] in LB reminiscent in [33,34,35]. In another study reports, paraquat has also shown reduction NA (noradrenergic) neurons in the locus coeruleus [11,15,21,34].

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1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

The MPTP model of PD was discovered in the early 1980s when several users of intravenous drug administration in California users shown severe Parkinson's like symptoms and were got hospitalizations [36,37]. The involvement of exogenous chemicals in the PD pathophysiology was indicated firstly by this discovery [38]. The PD clinical features such as slow movements, instable posture, freezing, rigidity and tremors were found to be exhibited by intoxication with MPTP [39-41]. Autopsy reports have shown damage to DA neurons in SN in patients died of PD but no LB were found unlike PD [39,40,42].

Numerous species of mammals including rats, mice, cats, guinea pigs, dogs, sheep and monkeys have been used in animal models of PD giving them MPTP treatment [43,44]. MPTP crosses the BBB readily as it is highly lipophilic. As it is MPTP has not found to be toxic to DA neurons as a parent compound but after metabolism, it is readily converted into a metabolite that is more toxic [7,39]. MPTP has been first found to be converted into MPDP by MAO- B in astrocytes, after that it gets oxidized to a toxic metabolite MPP^+ (pyridinium ion) [38,39,45]. From astrocytes, MPP^+ is released and then DA take up it [39]. MPP^+ has high binding affinity towards DA transporter. MPTP toxicity is not exhibited by mice as they lack the DA transporter [7,39,45]. In the mitochondria of normal DA neurons, high levels of MPP^+ get accumulated and there it inhibits the mit- chain complex I through the generation of ROS [7,39,40,45,46-48]. The synaptic vesicles having stored DA also get transported MPP^+ via vesicular MA transporter [39,46]. The mice whose vesicular MA transporter has been depleted significantly would be more prone to the toxicity mediated by MPP^+ as mitochondria will be accessible to all of MPP^+ and this uptake system would serve as a mechanism of detoxification [39]. MPP^+ gives rise to mitochondrial ROS production in DA cell lines, ROS then trigger the cascade of apoptosis including fragmentation of DNA and activation of caspases [47]. The toxicity induced by MPTP has been found to share many features PD except the absence of LB [39,40,42].

6-Hydroxydopamine (6-OHDA)

6-OHDA was discovered as the first chemical having neurotoxicity towards dopaminergic neurons. It has been successfully used in experimental PD models for over three decades [7,40]. 6-OHDA can be easily taken up by DA and NE transporters to the catecholaminergic neurons as this an analog of DA and NE [39]. Catecholaminergic neuronal

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damage can be caused by it throughout the body and it even causes NE depletion in cardiac sympathetic nerves [40]. 6-OHDA is not only a neurotoxic but is also able to cause the induction of glial cell activation (Bove *et al.,* 2005). It can not cross the BBB readily, like DA, but if directly injected into the ventricles, accumulation does occurs inside the brain [39,40]. In PD patients, endogenous 6-OHDA accumulation has been reported [39]. Upon neuronal transportation, 6-OHDA, like DA, has been found to be oxidized to cause the generation of quinones and free radicals [40]. It also causes the mit- complex I inhibition and give rise to the production of hydroxyl and superoxide radicals via Fenton reaction participation (Schober, 2004). 6-OHDA treatment, although, is able to produce many PD resembling features, however, it is worth to note that its administration does not give rise to the LB formation [7,40].

Rotenone

Rotenone is a pesticide that has been used as s fish poison by Indian people. This observation led to the development of cellular models for studying PD [7,40]. Rotenone belongs to the family rotenoids and has been known as a most potent of these cytotoxic family members [40]. Rotenone has been commonly used as a pesticide and insecticide around the world [7,40,47]. Rotenone has been known to be used for killing insects in vegetable farms and for killing the overpopulated and invasive fish in lakes [7,47]. In healthy individuals, rotenone ingestion has not been likely to have any toxic effects. Its absorption from stomach and small intestine is slow and incomplete and is also degraded efficiently in the first pass metabolism [40]. Once it enters the circulation, being highly lipophilic, crosses the BBB and is evenly distributed throughout in the brain [7,40]. Being highly lipophilic, rotenone also enters the cellular organelles including mitochondria and here it causes the inhibition of mit- electron transport chain complex I of high affinity [7,40,45,47]. By complex I inhibition, it causes the generation of ROS, depletion of ATP, and neuronal death. It leads to α-synuclein aggregation and LB formation in PD [40].

