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REVIEW ARTICLE OPEN ACCESS

Rotenone and its Underlying Mechanisms of Neurodegeneration in Different Animal Models

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Abstract:

Neurodegenerative disorders are characterized by progressive loss of selectively vulnerable populations of neurons. Parkinson's disease is a late-onset, progressive motor disease that is characterized by dopaminergic neuron degeneration. Several models have recently been developed in which research animals were exposed to various pesticides such as rotenone and paraquat to cause Parkinsonism. As a result, paraquat should not be used in preclinical studies or animal studies with neuroprotective drugs because it crosses the blood-brain barrier (BBB) less efficiently than rotenone whereas rotenone can be used to examine neuroinflammatory responses, mitochondrial inhibition, and mitochondrial apoptotic pathways in neurodegeneration diseases. Rotenone is involved in the inhibition of mitochondrial complex I, ROS production, microglia activation, oxidative damage to proteins, lipids, and DNA, induction of apoptosis, and acceleration of α-synuclein aggregation and fibrillation. The review is focusing on details of the mechanisms, advantages, and limitations of rotenone and its application as inducing agent in different animal models.

Keywords **— Neurodegenerative, Parkinson's diseases, Rotenone.**

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I. INTRODUCTION

Neurodegenerative disorders are a significant threat to people's health. These age-related disorders are becoming more common, owing to an increase in the older population in recent years. Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia are examples of neurodegenerative disorders. The pathophysiology of these diseases varies, with some impairing memory and cognition and others affecting a person's capacity to move, speak, and breathe. Models extending from cell-based systems to unicellular creatures to large animals have proven to be an incredible resource in aiding research into the mechanisms behind neurodegenerative diseases, and these advancements have already begun to open up intriguing therapeutic possibilities. For many years, neurodegenerative diseases have been studied using powerful experimental model species such as the mouse, fruit fly, rat, and various cell lines.

Parkinson's disease is a late-onset, progressive motor disease and the second most prevalent neurodegenerative disease that is characterized by dopaminergic neuron degeneration. Rest tremor, rigidity, bradykinesia, and postural instability are the cardinal clinical symptoms of Parkinson's disease (PD), the second most prevalent neurodegenerative disease. The loss of dopamine neurons in the substantia nigra of the ventral midbrain, as well as the loss of dopamine innervations of the neostriatum is the fundamental etiology of Parkinson's disease. The pathologic feature of PD is intracellular deposits of aggregated α synuclein, ubiquitin, and other proteins (known as Lewy bodies) Abnormal protein aggregation and inadequate clearance of aggregates, altered dopamine metabolism, impaired mitochondrial function, oxidative stress, inflammation, necrosis, and accelerated apoptosis are all involved in the etiology of PD. It also comprises the loss of cognitive function, accompanied by significant speech difficulties. Parkinsonism and other involuntary movement are more easily mimicked in animals than any other functional neurological disorder and allowing researchers to better understand their processes at the cellular and molecular level and discover new treatment targets. The loss of dopamine neurons in the substantia nigra of the ventral midbrain, and even the associated loss of dopamine innervations in the neostriatum, can be easily manipulated in experimental animals using a variety of neurotoxins, including 6-hydroxydopamine (6-OHDA) and 1-methyl 4- phenyl 1,2,3,6-tetrahydropyridine (MPTP), rotenone, etc. The link between increased PD risk and environmental variables such as rural residency, farming, and drinking water from wells, and exposure to agricultural pesticides is one of the most important and consistent results of epidemiological research directly connected to the topic of this review. These findings indicate that pesticides may serve as dopaminergic toxins, paving the way for the establishment of various animal models of Parkinson's disease. The scope of this review is focusing on details of

the mechanism, advantages, and limitations, of rotenone-induced Parkinsonism and how rotenone affects in different animal models.

