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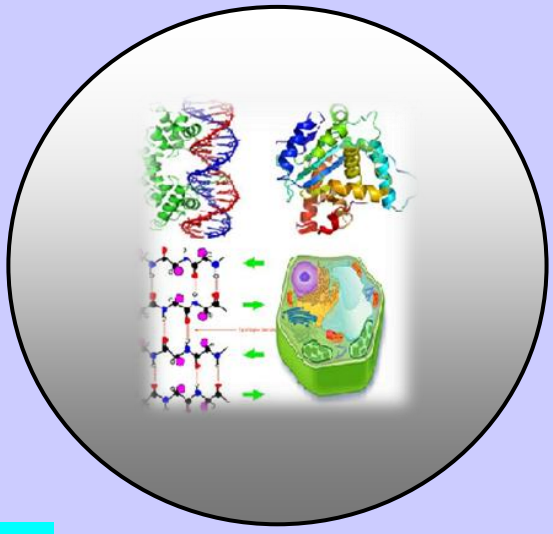

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Role of Major Neurotoxins in the Pathogenesis of Parkinson's Diseases

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ABSTRACT

Parkinson's disease (PD) is a second most common progressive neurodegenerative disorder. The major pathological hallmarks of PD are the selective loss of nigrostriatal dopaminergic neurons but the patho-physiological mechanisms are not fully understood. Epidemiologically, environmental neurotoxins such as pesticides are promising candidates for causative factors of PD. Oxidative stress and mitochondrial dysfunction induced by these toxins could contribute to the progression of PD. Animal models for PD have significantly contributed to novel strategies in the assessment of therapeutics target and for drug development. Several toxins have been utilized based on their mechanism of action like 6-hydroxy dopamine (6-OHDA), 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), rotenone, maneb, paraquat and cypermethrin which imitate pathology of Parkinson's disease. This paper focuses on toxin based animal models of PD that have provided significant insight for understanding this disease.
Keywords: Parkinson's Disease; Toxin; Animal Model and Oxidative Stress.

INTRODUCTION

Parkinson's disease (PD) is one of the second most common neurodegenerative diseases and it occurs as a global endemic. The key physiological feature of PD is the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta region of the mid brain **(Singh et al., 2006; Miller et al., 2009; Yadav et al., 2012)**. This degeneration of dopaminergic neurons leads to the mutilation of motor neurons resulting in tremors, stiffness, bradykinesia and postural instability **(Fahn, 2003)**. Major factors associated with the onset of PD include aging, environmental toxins (pesticides, heavy metals, etc.) and

hereditary traits. Farmers and villagers residing in rural areas where the drinking water source is contaminated with pesticides and heavy metals are at high risk of PD **(Uversky, 2004)**. 1-Methyl-4-phenyl-1,2,3, 6 -tetrahydropyridine (MPTP), rotenone, manganese ethylenebisdithiocarbamate (maneb), 1, 1´-dimethyl-4, 4´-bipyridinium (paraquat, PQ), dieldrin, cypermethrin and several other herbicides have been reported to induce PD. In experimental animal models, age factor is also reflected as aged animals are found more susceptible to chemicals that induce PD as compared to 2-3 months old animals **(Singh et al. 2012).** Several animal models have been shown to mimic one or more stages of PD, particularly, if partial or graded lesions are induced **(Bove et al., 2005; Chesselet et al., 2008)**. These models are particularily useful in developing valuable tools to test the therapeutic efficacy of anti-PD compounds. None of the animal models mimic all the main clinical and pathological characteristics of PD **(Meredith et al. 2008)** although significant progress have been made to develop a suitable model of PD that could reproduce all cardinal features of PD. Dynamic studies using experimental animal models that share genetic, molecular biologic, morphologic and clinical features of human diseases were imparted enormously for understanding of cell death mechanisms and have opened new possible remedies, hopefully applicable to human studies.

Animal Models for PD

Extreme efforts have been made to develop a suitable animal model to understand the pathological and molecular events leading to PD. Recently animals models of PD are being used to explore new therapeutic approaches and to screen novel chemical entities. Owing to strong correlation between environmental toxins and PD as reported in various epidemiological studies, several toxin based Primate and rodent models have been developed to understand the pathological and molecular mechanisms of the disease (Bove *et al.* 2005; Meredith *et al.* 2008). Rats and mice are the most common rodents used to develop toxin based models of PD. A few of them are described below.