Endosulfan

Endosulfan is a cyclodiene group member belonging to the organochlorine family which are the widely used agricultural pesticides. Chemically, it is 6, 7, 8, 9, 10, 10-hexachloro-1, 5, 5a, 6, 9, 9a-hexahydro-6, 9-methano-2, 4,3-benzadioxathiepin 3-oxide. It is used commonly for killing insects on varoius food crops like vegetables, fruits, tea and grains

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and also on cotton and tobacco crops. Endosulfan exposure occurs by the ingestion of food contaminated with endosulfan, contact through skin, drinking contaminated water or through inhalation of contaminated air. The major characteristic of poisoning with endosulfan in humans is CNS overstimulation [49-55].

Neurobehavioral alterations and changes in the levels of neurotransmitters after endosulfan exposure have been reported by various animal studies [56,57]. The most prominent signs of acute endosulfan overexposure in animals as well as in humans has shown tonic clonic convulsions, salivation, dyspnea, depressed respiration, tremors and hyperactivity as acute signs to overexposure.

3. Conclusion

The availability of experimental PD models have provided the better understanding of the process and pathogenesis of PD that can lead to the better identification of the therapies that could modify the disease. PD, being a multifactorial disease which is caused through environmental etiological factors and genetic reasons, most of the models that are existing currently are not able to reproduce the lesions and symptoms of a given disease in full spectrum. Probably due to this reason why animal neurodegenerative disease models poorly indicate the effectiveness of neuroprotective agents in man. A single model may have some advantages and some limitations so in future studies neurotoxin models might be combined with genetical models.

REFERENCES

[1] M. E. Omar, S. Abdel, “Drugs used to treat Parkinson’s disease, present status and future directions,” CNS & Neurological Disorders - Drug Targets, vol. 7, pp. 321-342, 2015.

[2] M. Aschner, “Manganese in health and disease: from transport to neurotoxicity,” Handbook of neurotoxicology. *NJ*: Humana Press, pp. 195–209, 2000.

[3] B. S. Shastry, “Parkinson disease: etiology, pathogenesis and future of gene therapy,” Neurosci. Res, vol. 41, pp. 5–12, 2001.

[4] M. L. Bekris, F. I. Mata, C. P. Zabetian, “The genetics of Parkinson disease,” J Geriatr Psychiatry Neurol, vol. 23, pp. 228-242, 2010.

ISSN:0971-1260

Vol-22-Issue-16-August-2019

[5] T. H. Kim, K. H. Cho, S. W. Jung and S. L. Myeong, "Herbal Medicines for Parkinson's Disease: A Systematic Review of Randomized Controlled Trials," PLoS One, vol. 7, 2012.

[6] H. Takahashi, K. Wakabayashi, "The cellular pathology of Parkinson's disease," Neuropathology, vol. 21, pp. 315–322, 2001.

[7] V. N. Uversky, "Neurotoxicant-induced animal models of Parkinsons disease: understanding the role of rotenone, maneb and paraquat in neurodegeneration," Cell and Tissue Research, vol. 318, pp. 225–241, 2004.

[8] E. C. Hirsch, "Animal models in neurodegenerative diseases," J Neural Transm, pp. 87- 90, 2007.

[9] F.M. Ribeiro, C. Elizabeth Ribeiro da Silva, L. Cruz de Souza, F. Blandini and M. T. Armentero, "Animal models of Parkinson's disease," 2012.

[10] Gerlach, "Animal models of Parkinson's disease," Journal of Neural Transmission, vol. 103, 1996.

[11] A. I. Brooks, CA. Chadwick, HA. Gelbard, DA. Cory-Slechta and HJ. Federoff, "Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss," Brain Research, vol. 823, pp. 1-10, 1999.

