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6-Ohda Induced Oxidative Stress in Different Animal Models

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ABSTRACT: Parkinson's disease (PD) is the second most common neurodegenerative disease characterized by loss of dopaminergic neurons in the substantia nigra. The main cause of PD has been reported to be environmental variables such as water, pesticides, herbicides, farming operations, and human activities. 6-OHDA(6-Hydroxydopamine) is one of the most commonly used neurotoxins in degeneration of in vivo and in vitro models of central catecholaminergic projections, including the nigrostriatal system. 6-OHDA has advantages like it is able to induce massive destruction of dopaminergic neuron in substantia nigra (SN). Injection of 6-OHDA into the striatum or substantia nigra, kills dopaminergic neurons and induces quantifiable motor deficits, it is the major advantage of this model. This review is mainly focusing on various important aspects of 6-OHDA as experimental neurotoxin in different animal models including the mechanism, advantages, induction techniques.

KEYWORDS: Neurodegenerative disorder, Parkinson's disease (PD), 6-OHDA Neurotoxicity, Locomotor assessment.

I. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease. Neurodegenerative disorders (NDD) is a sporadic condition characterised by the gradual and irreversible loss of neurons as well as a steady decline in brain function. A neurodegenerative disorder is a disease or illness that predominantly affects neurons (1).

PD primarily affecting people of ages over 55 years, although young adults and even children can also be affected. PD is characterized by the loss of 50–70% of dopaminergic neurons located in the substantial nigra.

Parkinson's disease (PD) is a disorder with increasing prevalence worldwide.(2)Although the pathogenesis of the disease remains undetermined, aging, mitochondrial dysfunction, oxidative stress and apoptosis are major contributing factors(3).

II. ETIOLOGY OF PD

The main causes of Parkinson's disease are not known. Several studies have reported common causes of Parkinson's disease. The main cause of PD has been reported to be environmental variables such as water, pesticides, herbicides, farming operations, and human activities. Neurotoxins like (6-OHDA, MPTP), heavy metals (mercury, iron), and agricultural pesticides like rotenone and paraquat shows dopaminergic neuron damage (4).Apart from the environmental factors genetic factors are also important cause of the PD.There are several genes which are linked with PD. The 16 PARK1 through PARK16 (PTEN induced kinase 1-16) loci, as well as 11 additional genes on different chromosomes, have been linked to PD(5). As mentioned in reported study, entire mitochondrial DNA being sequenced in five sporadic PD patients, and distinct point mutations in a complex I subunit have been found in each patient. In a family with PD, a mutation been discovered in the gene that encodes the protein α-synucelin. Parkin and ubiquitin C mutations are responsible for the formation of PD in some hereditary forms of the disease, hence parkin genes are recommended candidates for PD modelling. A mutation in the gene that codes for the protein α -synucelin has been detected in Parkinson's disease. Oxidative damage induces PD by changing the structure of α-synucelin and promoting self-aggregation. Lewy bodies and Lewy neurites, both of which are hallmarks of Parkinson's disease, contain a substantial amount of α-synucelin protein. These findings back with the idea that Parkinson's disease is caused by a single α-synucelin mutation. As a result, α-synucelin can be used to imitate Parkinson's disease in research(4).

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III. PATHOLOGY OF PD

Parkinson's disease is caused by a specific degeneration of dopaminergic neurons in the Substantia Nigra, resulting in a decrease in dopamine levels in the striatum and impaired motor function. Bradykinesia, muscle tone stiffness, resting tremor, and postural instability are some of the motor symptoms. In addition, non-motor symptoms such as insomnia, dementia, sensory abnormalities, and autonomic dysfunctions are common inpeople with Parkinson's disease(6). The loss of dopaminergic cells in the substantia nigra pars compacta of the basal ganglia is thought to be the aetiology of Parkinson's disease. The ability of the basal ganglia to coordinate inhibitory and excitatory neural motor impulses in cortical-subcortical circuits is affected when dopamine levels are low. Rigidity, tremor, and dyskinesia are the motor consequences of such a dysfunction(7).Many characteristics of Parkinson's disease (such as cognitive impairment and autonomic dysfunction) are caused by neurodegeneration in various parts of the central nervous system, as well as the enteric and autonomic nervous systems(8).

