NEURO

Openventio PUBLISHERS

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-4-e007

Editorial

*Corresponding author
Gokul Krishna, PhD
Department of Integrative Biology and Physiology
University of California Los Angeles (UCLA), 621 Charles E. Young Drive South, Los Angeles
CA 90095, USA
E-mail: gokul2411@gmail.com

Volume 4 : Issue 1
Article Ref. #: 1000NOJ4e007

Article History
Received: October 30th, 2017
Accepted: December 5th, 2017
Published: December 13th, 2017

Citation
Krishna G. Toxin-induced parkinson's disease models. *Neuro Open J*. 2017; 4(1): e1-e5. doi: 10.17140/NOJ-4-e007

Toxin-Induced Parkinson's Disease Models

Gokul Krishna, PhD*

Department of Integrative Biology and Physiology, University of California, Los Angeles, CA 90095, USA

The Topic "Toxin-Induced Parkinson's Disease Models' includes articles on experimental neurotoxic chemicals models of Parkinson's Disease (PD). The model toxicants with differing chemical structures recapitulate PD owning to their action on multiple molecular targets. These reports have provided with deeper understanding on the neurodegenerative events associated with the progressive disease. Several toxin-based models are developed in an attempt to experimentally mimic dopaminergic neurodegeneration, oxidative stress, cytoplasmic inclusions, proteasome dysfunction, altered protein trafficking, calcium overload and potentially mapping the events in the PD pathology. This spectrum includes research reports and reviews that discuss neurotoxin-based models (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-OHDA, rotenone, paraquat) that have greatly contributed to unravel the key mechanisms of neuronal cell death. In relevance to PD in humans, toxin-induced PD models have provided for observable behavioral deficits (motor and non-motor features). Moreover, the etiologic specific insights gained into the disease with the chemical modelling of PD has aided to screen/develop novel therapies.

PD is the most common progressive neurodegenerative condition affecting 1-2% of elderly population.[1] PD is characterized clinically by cardinal features involving resting tremor, rigidity and bradykinesia with loss of postural stability. The sporadic form of the PD involves progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) of the nigrostriatal system. Mutations in alpha-synuclein, parkin, ubiquitin carboxy-terminal hydrolase L-1 (UCHL1) and DJ-1 genes have been linked to familial forms of the disease.[2-4] Importantly, the PD pathology is characterized by the presence of fibrillary Lewy bodies and neurites, the intracytoplasmic proteinaceous inclusions containing neurofilament proteins. The occurrence of late-onset idiopathic form of the disease is likely due to gene mutation and environmental influence.[5] Nevertheless, there is a growing concern with the environmental factors particularly the chemicals to either induce PD or increase the disease risk.

Exposure to agricultural chemicals has been proposed to be a potential risk factor for the PD among the human population associated with farming, rural living and drinking contaminated well water.[6,7] Epidemiological data obtained from case reports, mortality reports, case-control studies relates to the possible link between chemical exposures and PD.[8-10] Also, *in vivo*, the chemical models possess certain limitations involving lack of specificity in their actions, systemic toxicity and failure to exactly model the non-motor features. Indeed, several reports suggest lack of an association between chemical exposure and PD development.[11-14] As will be discussed in the ensuing section, these findings are attributed to several factors involving exposure route, period (acute/chronic), and the relationship of chemical-induced neurotoxicity leading to development of disease. MPTP is highly lipophilic compound that is converted into active metabolite 1-methyl-4-phenylpyridinium (MPP+) by monoamine oxidase B to be taken up by the dopamine transporters (DATs). The metabolite translocates into mitochondrial matrix, inhibits complex I of the respiratory chain leading to adenosine triphosphate (ATP) depletion with increased formation of superoxide anion radical ($^{\bullet}O_{2^-}$).[15] Dysregulation in intracellular calcium homeostasis has also been proposed for neuronal degeneration with MPTP.[16] Additionally, MPTP treated has displayed enhanced neuronal oxidative and mitochondrial pathology.[17] MPTP intoxication has shown to enhance extracellular glutamate contributing to reactive oxygen species (ROS) release[18] leading to enhanced excitatory neurotransmitter activity in the basal ganglia. Importantly, MPTP promotes protein misfolding modifying