[12] C. Wesseling, B. van Wendel de Joode, C. Ruepert, C. Leon, P. Monge, H. Hermosillo, T. J. Partanen, "Paraquat in developing countries," International Journal of Occupational and Environmental Health, vol. 7, pp. 275-286, 2001.

[13] W. Yang and E. Tiffany-Castiglioni, "The bipyridyl herbicide paraquat produces oxidative stress-mediated toxicity in human neuroblastoma SH-SY5Y cells: relevance to the dopaminergic pathogenesis," J Toxicol Environ Health, vol. 68, pp. 1939- 61, 2005.

[14] W. L. Yang, A. Y. Sun, "Paraquat-induced free radical reaction in mouse brain microsomes," Neurochemical Research, vol. 23, pp. 47-53, 1998a.

[15] M. Thiruchelvam, B. J. Brockel, E. K. Richfield, R. B. Baggs and D. A. Cory-Slechta, "Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal

ISSN:0971-1260

Vol-22-Issue-16-August-2019

dopamine systems: environmental risk factors for Parkinson's disease?," Brain Res. vol. 873, pp. 225-34, 2000.

[16] H. S. Chun, GE. Gibson, LA. DeGiorgio, H. Zhang, VJ. Kidd, JH. Son, "Dopaminergic cell death induced by MPP^+, oxidant and specific neurotoxicants shares the common molecular mechanism" Journal of Neurochemistry, vol. 76, pp. 1010–21, 2001.

[17] K. Shimizu, K. Matsubara, K. Ohtaki, H. Shiono, "Paraquat leads to dopaminergic neural vulnerability in organotypic midbrain culture," Neuroscience Research. vol. 46, pp. 523-32, 2003.

[18] J. Peng, F. F. Stevenson, S. R. Doctrow and J. K. Andersen, "Superoxide dismutase/catalase mimetics are neuroprotective against selective paraquat-mediated dopaminergic neuron death in the substantial nigra," Journal of Biological Chemistry, vol. 280, pp. 29194-8, 2005.

[19] W. L. Yang, A. Y. Sun, "Paraquat-induced cell death in PC12 cells," Neurochemical Research. vol. 23, pp. 1387-94, 1998b.

[20] A. L. McCormack, M. Thiruchelvam, A. B. Manning-Bog, C. Thiffault, J. W. Langston, D. A. Cory-Slechta and D. A. Di Monte, "Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat," Neurobiol Dis, vol. 10, pp. 119-27, 2002.

[21] D. Kang, K. Miyako, F. Kuribayashi, E. Hasegawa, "Changes in energy metabolism induced by 1-methyl-4-phenylpyridinium (MPP+)-related compounds in rat pheochromocytoma PC12 cells," Archives of Biochem and Biophy, vol. 337, pp. 75-80, 1997.

[22] K. Shimizu, K. Ohtaki, K. Matsubara, K. Aoyama, T. Uezono, O. Saito, M. Suno, K. Ogawa, N. Hayase, K. Kimura and H. Shiono, "Carrier-mediated processes in blood-brain barrier penetration and neural uptake of paraquat," Brain Research, vol. 906, pp. 135–142, 2001.

ISSN:0971-1260

Vol-22-Issue-16-August-2019

[23] J. L. Naylor, P. S. Widdowson, M. G. Simpson, M. Farnworth, M. K. Ellis and E. A. Lock, "Further evidence that the blood/brain barrier impedes paraquat entry into the brain," Hum. Exp. Toxicol, vol. 14, pp. 587–594, 1995.

[24] M. T. Corasaniti, R. Defilippo, G. Rodino, G. Nappi and G. Nisticb, "Evidence that paraquat is able to cross the blood-brain barrier to a different extent in rats of various age," Funct. Neurol, vol. 6, pp. 385-391, 1991.

[25] M. T. Corasaniti, MC. Strongoli, A. Pisanelli, P. Bruno, D. Rotiroti, G. Nappi, G. Nisticò, "Distribution of paraquat into the brain after its systemic injection in rats," Funct Neurol, vol. 7, pp. 51-6, 1992.