IV. OXIDATIVE STRESS AND PARKINSON'S DISEASE

In the case of Parkinson's disease, oxidative stress is caused by auto-oxidation of dopamine, which, when free in the cytoplasm of dopaminergic (DA) neurons, causes a constant flow of Ca2+ in these neurons, causing them to have a low firing rate but also making them more vulnerable to oxidative stress. Because this type of neuron has a high energy requirement, it produces more free radicals due to increased mitochondrial respiratory action(9). The brain utilizes around 20% of the basal oxygen from the total oxygen supplied to the human body. ROS(Reactive oxygen species) mediated oxidative DNA damage is one of the prominent features in PD. Several studies have reported impaired respiratory chain and somatic mitochondrial DNA mutations in the brain of patients with PD, which suggests the extensive role of oxidative metabolism in PD. Enhanced dopamine metabolism in the brain of patients with PD could account for the accumulation of toxic radicals such as hydroxyl in the brain. Iron accumulation in the neurons in the redox active form plays a crucial role in pathogenesis of this disease. Reduced antioxidant enzyme and nonenzymatic antioxidant activity may be to responsible for the advancement of PD. Patients with PD have been found to have decreased glutathione levels and higher oxidised glutathione levels, as well as lower glutathione content in the substantia nigra due to neuronal damage. In the brains of PD patients, decreased glutathione peroxidase activity and glutathione content have been documented, and lower glutathione content has been identified in both human and experimental models of PD. GSH levels in the substantia nigra and corpus striatum of Parkinson's disease patients were shown to be lower (10).

V. 6- OHDA MODEL

6-OHDA shares some structural similarities with dopamine and norepinephrine, exhibiting a high affinity for several catecholaminergic plasma membrane transporters such as the dopamine (DAT) and norepinephrine transporters (NET). Consequently, 6-OHDA can enter both dopaminergic and noradrenergic neurons and inflict damage to the catecholaminergic pathways of both the peripheral and the central nervous systems(11). 6-OHDA has advantages like it is able to induce massive destruction of dopaminergic neuron in substentia nigra (SN). Also it induces major behavioural deficits which are seen in PD and used to test pre- clinical diagnosis. 6-OHDA shows disadvantage, it lack the formation of Lewy bodies which is the main pathology hallmark of PD(6).

VI. STRUCTURE

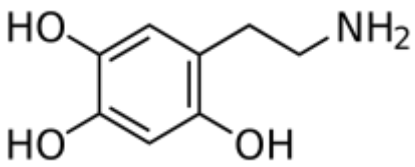

Fig.1 – Chemical structure of 6-OHDA

6-Hydroxydopamine (6-OHDA) is a hydroxylase derivative of dopamine, a catecholaminergic neurotoxin and it is a naturally occurring neurotransmitter. This is used in animal models to study Parkinson's disease experimentally. 6-OHDA is one of the most commonly used neurotoxins in degeneration of in vivo and in vitro models of central catecholaminergic projections, including the nigrostriatal system. In the presence of iron, 6-OHDA-induced neuron degeneration involve the processing of hydrogen peroxidase and hydroxyl radicals.

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6-OHDA promotes respiratory inhibition and oxidative stress in neurodegenerative processes, which is generated by free radical production. 6-OHDA is easily oxidizable and can lead to free radicals formation. 6 OHDA does not connected the blood brain barrier when administered by systemic route. For the specific administration either in substantia nigra, medial forebrain bundle, and striatum injection technique is required i.e. stereotaxic apparatus.

VII. MOA OF 6- OHDA

6-0HDA has two ways of action i.e. it easily forms free radicals and is a potent inhibitor of the mitochondrial respiratory chain complexes I and IV. Intra- or extracellular auto-oxidation which favors the production of hydrogen peroxide, superoxide and hydroxyl radicals. And by the effect of monoamine oxidase there is formation of hydrogen peroxide(12). The inhibition of respiratory enzymes by 6-0HDA is reversible and insensitive towards radical scavengers and iron chelators with the exception of deferoxamine(13).6-OHDA treatment shows reduction in the striatal glutathione (GSH) and superoxide dismutase (SOD) enzyme activity and increasing malondialdehyde levels. 6-OHDA appears to be harmful to mitochondrial complex I. Systemic administration of dopaminergic receptor agonists (e.g., apomorphine), L-dopa, or dopamine releasing medications (e.g., amphetamine) generates an asymmetric and measurable motor behaviour generated by 6-OHDA injection(14). Toxicity of 6-0HDA is proposed to be related to its ability to produce free radicals and to cause oxidative stress. The availability of reduced glutathione is decreased after 6-0HDA intoxication and the activation of glutathione reductase in presence of exogenous brain-derived neurotrophic factor promoted the survival of cultured dopaminergic neurons. Stimulated by 6-0HDA, glia were found to release basic fibrillary growth factor nerve growth factor, brain derived neurotrophic factor and proenkephalin as well as glia derived neurotrophic factor). Neurotrophins do not only improve the availability of reduced glutathione, they also raise catalase and glutathione peroxidase levels) and thus increase the cellular defense against oxidative stress. Iron dependent mechanisms and free radicals may also contribute to the toxicity of 6-0HDA, which has been shown to liberate iron from ferritin and to increase the availability of ferrous iron (Fe^{2+}) for the Fenton reaction. Such a mechanism could explain the finding that the iron chelator deferoxamine provides protection against brain lesioning induced by 6-0HDA injections in rats(13).