ISSN 2377-1607 http://dx.doi.org/10.17140/NOJ-4-e007

chaperones such as alpha-synuclein by forming covalent adducts further leading to accumulation of aggregated proteins (Lewy bodies).[19]

6-hydroxydopamine (6-OHDA) continues to be a valuable PD model in rats[19] and is a structural analogue of biogenic amines-dopamine and noradrenaline. 6-OHDA injection into the ventrolateral caudate-putamen closely mimics human PD pathology through oxidative stress mechanism leading to nigrostriatal degeneration, inflammatory response and metabolic changes.[20,21] The molecule accumulates to generate reactive species to attack biological macromolecules by generating oxidative metabolites (reactive species and quinones) without Lewy body formation.[22] Several behavioral tests have been used to characterize the unilateral lesion associated with 6-OHDA injection.[23] The unilateral lesion has provided for quantitative assessment and behavioral deficits in rodents.[24]

Rotenone, a naturally occurring cytotoxic pesticide is highly lipophilic and potent inhibitor of mitochondrial complex I. Rotenone exposure reproduces many characteristic features of PD including nigrostriatal dopaminergic degeneration and formation of alpha-synuclein filamentous inclusions.[25] The pesticide treatment has shown to induce mitochondrial dysfunction with development of postural instability characteristic of PD.[26,27] Several studies in animals with rotenone exposure have implicated parkinsonism neurobehavioral abnormalities including locomotor defects,[28] depressive-like syndrome[29] and cognitive deficits[30]. Moreover, accumulating evidence points towards neuroprotective therapeutic intervention targeting vulnerable pathways involved in degenerative events following rotenone exposure.[31,32]

Paraquat (N,N-dimethyl-4-4-bipiridinium) is a member of the widely used bipyridyl herbicide with structural similarity to MPP^+ induces nigral dopaminergic neuronal loss and behavioral phenotype changes associated with human PD. The herbicide toxicity appears to be mediated through monocationic radical formation by NADPH:cytochrome P-450 reductase and NADH: ubiquinone oxidoreductase reduction of paraquat.[33] Reports indicate that paraquat crosses blood-brain barrier through the neutral amino acid transporter.[34] It is suggested that the pathological hallmarks of PD involving selective vulnerability of dopaminergic degeneration, a characteristic feature of paraquat neurotoxicity.[35] Studies have shown that paraquat-induced cell loss results from Bak-dependent pathway involving mitochondrial membrane permeabilization and subsequent activation of caspase-3. Apart from motor deficits, patients with PD often display neuropsychiatric pathology[39,40] and studies on animal behaviors related to affective-like state has been assessed with exposure to paraquat. Given the involvement of oxidative stress and dopaminergic cell loss in paraquat toxicity, various phytochemicals and other compounds have been studied to abrogate neurotoxic response.[41-45] Maneb (manganese ethylene-bis-dithiocarbamate), is a contact fungicide that synergistically interacts with paraquat to markedly reduce locomotor function and increased striatal terminals and nigral neuronal damage.[46] Such synergistic interactions have been considered for the role in PD etiology and are of interest since they reflect actual human exposures.[47]

Although, the toxic models reproducing PD neuropathological features have tremendously influenced our understanding of the disease, it is important to elucidate the causal relationship between toxin exposure and PD (that warrants quantitative data) since existence of methodological issues in establishing pesticide role in disease was suggested earlier.[48] However, pre-clinically the etiologic-specific neurotoxin PD models continue to investigate disease pathology owing to their merits to produce neuropathological features. Moreover, novel imaging modalities have provided better understanding of changes in neuronal activity responsible for behavioral outcome by neurotoxin challenge.[49] These advances have greatly aided in delineating mechanisms of PD neurodegeneration and potential therapeutics that may be applied. Further, environmental importance and likelihood of population exposure to toxicants must be taken into account when considering their use as model toxicants for PD.