[26] M. Thiruchelvam, O. Prokopenko, D. A. Cory-Slechta, E. K. Richfield, B. Buckley and O. Mirochnitchenko, "Overexpression of superoxide dismutase or glutathione peroxidase protects against the paraquat + maneb–induced Parkinson disease phenotype," J Biol Chem, vol. 280, pp. 22530-39, 2005.

[27] S. Patel, V. Singh, A. Kumar, Y. K. Gupta and M. P.Singh, "Status of antioxidant defense system and expression of toxicant responsive genes in striatum of maneb- and paraquat-induced Parkinson's disease phenotype in mouse: mechanism of neurodegeneration," Brain Res, pp. 9-18, 2006.

[28] J. P. Gray, D. E. Heck, V. Mishin, P. J. S. Smith, JY. Hong, M. Thiruchelvam, D. A. Cory-Slechta, D. L Laskin, J. D. Laskin, "Paraquat increases cyanide-insensitive respiration in murine lung epithelial cells by activating an NAD(P)H: Paraquat Oxidoreductase: Identification of the enzyme as thioredoxin reductase," J Bio Chem 2007.

[29] T. Fukushima, K. Yamada, A. Isobe, K. Shiwaku and Y. Yamane, "Mechanism of cytotoxicity of paraquat. I. NADH oxidation and paraquat radical formation via complex I," Exp Toxicol Pathol, vol. 45, pp. 345-9, 1993.

[30] D. Bonneh-Barkay, S.H. Reaney, W.J. Langston, D.A. Di Monte, "Redox cycling of the herbicide paraquat in microglial cultures," Brain Research. Molecular Brain Research, Vol. 134, pp. 52-6, 2005.

ISSN:0971-1260

Vol-22-Issue-16-August-2019

[31] R. L. Miller, G. Y. Sun, A. Y. Sun, "Cytotoxicity of paraquat in microglial cells: Involvement of PKCdelta- and ERK1/2-dependent NADPH oxidase," Brain Res, pp. 129–139, 2007.

[32] A. C. Cristovao, S. Guhathakurta S, E. Bok, DS. Yoo, D. Choi-Hee and Y.S. Kim. The Journal of Neuroscience, vol. 32, pp. 14465-14477, 2012.

[33] A. B. Manning-Bog, A.L. McCormack, V. N. Li J. Uversky, A. L. Fink, D. A. Di Monte, "The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein," J Biol Chem, vol. 277:pp. 1641–1644, 2002.

[34] P. O. Fernagut, C.B. Hutson, S.M. Fleming, N.A. Tetreaut, J. Salcedo, E. Masliah, M.F. Chesselet, "Behavioral and histopathological consequences of paraquat intoxication in mice: Effects of alpha-synuclein over-expression," Synapse, vol. 61, pp. 991–1001, 2007.

[35] S. K. Mak, A. L. McCormack, A. B. Manning-Bog, A. M. Cuervo, D. A. Di Monte, "Lysosomal degradation of alpha-synuclein in vivo," J Biol Chem, vol. 285, pp. 13621–13629, 2010.

[36] G. C. Davis, A.C. Williams, S.P. Markey, M.H. Ebert, E.D. Caine, C.M. Reichert and I.J. Kopin, "Chronic Parkinsonism secondary to intravenous injection of meperidine analogues," Psychiatry Res, vol. 1, pp. 249–254, 1979.

[37] J. W. Langston, P. A. Ballard, J. W. Tetrud, I. Irwin, "Chronic parkinsonism in humans due to a product of meperidine analog synthesis," Science, vol. 219, pp. 979–80, 1983.

[38] C. Wersinger A. Sidhu, "An inflammatory pathomechanism for Parkinson's disease?," Current Medicinal Chemistry, vol. 13, pp. 591-602, 2006.

[39] A. Schober, "Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP," Cell & Tissue Research, vol. 318, pp. 215-24, 2004.

[40] J. Bove, D. Prou, C. Perier, S. Przedborski, "Toxin-induced models of Parkinson's disease," NeuroRx, vol. 2, pp. 484-94, 2005.