VIII. INDUCTION OF PARKINSONISM BY 6-OHDA(15)

For induction of 6-OHDA in different animal models required stereotaxic apparatus as it does not crosses the blood brain barrier. Mostly 6-OHDA is injected into the substantia nigra (SNC), medial forebrain, MFB of the targeted site. After that, the needle should left in place for another 5 minutes. The skull is then screwed into place with stainless steel screws, and the wound is sealed with dental cement.6- Dopaminergic neurons degenerate after 12 hours of OHDA injections into the substantia nigra or the medial forebrain bundle, and striatal dopamine levels are decreased 2–3 days later. In contrast to injections into the substantia nigra–ventral tegmental region combination, nigrostriatal injection of 6-OHDA produces more progressive, retrogradely triggered neuron death.

IX. ANIMAL MODELS OF 6-OHDA INDUCED PD

Different animal models has been generated to study different aspects of the disease for understanding the pathogenesis and therapeutic development. The disease model can be generated through neurotoxin 6-OHDA based approaches in a wide range of animals such as rodents, zebra fish and drosophila. Because of the widespread use of rodents, Zebra fish, fruit fly models and their similarities to humans, these animal models are focused in this review. Animal study should be approved by the Institute Animal Ethics Committee and all the animal experiments are carried out according to CPCSEA guidelines. As per the reported study following are the routes of administration of 6-OHDA induction.

SR. NO.	ANIMAL MODEL	PREFERRED ROUTE OF ADMINISTRATION
1.	Rat	Unilateralinto Right striatum, Medial forebrain bundle. (Stereotaxic Apparatus)
2.	Zebra fish	Intracerebroventricular (ICV) or Intramuscular

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		injections(Hamilton syringe)
3.	Drosophila	Oral route (mixed with diet)

X. 6-OHDA INDUCED PD IN RAT MODEL

6-OHDA-induced Parkinson's disease rat model involves chronic inflammation, mitochondrial dysfunction, and oxidative stress, and the loss of the dopaminergic neurons in the substantia nigra is the predominant lesion. To investigate the rotational abnormalities caused by dopamine neuron injury in rats, a partial lesion of the nigrostriatal DA system by nigrostriatal administration was selected(3). The intensity of symptoms in the 6-OHDA model is determined by the injection site and the 6-OHDA dose administered. Injections of the toxin into the medial forebrain bundle (MFB) induce an abrupt and near complete loss of DA neurons in the SNc, as well as a considerable reduction of striatal DA content, in the whole lesion model(16). The most widely used 6-OHDA rat model for studying PD uses animals with unilateral lesions. In the unilateral 6-OHDA model, which is also known as the hemi Parkinson model, the intact hemisphere serves as an internal control structure, causing asymmetric and quantifiable motor behaviour induced by systemic administration of either dopaminergic receptor agonists (e.g. apomorphine), L-dopa, or dopamine releasing drugs. As per the different study reported 6-OHDA can be injected unilaterally into two sites of the right striatum and bilaterally with different dimensions from bregma(15). Before starting the experimental procedure animals should be housed under specific conditions like quiet environment, day-night rhythm that is 12 h light–dark cycles, at 22–23 °C and given free access to food and water ad libitum(3).Rats weighing 180–220g must be anaesthetized with a 50 mg/kg intraperitoneal dose of sodium pentobarbital before being placed on a stereotaxic device. The following locations have been placed unilaterally into the substantia nigra with a stainless steel needle (0.28 mm o.d.) (15).