CONFLICTS OF INTEREST

The author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

1. McDonald WM, Richard IH, DeLong MR. Prevalence, etiology, and treatment of depression in Parkinson's disease. *Biol Psychiatry.* 2003; 54: 363-375. doi: 10.1016/S0006-3223(03)00530-4

2. Moore DJ, West AB, Dawson VL, Dawson TM. Molecular pathophysiology of Parkinson's disease. *Annu Rev Neurosci.* 2005; 28: 57-87. doi: 10.1146/annurev.neuro.28.061604.135718

3. Jankovic J. Parkinson's disease: Clinical features and diagnosis. *J Neurol Neurosurg Psychiatry.* 2008; 79: 368-376. doi: 10.1136/jnnp.2007.131045

ISSN 2377-1607 http://dx.doi.org/10.17140/NOJ-4-e007

4. Mattila PM, Rinne JO, Helenius H, et al. Alpha-synuclein-immunoreactive cortical Lewy bodies are associated with cognitive impairment in Parkinson's disease. *Acta Neuropathol (Berl).* 2000; 100: 285-290. doi: 10.1007/s004019900168

5. Warner TT, Schapira AH. Genetic and environmental factors in the cause of Parkinson's disease. *Ann Neurol.* 2003; 53. doi: 10.1002/ana.10487

6. Peng J, Mao XO, Stevenson FF, Hsu M, Andersen JK. The herbicide paraquat induces dopaminergic nigral apoptosis through sustained activation of the JNK pathway. *J Biol Chem.* 2004; 279: 32626-32632. doi: 10.1074/jbc.M404596200

7. Alder T. Pesticides and Parkinson's disease: The legacy of contaminated well water. *Environ Health Perspect.* 2009: 117: A553.

8. Ballard PA, Tetrud JW, Langston JW. Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): Seven cases. *Neurology.* 1985; 35: 949-956.

9. Costello S, Cockburn M, Bronstein J, Zhang X, Ritz B. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. *Am J Epidemol*. 2009; 169: 191-26. doi: 10.1093/aje/kwp006

10. Dhillon AS, Tarbutton GL, Levin JL, et al. Pesticide/environmental exposures and Parkinson's disease in East Texas. *J Agromedicine.* 2008; 13: 37-48. doi: 10.1080/10599240801986215

11. Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT Jr, Checkoway H. Pesticides and risk of Parkinson disease: A population-based case-control study. *Arch Neurol.* 2005; 62: 91-95. doi: 10.1001/archneur.62.1.91

12. Freire C, Koifman S. Pesticide exposure and Parkinson's disease: Epidemiological evidence of association. *Neurotoxicology.* 2012; 33: 947-971. doi: 10.1016/j.neuro.2012.05.011

13. Brown TP, Rumsby PC, Capleton AC, Rushton L, Levy LS. Pesticides and Parkinson's disease-is there a link? *Environ Health Perspect.* 2006; 114: 156-164. doi: 10.1289/ehp.8095

14. Searles Nielsen S, Hu SC, et al. Parkinsonism Signs and Symptoms in Agricultural Pesticide Handlers in Washington State. *J Agromedicine.* 2017; 22: 215-221. doi: 10.1080/1059924X.2017.1317684

15. Przedborski S, Vila M. The 1-Methyl-4-Phenyl-1, 2, 3, 6-Tetrahydropyridine Mouse Model. *Ann N Y Acad Sci.* 2003; 991: 189-198. doi: 10.1111/j.1749-6632.2003.tb07476.x

16. Surmeier DJ, Schumacker PT. Calcium, bioenergetics, and neuronal vulnerability in Parkinson's disease. *J Biol Chem.* 2013; 288: 10736-10741. doi: 10.1074/jbc.R112.410530

17. Hoang T, Choi DK, Nagai M, et al. Neuronal NOS and cyclooxygenase-2 contribute to DNA damage in a mouse model of Parkinson disease. *Free Radic Biol Med.* 2009; 47: 1049-1056. doi: 10.1016/j.freeradbiomed.2009.07.013

18. Lee DH, Kim CS, Lee YJ. Astaxanthin protects against MPTP/MPP+-induced mitochondrial dysfunction and ROS production in vivo and in vitro. *Food Chem Toxicol.* 2011; 49: 271-280. doi: 10.1016/j.fct.2010.10.029

19. Dehmer T, Lindenau J, Haid S, et al. Deficiency of inducible nitric oxide synthase protects against MPTP toxicity in vivo. *J Neurochem.* 2000; 74: 2213-2216. doi: 10.1046/j.1471-4159.2000.0742213.x