II. DIFFERENT PESTICIDE MODELS

Several models have recently been developed in which research animals were exposed to various pesticides to cause Parkinsonism. The most commonly used pesticide-induced parkinsonism are paraquat and rotenone. The paraquat (N, N′-dimethyl-4-4-4′-bipyridinium) is frequently used and structurally similar to MPP^+. The degeneration of dopaminergic neurons in the substantia nigra (SN) and the related neurobehavioral syndrome indicating dopamine terminal depletion within the striatum must be demonstrated before paraquat can be considered a possible neurotoxicant. Initial attempts to generate convincing evidence of a direct link between paraquat exposure and Parkinson's disease (PD) were unsatisfactory. Nonetheless, it is frequently used in conjunction with Maneb, a herbicide that has been shown to inhibit locomotor activity and SN neuron loss. Paraquat also kills dopaminergic mesencephalic neurons. Paraquat has been found to cause neurotoxicity through a variety of mechanisms, with the formation of reactive oxygen species (ROS) being a prominent factor in paraquat cytotoxicity. Paraquat (PQ) produces reactive oxygen species (ROS) because of oxidative stress mediated by redox cycling. This mechanism, on the other hand, is not dependent on Na+ or dopamine transporter (DAT). Furthermore, paraquat, as a redox-cycling compound, causes oxidative stress and neuronal death by decreasing glutathione and thioredoxin redox recycling. Paraquat also causes mitochondrial complex I damage by inducing apoptosis through the mitochondria-mediated apoptotic mechanism. Paraquat does not inhibit complex I activities because it crosses the blood-brain barrier (BBB) less efficiently than rotenone; yet, paraquat causes the production of Lewy bodies (LB) in dopamine (DA) neurons in mice and rats. Paraquat also induces Parkinson's disease through the Jun N-terminal kinases (JNK) and respiratory damage pathways. The studies examined at the onset of PD and signs of Parkinsonism in people who had been exposed to paraquat for a long time or at high doses found that paraquat does not cause PD in humans. Rotenone is a naturally occurring complex ketone found in the roots of the Lonchocarpus genus. It binds exclusively with the ND1 and PSST subunits of complex I and is a traditional, high- affinity inhibitor of complex I that is often employed to characterize the complex's particular activity.

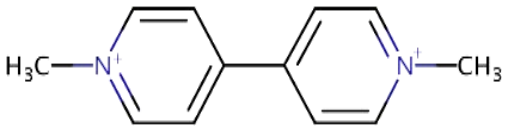

Fig.1.Paraquat

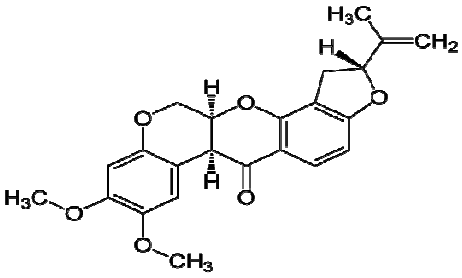

Fig.2. Rotenone

Rotenone is extremely lipophilic, so it crosses cellular membranes without the help of transporters, easily crosses the blood-brain barrier, enters the brain easily, and accumulates in subcellular organelles like mitochondria, where it restricts oxidative phosphorylation by inhibiting complex I of the electron transport chain. Although, it is ideally adapted for the production of complex I systemic inhibition in experimental animals. Indeed, injecting 2–3 mg kg^{-1} d^{-1} rotenone intrajugularly and subcutaneously into male Lewis rats for 28–56 days (alternatively, until behavioral impairments appear) causes specific nigrostriatal dopaminergic neurotoxicity. In a different study, male Sprague-Dawley rats were given rotenone in two distinct doses: 1.5 mg/kg (low dosage) and 2.5 mg/kg (moderate dose) intraperitoneally every day for two months. The rat brain was observed to be uniformly inhibited by complex I after chronic exposure to low concentrations of rotenone. Importantly, this continuous inhibition of complex I, which was uniformly distributed throughout the brain, produced selective degeneration of dopaminergic neurons in the SN for weeks. The disease was similar to that found in typical PD, with neurodegeneration originating in the nerve terminals and progressing retrogradely to the cell bodies. Furthermore, several of the dying neurons factors led to cytoplasmic inclusions that morphologically resembled LBs and contained α-synuclein and ubiquitin, just like true LBs. This dopaminergic degeneration was followed by an increase in oxidative protein damage, which was identical to the oxidative damage seen in Parkinson's disease. In other words, rotenone-treated rats developed all of the pathological markers of Parkinson's disease, including pathological distribution, nigrostriatal dopaminergic neurodegeneration, LB-like cytoplasmic inclusions, and oxidative damage. Finally, seriously damaged rats showed

the flexed posture and motor freezing that are hallmarks of advanced Parkinson's disease. As a result, complex I inhibition in animals via systemic rotenone exposure can be employed as a model of PD. Rotenone has a high affinity for passing across the BBB to the mitochondria complex 1 and inhibiting its activity, whereas paraquat enters the dopaminergic neurons by the Neutral Amino Acid Transporter and a Na+ dependent entry. Paraquat was suggested for PD investigations on LB inclusion and antioxidant enzyme activity. The data linking paraquat to Parkinson's disease is incomplete in both animal and human epidemiologic investigations and does not support the presence of a causal relationship between the two. As a result, paraquat should not be used in preclinical studies or animal studies with neuroprotective drugs, whereas rotenone can be used to examine neuroinflammatory responses, mitochondrial inhibition, and mitochondrial apoptotic pathways in neurodegeneration diseases.