Toxin induced PD Model

Toxin induced model represent the classic experimental PD models; they aim to reproduce the pathological and behavioural changes of the human disease in primates or rodents by using pharmacological agents (neurotoxins) that induce the selective degeneration of nigrostriatal neurons. These toxins can be administered either systemically or locally, depending on the type of agent used and the species involved.

Primate model

Non-human primate models are considered to be the best models as they are genetically similar to humans **(Taylor et al., 1997; Mounayar et al., 2007)**. 1-methyl -4 –phenyl-1, 2, 3, 6-Tetrahydropyridine (MPTP) exposure causes severe PD features and exhibits persistant long term impairment in monkeys after six months of exposure, therefore it can be used as better model to study phenotypic as well as neurophathological changes associated with PD **(Taylor et al., 1997)**. Monkeys that developed a severe pakinsonian score after MPTP exposure showed a significant depletion of dopamine in the striatum and a linear relationship with neurobehaviour and dopamine metabolites to dopamine ratio **(Elsworth et al., 2000)**. The similarity between sporadic PD and MPTP-induced Parkinsonism in monkeys is evidenced from the study, which has shown significant reduction of dopaminergic fibres in internal and external palladium in both the cases **(Jan et al., 2000)**.

Further, similar trends of dopaminergic innervation and loss of Tyrosine hydroxylase (TH) fibres in the subthalmic nucleus of MPTP treated monkey and PD patient is also observed **(Francois et al., 2000)**. The MPTP monkey model exhibits resting tremor, which is extremely difficult to observe in any other animal models. Since human and monkeys both are primates, this model can offer better ways to understand the pathogenesis treatment outcomes and easily extrapolates the data to PD patients **(Mounayar et al., 2007)**.While MPTP is widely used to assess pathogenesis in monkeys, the effect of other neurotoxins, such as paraquat, rotenone, maneb and dieldrin are not yet studied **(Elsworth et al., 2000)**. Further, the rapid destruction of dopaminergic neurons and onset of variability response at the same dose of MPTP in monkeys also may make this model less ideal **(Mounayar et al., 2007)**.

Rodent models

6-Hydroxydopamine (6-OHDA)

6-Hydroxydopamine (6-OHDA) is one of the most widely used models of PD. 6-OHDA is a hydroxylated analogue of dopamine, first isolated in 1959 **(Senoh et al., 1959)**. It has been used most extensively in rodents. By virtue of its structure, 6-OHDA possesses a high affinity for many catecholamine membrane transporters including Dopamine transporter (DAT) and norepinephrine transporters, allowing the compound to freely enter both dopaminergic and noradrenergic neurons **(Bove et al., 2005)**. Local injection is required because 6-OHDA does not cross the BBB. After injection into the SNpc or, preferably, into the medial forebrain bundle that conveys the efferent fibres from nigral cell bodies to the striatum, 6-OHDA causes massive anterograde degeneration of the nigrostriatal pathway. SNpc neurones begins to die within the first 12 h post-injection, whereas marked lesion of striatal dopaminergic terminals, paralleled by DA depletion, is established within 2–3 days. This procedure grants the highest level of nigral cell loss and striatal DA depletion obtainable in PD animal models (90–100%). The injection is commonly carried out unilaterally, with the contralateral hemisphere serving as control, because a high mortality rate is associated with bilateral injections. 6-OHDA administration needs to be precise: stereotaxic injection is usually the route used to create a Parkinsonian lesion, which represents a technical challenge. The degree of SNpc damage obtained with this procedure is less marked compared to the intra-medial forebrain bundle injection, remaining confined to 50–70% of the nucleus, and evolves over a period of 4–6 weeks. This alternative modality thereby provides a progressive model of nigrostriatal degeneration, which is more similar to the gradual evolution of the neurodegenerative process of human PD **(Blandini et al., 2007)**. The mechanism of action of 6-OHDA is substantially related to its prooxidant properties. Once in the neuron, 6-OHDA accumulates in the cytosol and undergoes prompt auto-oxidation, promoting a high rate of hydrogen peroxide formation. As an additional mechanism, 6-OHDA can accumulate in the mitochondria, where it inhibits complex I activity. Once in catecholamine cells, 6-OHDA causes damage through reactive oxygen species and quinones **(Cohen, 1984)**. The fine molecular details of neuronal death are more difficult to understand with this model, however, as the ways by which cytotoxic events occur may differ depending upon the distance between them and the site of injection **(Bove et al., 2005)**.