Stainless-steel needle with outer diameter 0.28 mm is usually used in stereotaxic device inserted unilaterally or bilaterally into the substantia nigra with the coordinates. Following are the induction sites and different dimensions of unilateral injection (most common) which are used for the induction of 6-OHDA in rodents.

Sr. No.	Site of induction	Dimensions/coordinate
A.	Right striatum(16)	1. A/P(0.1mm) M/L(3.2mm) D/V(5.0mm)
B.	Right striatum (unilaterally into two sites of the right striatum)(17),(3)	1. A/P(0.0mm) M/L (-3.2mm) D/V(-7.0mm) 2. A/P(-1.2mm) M/L(-4.0mm) D/V(-7.0mm) 3. A/P (-0.7mm) L (3.0 mm) D/V(-5.5mm &4.5mm) 4. A/P(-0.2mm) L(-2.6mm) D/V(-5.5mm &4.5mm)
C.	Medial forebrain bundle(MFB) (18)	1. A(-4.0mm) L(1.1mm) V(-7.6mm)
D.	MFB of the right hemisphere	1. A/P(4.4mm) M/L(1.1mm) D/V(8.0mm)

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Where, A-Anterior, L-Lateral, V-Ventral, A/P-Anteroposterior, M/L-Mediolateral, D/V-Dorsoventral(Distance given in parentheses is from the bregma).

6-OHDA being administered using a 10-µl Hamilton micro syringe at a dose of 10 g of 6-OHDA hydrochloride dissolved in 2 L of 0.9 percent saline. The injection rate has to be set at 1 µl/min, and then syringe is left in place for another 2 minutes before being slowly withdrawn. Dental cement would be used to cover the burr hole. After that, sterile non-absorbable surgical sutures have been used to secure the skull. Following the surgical surgery, each rat should be maintained separately. Sham-operated animals are likewise given the same treatment, but instead of 6-OHDA, they are given similar quantities of normal saline(15).

Post-operative care

Recovery of anaesthesia take approximately 3-4 hrs. The rats has to kept in separate cages until they regained full consciousness, then placed together in groups of animals per cage after seven days of recuperation. To avoid postoperative infection, gentamicin injection 40mg/ml/kg is administered once day for three days. After surgery, administration of glucose water to rats is necessary because it induces hyperglycaemia, which causes an increase in glucose levels and resistance to insulin uptake in rats.

1. Behavioural assessment(15)

Rota rod (muscle rigidity test)

Muscle rigidity test can be conducted using rota rod apparatus. Each rat is given a prior training session before preceding the therapy to acclimatize them to apparatus. It is assessed at different time intervals after 30min, 60min and 120min. The test is performed on the 7th, 14th and 21st day of treatment. Wherein, the animals from each group will be placed on a rotating rod. Rotating speed: 12 revolutions/min) for 3 min and the latency to fall of rats from the rotating rod will be recorded.

Locomotor activity test (actophotometer)

Locomotor activity test can be conducted using actophotometer apparatus. It should be assessed at different time intervals after 30min, 60min and 120min the test was performed on 8th, 15th and 22nd day of treatment. The activity is then expressed in terms of count recorded when a beam of light falling on the photocell is cut off by animal movement, each animal is then observed for 3 min.

I. ZEBRA FISH MODEL

Zebra fish considered to be an excellent and popular model among non-mammalian vertebrates, for a number of reasons, such as their CNS regenerative capability with behavioural and neural circuit reintegration and largely similar and conserved genes and proteins (approximately 80%) with human(19). Because of their parallels to human brain physiology and structure, zebra fish have been used to research a variety of human disorders, including neuropsychiatric and neurodegenerative diseases.The blood brain barrier exists in zebra fish, and permeability studies have found that its physiological features are similar in humans and zebra fish. Zebra fish show advanced cognitive behaviours, such as learning and retaining associations, as well as well-documented anxiety behaviours, in addition to their physiological benefits.Dopaminergic signalling pathways in zebra fish and humans are identified to be similar, and transcription factors are discovered to have evolutionarily conserved functions in the development of zebra fish dopaminergic neurons. Oxidative stress makes dopaminergic neurons in zebra fish vulnerable, which is one of the main causes of mortality in Parkinson's disease. Hence zebra fish is proved to be an excellent model for investigating Parkinson's disease because of its well-studied dopaminergic system. Additionally, the dopaminergic neurons in zebrafish's posterior tuberculum (homologous to SN in human) are well characterized. When exposed to neurotoxin, zebrafish displayed alteration in locomotor activity(6).

