

## Editorial

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## Toxin-Induced Parkinson's Disease Models

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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 owing 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.<sup>1</sup> 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.<sup>2-4</sup> 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.<sup>5</sup> 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.<sup>6,7</sup> Epidemiological data obtained from case reports, mortality reports, case-control studies relates to the possible link between chemical exposures and PD.<sup>8-10</sup> 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.<sup>11-14</sup> 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<sup>+</sup>) 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 ( $\cdot\text{O}_2$ ).<sup>15</sup> Dysregulation in intracellular calcium homeostasis has also been proposed for neuronal degeneration with MPTP.<sup>16</sup> Additionally, MPTP treated has displayed enhanced neuronal oxidative and mitochondrial pathology.<sup>17</sup> MPTP intoxication has shown to enhance extracellular glutamate contributing to reactive oxygen species (ROS) release<sup>18</sup> leading to enhanced excitatory neurotransmitter activity in the basal ganglia. Importantly, MPTP promotes protein misfolding modifying

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chaperones such as alpha-synuclein by forming covalent adducts further leading to accumulation of aggregated proteins (Lewy bodies).<sup>19</sup>

6-hydroxydopamine (6-OHDA) continues to be a valuable PD model in rats<sup>19</sup> 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.<sup>20,21</sup> The molecule accumulates to generate reactive species to attack biological macromolecules by generating oxidative metabolites (reactive species and quinones) without Lewy body formation.<sup>22</sup> Several behavioral tests have been used to characterize the unilateral lesion associated with 6-OHDA injection.<sup>23</sup> The unilateral lesion has provided for quantitative assessment and behavioral deficits in rodents.<sup>24</sup>

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.<sup>25</sup> The pesticide treatment has shown to induce mitochondrial dysfunction with development of postural instability characteristic of PD.<sup>26,27</sup> Several studies in animals with rotenone exposure have implicated parkinsonism neurobehavioral abnormalities including locomotor defects,<sup>28</sup> depressive-like syndrome<sup>29</sup> and cognitive deficits<sup>30</sup>. Moreover, accumulating evidence points towards neuroprotective therapeutic intervention targeting vulnerable pathways involved in degenerative events following rotenone exposure.<sup>31,32</sup>

Paraquat (N,N-dimethyl-4,4-bipyridinium) is a member of the widely used bipyridyl herbicide with structural similarity to MPP<sup>+</sup> 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.<sup>33</sup> Reports indicate that paraquat crosses blood-brain barrier through the neutral amino acid transporter.<sup>34</sup> It is suggested that the pathological hallmarks of PD involving selective vulnerability of dopaminergic degeneration, a characteristic feature of paraquat neurotoxicity.<sup>35</sup> 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<sup>39,40</sup> 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.<sup>41-45</sup> 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.<sup>46</sup> Such synergistic interactions have been considered for the role in PD etiology and are of interest since they reflect actual human exposures.<sup>47</sup>

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.<sup>48</sup> 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.<sup>49</sup> 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.

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