Despite this, some of these details have begun to be uncovered, including the induction of autophagy through activation of extracellular signal-regulated kinase (ERK) **(Kulich and Chu, 2001; Kulich et al., 2007)**. Inhibition of the ERK pathway confers neuroprotection in 6-OHDA-treated cells **(Kulich et al., 2007)**. The mitochondrial localisation of ERK2 in particular causes enhanced autophagy to levels which cause a pathologic reduction in ATP production due to the degradation of healthy mitochondria **(Kulich and Chu, 2001)**, providing a molecular component in 6-OHDA cytotoxicity. The lesion obtained with 6-OHDA is highly reproducible, which represents a considerable added value when new therapeutic strategies are to be investigated and clear neuroprotective effects must be demonstrated.

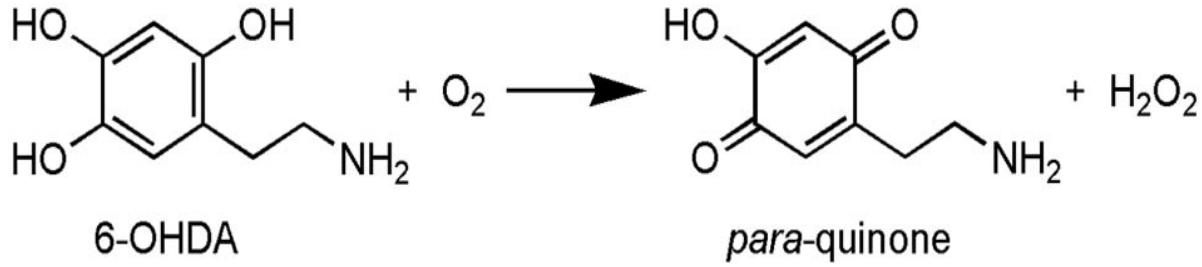

Figure 1. Oxidation of 6-OHDA.

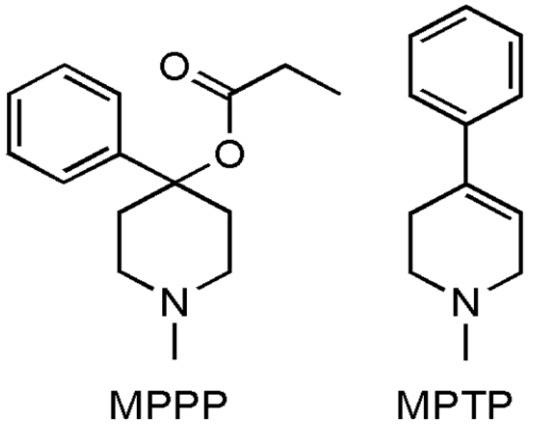

Figure 2. Comparison of chemical structures of MPPP and MPTP.

MPTP

The selective toxicity of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) was explored once onsets of Parkinson like features were observed in young heroin addicts in North California in 1981. Later, Langston and associates identified the presence of MPTP as a by-product in synthetic heroine as the causative factor. MPTP readily crosses the blood-brain-barrier (BBB) and gets transformed into MPP+ in non dopaminergic neurons (primarly astrocytes) by the enzyme monoamine oxidase B (MAO-B) **(Schober, 2004)**. MPTP exhibits high affinity for dopamine transporters (DATs) and they transport MPP+ into the dopaminergic neurons **(Bove *et al.* 2005)**. MPP+ induces dopamine autoxidation and free radical generation ultimately leading to inhibition of complex I in mitochondria **(Bove *et al.* 2005; Meredith *et al.* 2008)**.