II. 6-OHDA INDUCED PD IN ZEBRAFISH MODEL

According to the reported study method of injecting 6-OHDA into the brain of adult zebrafish is intracerebroventricularly (ICV) or intramuscularly (IM). Effective dose of 6-OHDA in adult zebrafish is 25 mg/kg. In order to specifically administer 6-OHDA to the targeted DpN population, an ICV injection is to be carried out by employing a microinjector capillary. ICV injection usually requires only a small volume of compounds to be injected into the brain cavity(19). Intramuscular injections of 6-OHDA in zebra fish causes locomotors defects and decreased dopamine levels which indicate that 6-OHDA crosses the blood-brain barrier (BBB) more readily in zebra fish than in mammals. After administration of 6-OHDA to larval zebra fish, it shows oxidation throughout the brain and a significant reduction in

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the number of TH-positive neurons in the diencephalon (20).

During the experimental work zebrafish should first anaesthetised using 0.02% (w/v) tricaine methanesulfonate. A hole is to be then made in the skull of the fish with sterile surgical tweezers. Microinjector is used to induce the neurotoxin.6-OHDA induction should be given at the point of entry of the microinjection capillary could be found immediately above the habenula (Hab) in between both hemispheres. Parameters for injection i.e. angle (50°, 55° and 60°) and depth (800, 1000 and 1200 µm) to be optimised as per the reported study. For tracing purposes, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanineperchlorate (DiI), a fluorescent neuronal tracer, is to be used to monitor the location of injection. The entire injection procedure should be conducted under a stereomicroscope(19). Locomotor behavioural assessment should be done by video tracking.

1. Locomotor assessment

The locomotion of the fish is assessed at post-6-OHDA lesion. Locomotor assessments include behavioural parameters like catalepsy (swimming pattern, speed, latency to travel between two fix point, time spent near bottom of tank).

Following are the behavioural parameters to be evaluated by using camera such as,First, latency time is calculated. Fish shouldtravel from first vertical line to last.This gives an idea about the speed of fish under examination.Second, complete cataleptic time is calculated. The time is recorded in which fish did not move at all, i.e., the time for which fish remained completely cataleptic during 1 h examination period.Last, time spent near the bottom of the tank, in which time spent below the horizontal line drawn on the examination tank is measured at different time intervals. This gave an idea about the anxious behaviour of the fish under study. In addition to this, visual observations also noted down throughout the experiments and any erratic swimming pattern like vertical swimming, sideway swimming,upside- down, arrow- like swimming (darting behaviour) should be observed.

I. DROSOPHILA MODEL

The dopamine generation mechanism in Drosophila is comparable to that in humans. Drosophila has thus emerged as a promising model for researching neurodegeneration in Parkinson's disease. Drosophila treated with neurotoxins shows PD-like symptoms such as dopaminergic neuron loss, locomotor abnormalities, and oxidative stress. Flies shows complex motor behaviours such as walking, climbing, and flying and their brain is complex enough to make these behaviours relevant to humans(21).

Most widely Drosophila melanogaster wild type strain is used for the experiments. Flies being kept and maintained in the fly lab under standard conditions of 22°± 1 C, 70–80% relative humidity, and a conventional wheat flour–agar diet with yeast granules as the protein source. The incidence of mortality in flies is evaluated on a regular basis, and locomotor impairments are determined using a negative geotaxis assay(22).

Flies should be starved for 24 hours in empty vials before being transferred to vials containing 6-OHDA (1 mM) in culture medium to induce neurotoxicity. The flies should be placed into vials with new supplies of their individual diets after 24 hours and utilised for the climbing test(23).

1. **Negative geotaxis (climbing) assay:**

A negative geotaxis assay is used to evaluate motor function. 15 flies are placed in a graduated flat bottom glass vial (length 12 cm; diameter 2 cm) during their light cycle and kept to habituate for at least 5 minutes. The vial should then be firmly tapped at the bottom and the climbing behaviour observed for 60 seconds. The percentage of flies escaping beyond a minimum distance of 10 cm in 60 seconds is referred to as locomotor behaviour(24).

CONCLUSION

This review concludes that the induction of 6-OHDA serves as a good neurotoxin mainly targeting dopaminergic neurons and hence leads to development of symptoms similar to Parkinsonism in different animal models.

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