ISSN:0971-1260

Vol-22-Issue-16-August-2019

[41] T. P. Brown, PC. Rumbsy, AC. Capleton, L. Rushton and LS. Levy, "Pesticides and Parkinson's Disease-is there a link?," Environ Health Project, vol. 114, pp. 156-164, 2006.

[42] P. J. Landrigan, B. Sonawane, R. N. Butler, L. Trasande, R. Callan and D. Droller D, "Early environmental origins of neurodegenerative disease in later life," Environ Health Perspect, vol. 113, pp. 1230-3, 2005.

[43] E. Bezard, C.E. Imbert, "Experimental models of Parkinson's disease: From the static to the dynamic," Rev Neurosci, vol. 9, pp. 71–90, 1998.

[44] S. Przedborski, V. Jackson-Lewis, A. Naini, M. Jakowec, G. Petzinger, R. Miller, M. Akram, "The parkinsonian toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): A technical review of its utility and safety," J Neurochem, vol. 76: pp. 1265–1274, 2001.

[45] K. A. Maguire-Zeiss, D. W. Short, H. J. Federoff, "Synuclein, dopamine and oxidative stress: co-conspirators in Parkinson's disease?," Brain Research. Molecular Brain Research, vol. 134, pp. 18-23, 2005.

[46] J. T. Greenamyre, T. B. Sherer, R. Betarbet, A.V. Panov, "Complex I and Parkinson's disease," IUBMB Life, vol. 52, pp. 135-41, 2001.

[47] Y. Kotake, S. Ohta, "MPP+ analogs acting on mitochondria and inducing neuro-degeneration," Current Medicinal Chemistry. vol. 10**,** pp. 2507-16, 2003.

[48] W. J. Schmidt, M. Alam, "Controversies on new animal models of Parkinson's disease pro and con: the rotenone model of Parkinson's disease (PD)," Journal of Neural Transmission. Supplementum, pp. 273-6, 2006.

[49] E. M. Boyd, I. Dobos, "Protein deficiency and tolerated oral doses of endosulfan," Arch Int Pharmacodyn Ther, vol. 178, pp. 152-165, 1969.

[50] E. M. Boyd, I. Dobos, CJ. Krijnen, "Endosulfan toxicity and dietary protein," Arch Environ Health, vol. 21, pp. 15-19, 1970.

[51] D. R. Aleksandrowicz, "Endosulfan poisoning and chronic brain syndrome," Arch Toxicol, vol. 43, pp. 65-68, 1979.

ISSN:0971-1260

Vol-22-Issue-16-August-2019

[52] J. L. Blanco-Coronado, M. Repetto, RJ. Ginestal, et al, "Acute intoxication by endosulfan," J Clin Toxicol, vol. 30, pp. 575-583, 1992.

[53] M. E. Gilbert, C. M. Mack, "Seizure thresholds in kindled animals are reduced by the pesticides lindane and endosulfan," Neurotoxicol Teratol, vol. 17, pp. 143-150, 1995.

[54] F. T. Boereboom, A. van Dijk, P. van Zoonen, et al, "Nonaccidental endosulfan intoxication: A case report with toxicokinetic calculations and tissue concentrations," Clin Toxicol, vol. 36, pp. 345-352, 1998.

[55] S. N. Chugh, R. Dhawan, N. Agrawal, et al, "Endosulfan poisoning in Northern India: A report of 18 cases," Int J Clin Pharmacol Ther Toxicol, vol. 36, pp. 474-477, 1998.

[56] M. K. Lakshmana,T. R. Raju, "Endosulfan induces small but significant changes in the levels of noradrenaline, dopamine and serotonin in the developing rat brain and deficits in the operant learning performance," Toxicology, vol. 91, pp. 139-150, 1994.

[57] V. Paul, E. Balasubramaniam, A. R. Jayakumar et al, "A sex-related difference in the neurobehavioral and hepatic effects following chronic endosulfan treatment in rats," Eur J Pharmacol, vol. 293, pp. 355-360, 1995.