MPTP causes dose and time dependent diminution in TH-immunoreactivity and simultaneous decrease in dopamine levels **(Meredith *et al.* 2008)**. MPTP also generates tremor, rigidity, bradykinesia and postural instability which are the cardinal characteristics of the Parkinsonian syndrome. The MPTP mouse model is one of the best standard models as it mimics most of the biochemical, phenotypic and behavioral characteristics of PD **(Schober, 2004)**. The main shortcoming of MPTP model is that it is a species specific response. Even after administration of high doses of MPTP, dopaminergic degeneration, persistent and progressive motor imbalance could not be observed in several species **(Przedborski et al., 2001)**. Furthermore, it is an acute model as dopaminergic neurons die rapidly and does not exhibit slow and progressive neurodegeneration and Lewy body formation **(Langston et al., 1999)**.

Rotenone

Rotenone is a naturally occurring pesticide extracted from the roots of the *Lonchocarpus* species. It was regularly used for fish poisoning by Indian fishermen. It is reported to readily cross the plasma membrane and BBB due to its lipophilic nature. Rotenone particularly inhibits mitochondrial complex I leading to impaired oxidative phosphorylation, which subsequently leads to declined adenosine triphosphate (ATP) biosynthesis. Furthermore, rotenone disrupts the mitochondrial inner membrane permeability resulting in deregulation of intracellular calcium levels **(Uversky, 2004)**. Owing to its free radical generation properties through complex-I inhibition of the mitochondria **(Kushnareva et al., 2002)**, its induced degeneration resembles PD pathogenesis. Rotenone also elicits cytoplasmic inclusions and Lewy body formation containing α-synuclein and ubiquitin **(Betarbet et al., 2000)**.

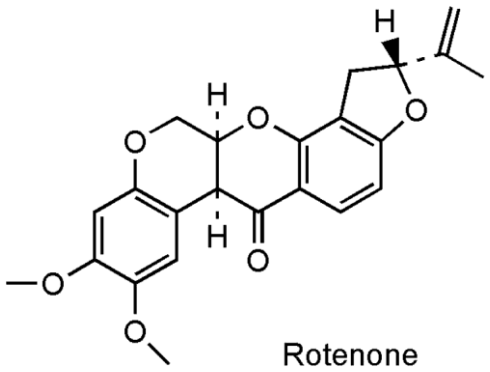

Figure 3. Chemical structure of rotenone.

Apart from impairment of the mitochondrial complex I and oxidative stress, rotenone also induces microglial apoptosis and Fe^{2+} accumulation. Rotenone also stimulates oxidative DNA damage, lipid peroxidation and protein modification **(Dexter et al., 1989)**. In addition it activates several proapoptotic genes including caspase 3 which could lead to programmed cell death. This could be directly correlated with declined TH-immunoreactivity and depletion of striatal dopamine, which are the principle indicators of selective degeneration of dopaminergic neurons.

Rotenone also activates microglia, the resident immune cells in the brain, to release pro-inflammatory cytokines thereby enhancing ROS and lipid oxidation, protein and DNA damage. Rotenone also activates NADPH oxidase leading to further increase in ROS and oxidative stress **(Tada-Oikawa et al., 2003)**. Owing to its non-specific response in various parts of brain and variable severity in the nigrostriatal dopaminergic neurons among different species, this model is not preferred **(Uversky 2004; Meredith et al., 2008)**.

Cypermethrin

Cypermethrin, dieldrin, organochlorines and organophosphates have been recently reported to induce PD in the experimental animals **(Singh et al., 2012)**. Acute oral and short time administration induces skeletal muscle contraction in the hind limbs without any signs of dyskinesia and tremor. Cypermethrin-induced neurotoxicity is mediated by the induction of ROS and reactive nitrogen species, which directly leads to oxidative stress and a disrupted antioxidant machinery **(Singh et al., 2012)**. Cypermethrin deregulates general transport across the placental barrier leading to harmful effects at the embryonic stage. Exposure to cypermethrin may lead to mutagenesis, genotoxicity and alteration in the activity of various ion channels including sodium and chloride channels. The primary site of cypermethrin activity in insects is voltage-gated sodium channel (VGSC). Cypermethrin delays the inactivation of VGSC and the long term opening of sodium channel impairs nerve impulse transmission **(Narahashi et al., 1992; Kirby et al., 1999)**. Having a long term exposure to cypermethrin is reported to induce nigrostriatal dopaminergic neurodegeneration in adult rats and pre-exposure in post-natal animals enhances the susceptibility to the chemical when rats were re-exposed in adulthood **(Singh et al., 2012; Kirby et al., 1999)**. Cypermethrin also induces neuro-behavioural anomalies, dopamine depletion, loss of TH-positive neurons and microglial activation and most other cardinal features of PD.