20. Blandini F, Armentero MT, Martignoni E. The 6-hydroxydopamine model: News from the past. *Parkinsonism Relat Disord.* 2008; 14: S124-S129. doi: 10.1016/j.parkreldis.2008.04.015

21. Guo S, Bezard E, Zhao B. Protective effect of green tea polyphenols on the SH-SY5Y cells against 6-OHDA induced apoptosis through ROS-NO pathway. *Free Radic Biol Med.* 2005; 39: 682-695. doi: 10.1016/j.freeradbiomed.2005.04.022

22. Iancu R, Mohapel P, Brundin P, Paul G. Behavioral characterization of a unilateral 6-OHDA-lesion model of Parkinson's disease in mice. *Behav Brain Res.* 2005; 162: 1-10. doi: 10.1016/j.bbr.2005.02.023

ISSN 2377-1607 http://dx.doi.org/10.17140/NOJ-4-e007

23. Betarbet R, Sherer TB, MacKenzie G, et al. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci.* 2000; 3: 1301-1306. doi: 10.1038/81834

24. Iancu R, Mohapel P, Brundin P, Paul G. Behavioral characterization of a unilateral 6-OHDA-lesion model of Parkinson's disease in mice. *Behav Brain Res.* 2005; 162: 1-10. doi: 10.1016/j.bbr.2005.02.023

25. Sherer TB, Kim JH, Betarbet R, Greenamyre JT. Subcutaneous rotenone exposure causes highly selective dopaminergic degeneration and alpha-synuclein aggregation. *Exp Neurol.* 2003; 179: 9-16. doi: 10.1006/exnr.2002.8072

26. Jenner P. Parkinson's disease, pesticides and mitochondrial dysfunction. *Trends Neurosci.* 2001; 24: 245-246. doi: 10.1016/S0166-2236(00)01789-6

27. Cannon JR, Tapias V, Na HM, et al. A highly reproducible rotenone model of Parkinson's disease. *Neurobiol Dis.* 2009; 34: 279-290. doi: 10.1016/j.nbd.2009.01.016

28. Holinger GU, Lannuzel A, Khondiker ME, et al. The mitochondrial complex I inhibitor rotenone triggers a cerebral tauopathy. *J Neurochem.* 2005; 95: 930-939. doi: 10.1111/j.1471-4159.2005.03493.x

29. Johnson ME, Bobrovskaya L. An update on the rotenone models of Parkinson's disease: Their ability to reproduce the features of clinical disease and model gene-envirnment interactions. *Neurotoxicology.* 2015; 46: 101-116. doi: 10.1016/j.neuro.2014.12.002

30. Santiago RM, Barbieiro J, Lima MM, Dombrowski PA, Andreatini R, Vital MABF. Depressive-like behaviors alterations induced by intranigral MPTP, 6-OHDA, LPS and rotenone models of Parkinson's disease are predominantly associated with serotonin and dopamine. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010; 34: 1104-1114. doi: 10.1016/j.pnpbp.2010.06.004

31. Kaur H, Chauhan S, Sandhir R. Protective effect of lycopene on oxidative stress and cognitive decline in rotenone induced model of Parkinson's disease. *Neurochem Res.* 2011; 36: 1435-1443. doi: 10.1007/s11064-011-0469-3

32. Gokul K, Muralidhara. Oral supplements of aqueous extract of tomato seeds alleviate motor abnormality, oxidative impairments and neurotoxicity induced by rotenone in mice: Relevance to Parkinson's disease. *Neurochem Res.* 2014; 39: 1382-1394. doi: 10.1007/s11064-014-1323-1

33. Anusha C, Sumathi T, Joseph LD. Protective role of apigenin on rotenone induced rat model of Parkinson's disease: Suppression of neuroinflammation and oxidative stress mediated apoptosis. *Chem Biol Interact.* 2017; 269: 67-79. doi: 10.1016/j.cbi.2017.03.016

34. Prakash J, Yadav SK, Chouhan S, Singh SP. Neuroprotective role of *Withania somnifera* root extract in Maneb-Paraquat induced mouse model of parkinsonism. *Neurochem Res.* 2013; 38: 972-980. doi: 10.1007/s11064-013-1005-4