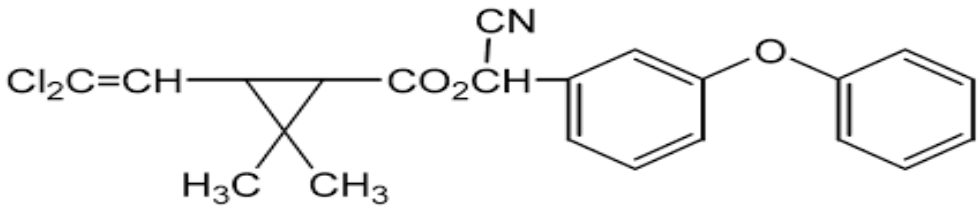

Figure. 4. Chemical structure of Cypermethrin.

Methamphetamine

Methamphetamine is present in many plants in minute quantities and its exposure is associated with neurobehavioral malfunctions. Methamphetamine depletes dopamine in the striatum, which is why it was projected to be useful in developing animal models for understanding the etiology of PD **(Thrash et al., 2009)**. Indeed, methamphetamine causes dopamine depletion and mimics some of the PD related symptoms **(Gerlach et al., 1996)**. Chronic or intermittent methamphetamine exposure induces temporary or permanent disturbance in dopaminergic neurons leading to PD like symptoms. Prolonged exposure to methamphetamine moderately reduces glial derived neurotrophic factors, which normally protect neurons and facilitate dopamine biosynthesis.

Mouse models highlight the role of c-fos, DATs, vesicular monoamine transporter-2 (VMAT-2), NOS and SOD induction by methamphetamine.Moreover, methamphetamine increases protein-1 and cAMP response element binding protein expression by activating the respective transcription factors in mesencephalic cells **(Asanuma et al., 2000)**. Methamphetamine increases the level of α-synuclein, decreases the level of phosphorylated TH and also decreases mitochondrial complex I proteins **(Klongpanichapak et al., 2008).** This model has also demonstrated the role of Bcl-2 activation by c-Jun N-terminal kinase 1 (JNK 1) negatively regulates autophagy. Methamphetamine model has validated the role of growth factors, particularly glial derived neurotropic factor, in the pathogenesis of PD **(Cass, 1996).** Although this model mimics dopamine depletion similar to that of sporadic PD, methamphetamine does not induce many cardinal features of PD; therefore, this is considered as a dopamine depletion model rather than PD model.

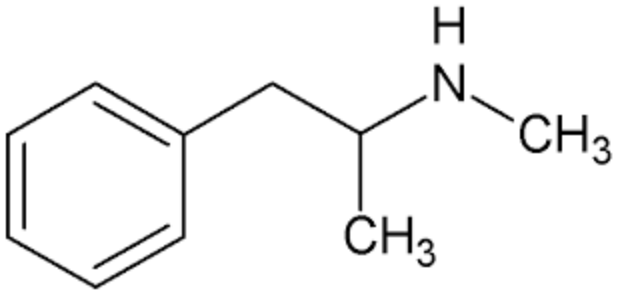

Figure 5. Chemical Structure of Methamphetamine.

Paraquat and Maneb

Paraquat (PQ), a bipyridyl herbicide, and Maneb, a fungicide have been implicated in PD pathogenesis through epidemiological and animal studies **(Singhal et al., 2011)**. Maneb crosses the blood–brain barrier owing to its lipophilic nature while paraquat crosses it through the neutral amino acid transporter **(Yadav et al., 2012)**. Maneb is reported to inhibit the mitochondrial complex III in a few reports but most of the studies did not observe any change in complex III activity. On the other hand, paraquat is consistently reported to inhibit the mitochondrial complex I **(Singhal et al., 2012)**. These two pesticides together induce more pronounced oxidative stress and neurodegeneration than either alone **(Singhal et al., 2011)**. Combined maneb and paraquat model of PD is widely accepted since it resembles sporadic PD owing to slow and progressive degeneration of dopaminergic neurons and is also environmentally relevant **(Singhal et al., 2012)**. PQ, a bipyridyl herbicide, is structurally similar to MPP^+ (1-methyl-4-phenylpyridinium ion), the hydrolyzed ion of MPTP **(Uversky, 2004)**. It is generally used to control weeds in orchards and plantations, to act as a defoliant and facilitate harvesting and has been used as a commercial pesticide **(Drechsel and Patel, 2008)**. It is banned in many countries due to its toxicity, but it is still vigorously used in other countries including the United State of America. Its neurotoxicity is mainly due to the inhibition of redox cycling as it readily converts into ROS. By this mechanism, it increases the genearation of other ROS species and generates oxidative stress in dopaminergic neuron of the substantia nigra pars compacta **(Jones and Vale, 2000)**.

Initially both PQ and maneb inhibits the mitochondrial complex activity and produces free radicals through NADPH oxidase leading to oxidative stress, DNA damage and apoptosis **(Singhal et al., 2012; Uversky, 2004)**. In addition, the generation of free radicals, mitochondrial dysfunctions, microglial activation, increased lipid per-oxidation and nitric oxide levels are well documented in PQ and Maneb both intoxicated mice **(Gupta et al., 2010)**.

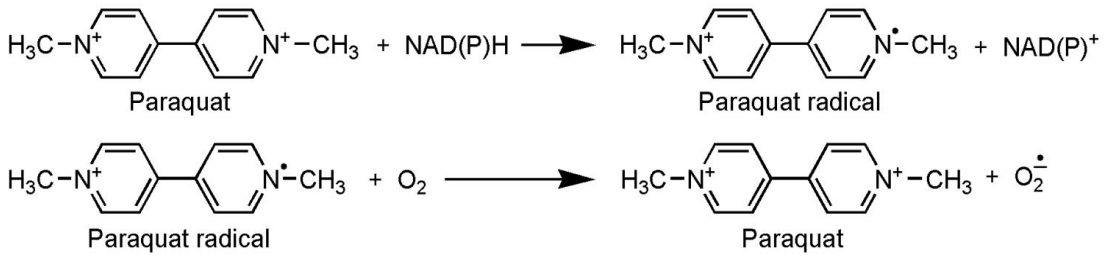

Figure 6. Reduction-oxidation cycling reaction of Paraquat.