35. Shimizu, K. Ohtaki K, Matsubara K, et al. Carrier-mediated processes in blood-brain barrier penetration and neural uptake of paraquat. *Brain Res.* 2001; 906: 135-142. doi: 10.1016/S0006-8993(01)02577-X

36. McCormack AL, Thiruchelvam M, Manning-Bog AB, et al. Environmental risk factors and Parkinson's disease: Selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. *Neurobiol Dis.* 2002; 10: 119-127. doi: 10.1006/nbdi.2002.0507

37. Fei Q, McCormack AL, Di Monte DA, Ethell DW. Paraquat neurotoxicity is mediated by a Bak-dependent mechanism. *J Biol Chem.* 2008; 283: 3357-3364. doi: 10.1074/jbc.M708451200

38. Dinis-Oliveira RJ, Remiao F, Carmo H, et al. Paraquat exposure as an etiological factor of Parkinson's disease. *Neurotoxicology.* 2006; 27: 1110-1122. doi: 10.1016/j.neuro.2006.05.012

39. Czerniczyniec A, Karadayian AG, Bustamante J, Cutrera RA, Lores-Arnaiz S. Paraquat induces behavioral changes and cortical and striatal mitochondrial dysfunction. *Free Radic Biol Med.* 2011; 51: 1428-1436. doi: 10.1016/j.freeradbiomed.2011.06.034

40. Litteljohn D, Mangano EN, Hayley S. Cyclooxygenase-2 deficiency modifies the neurochemical effects, motor impairment and co-morbid anxiety provoked by paraquat administration in mice. *Eur J Neurosci.* 2008; 28: 707-716. doi: 10.1111/j.1460-9568.2008.06371.x

ISSN 2377-1607 http://dx.doi.org/10.17140/NOJ-4-e007

41. Nuti A, Ceravolo R, Piccinni A, et al. Psychiatric comorbidity in a population of Parkinson's disease patients. *Eur J Neurol.* 2004; 11: 315-320. doi: 10.1111/j.1468-1331.2004.00781.x

42. Hosamani R, Krishna G, Muralidhara. Standardized Bacopa monnieri extract ameliorates acute paraquat-induced oxidative stress, and neurotoxicity in prepubertal mice brain. *Nutr Neurosci.* 2016; 19: 434-446. doi: 10.1179/1476830514Y.0000000149

43. Singh M, Murthy V, Ramassamy C. Neuroprotective mechanisms of the standardized extract of Bacopa monniera in a paraquat/diquat-mediated acute toxicity. *Neurochem Int.* 2013; 62: 530-539. doi: 10.1016/j.neuint.2013.01.030

44. Mangano EN, Peters S, Litteljohn D, et al. Granulocyte macrophage-colony stimulating factor protects against substantia nigra dopaminergic cell loss in an environmental toxin model of Parkinson's disease. *Neurobiol Dis.* 2011; 43: 99-112. doi: 10.1016/j.nbd.2011.02.011

45. Chau KY, Korlipara LP, Cooper JM, Schapira AH. Protection against paraquat and A53T alpha-synuclein toxicity by cabergoline is partially mediated by dopamine receptors. *J Neurol Sci.* 2009; 278: 44-53. doi: 10.1016/j.nbd.2011.02.011

46. Somayajulu-Nitu M, Sandhu JK, Cohen J, et al. Paraquat induces oxidative stress, neuronal loss in substantia nigra region and parkinsonism in adult rats: Neuroprotection and amelioration of symptoms by water-soluble formulation of coenzyme Q10. *BMC Neurosci*. 2009; 10: 88. doi: 10.1186/1471-2202-10-88

47. Thiruchelvam M, Brockel BJ, Richfield EK, et al. Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: Environmental risk factors for Parkinson's disease? *Brain Res.* 2000; 873: 225-234. doi: 10.1016/S0006-8993(00)02496-3

48. Brown TP, Rumsby PC, Capleton AC, Rushton L, Levy LS. Pesticides and Parkinson's disease-Is there a link? *Environ Health Perspect.* 2006; 114: 156-164. doi: 10.1289/ehp.8095

49. Durand E, Petit O, Tremblay L, Zimmer C, et al. Social behavioral changes in MPTP-treated monkey model of Parkinson's disease. *Front Behav Neurosci.* 2015; 9: 42. doi: 10.3389/fnbeh.2015.00042