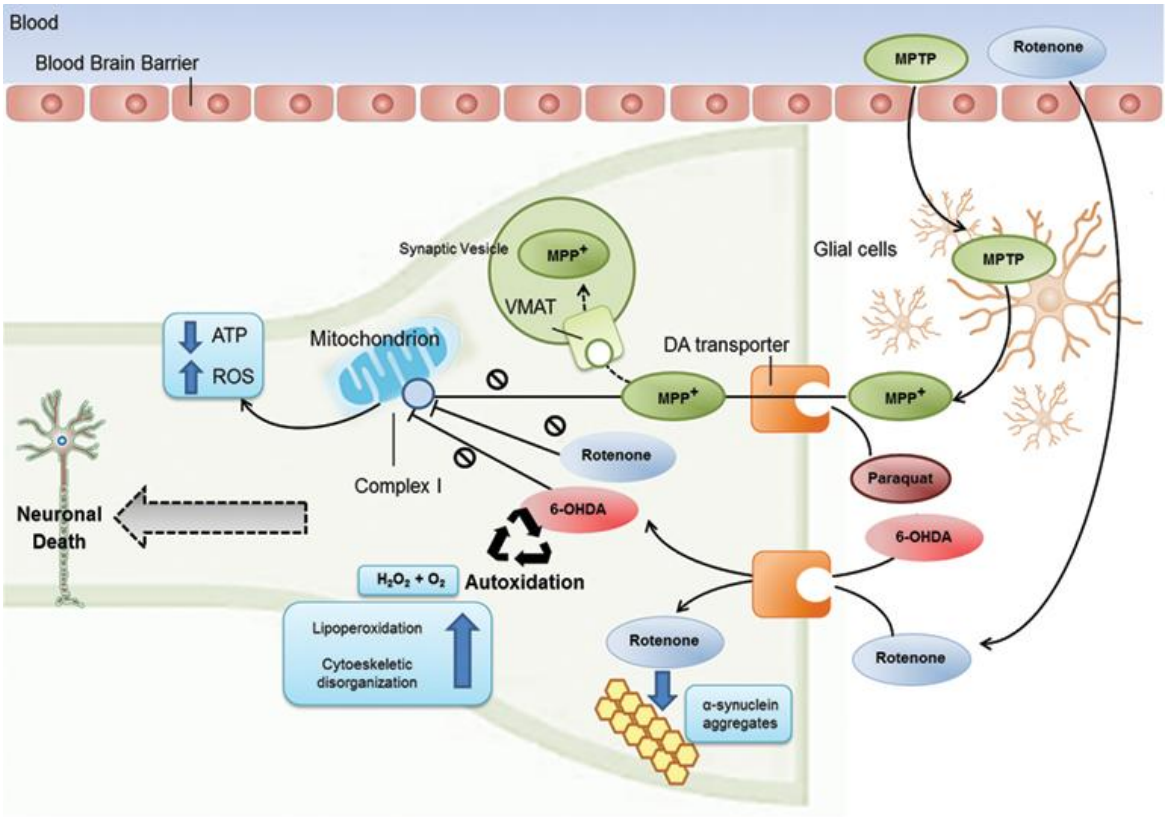

Figure 7. Pathogenesis of most common toxin-induced models.

Lipopolysaccharide

Neuroinflammation is involved in the pathogenesis of PD. Inflammation serve as a key player in PD pathogenesis and all neurotoxins currently used in experimental models generate a neuro-inflammatory response in the nigrostriatal tract.

These considerations have prompted the introduction of another toxic model, in which bacterial endotoxin lipopolysaccharide (LPS), which causes intense tissue inflammation, is directly infused into the nigrostriatal pathway of rats. Intranigral injection of LPS results in activation of microglia and degeneration of the dopaminergic system. LPS-induced neurotoxicity is mediated by the microglial activation and the resulting release of cytotoxic molecules because LPS per se is not toxic to neurons. More recently, it has shown that the injection of LPS into the striatum of rats induces progressive degeneration of the nigrostriatal pathway, characterized by a 41% cell loss in the injected SNpc, at week 4 post-injection, and a 42% reduction in the striatal levels of DA; accumulation of a-synuclein and ubiquitin in surviving SNpc neurons was also reported, along with marked rotational behaviour, ipsilateral to the lesioned side, in response to the systemic administration of amphetamine **(Hunter et al., 2009)**.

CONCLUSION

This review summarized the salient aspects characterizing the most popular toxic models of PD. Although all neurotoxins reviewed here are thought to kill dopaminergic neurons, they all produce specific clinical or neuropathological abnormalities that make them different from each other **(Blesa et al., 2012; Fig. 7)**. As we have stressed herein, each model has advantages and shortcomings, and none should be regarded as suitable to represent all aspects or to address all questions that pertain to PD. Thus, at end none of the presented models is perfect, and the selection of one over the other must be governed solely by the question and the type of investigations to be undertaken. In other word; the experiment based on neurotoxin induced model: which model will be suited to address the question is to be investigated by the investigator itself.

MPTP crosses the blood-brain barrier and is metabolized to 1-methyl-4-phenylpyridinium (MPP^+) by the enzyme monoamine oxidase B (MAO-B) in glial cells and then to the active toxic compound. MPP^+ is then taken up by dopamine transporter where it impairs mitochondrial respiration by inhibiting complex I of the electron transport chain, causing oxidative stress and activation of programmed cell death molecular pathways. Both paraquat and 6-hydroxydopamine (6-OHDA) easily cross cell membrane through the dopamine transporter and may also exert their toxicities, in part, by targeting mitochondria with the subsequent production of ROS and quinones causing the degeneration of the nigrostriatal dopaminergic neurons. Rotenone is extremely hydrophobic and penetrates easily the cellular membrane inducing the formation of α-synuclein aggregates and mitochondrial impairment with the subsequent production of ROS and quinines.

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