III. DIFFERENT MECHANISM IN ROTENONE-INDUCED NEUROTOXICITY MODELS

Complex I and rotenone

Complex I protrude into the matrix from the inner mitochondrial membrane. It is made up of at least 43 protein subunits, with seven of them encoded by the mitochondrial genome and the rest 36 polypeptides by the nuclear genome. NADH is oxidized by complex I, which then transfers electrons to ubiquinone. It also helps in establishing the electrochemical gradient that fuels ATP production by transporting protons from the mitochondrial matrix to the intermembrane space. The mitochondrial permeability transition pore, a large calcium-dependent pore in the inner mitochondrial membrane, may be regulated by electron transport through complex I. Mitochondria de-energize, depolarize, and lose pyridine nucleotide when the permeability transition pore opens under pathological conditions. Furthermore, the permeability transition pore opening signals the onset of apoptotic or necrotic cell death. Complex I activity deficiencies are thought to reduce ATP production, cause mitochondrial depolarization, and promote calcium dysregulation. They are also known to cause an excess of reactive oxygen species (ROS), resulting in severe oxidative stress. All of these risks together would result in severe, early-onset, and fast progressing neurological diseases

Rotenone, microglia, and the production of reactive oxygen species

The discovery that rotenone causes extensive oxidative damage implies that it regulates ROS generation. Rotenone inhibits the NADH dehydrogenase complex and/or activates NAD (P) H oxidase, resulting in superoxide (O2 •)-derived H2O2 production. Using these systems, a few key observations have been made: (1) NADPH oxidase inhibition or free radical scavenging provides significant neuroprotection; (2) rotenone and LPS synergistically stimulate the NADPH oxidase-mediated release of the free radical O2• (3) rotenone and LPS fail to induce neurotoxicity and the production of O2 • in cultures from NADPH oxidase-deficient animals. These findings suggest that µglial NADPH oxidase- mediated ROS production is a crucial factor in synergistic dopaminergic neurotoxicity. The activation of microglia may be involved in the rotenone-induced degeneration of dopaminergic neurons. microglial cells, which are the brain's resident macrophages, respond to a variety of insults by rapidly proliferating, hypertrophying, and releasing a variety of cytokines. In patients with idiopathic PD, there is an increase in reactive microglia in the striatum and SN. In vitro, rotenone-induced microglial activation results in the formation of reactive oxygen species (ROS). They can be produced by NADPH oxidase, which creates O2 •; (2) COX-2, which generates free radicals as a consequence of prostaglandin synthesis; or (3) inducible nitric oxide synthase (iNOS), which produces NO•.

Rotenone and apoptosis

Rotenone's cytotoxicity is thought to be due to the induction of apoptosis. Apoptosis is a programmed cell death that refers to a set of structural and molecular phenomena which distinguish the type of cell death from necrosis. The activation of one or more members of the caspase family of cysteine proteases, as well as the release of components from mitochondria, such as cytochrome c, appear to be involved in the metabolic cascades that lead to nuclear DNA condensation and fragmentation. The death receptor-mediated caspase-8 activation mechanism and the stress-mediated or mitochondria-mediated caspase-9 activation pathway are exemplified by Fas-mediated caspase-9 activation. Both processes converge on caspase-3 activation, which leads to nuclear fragmentation and morphological changes in cells. The exposure of cells to rotenone causes the generation of H2O2, which causes significant changes in the mitochondrial membrane potential and is accompanied by the fragmentation of internucleosomal DNA and the formation of DNA ladders, according to two cell models types such as human cultured cells HL-60 and BJAB.

Rotenone and dopamine

Dopamine (3, 4-dihydroxyphenethylamine) is neurotransmitter that regulates movement (nigrostriatal pathway) and motivated behavior (mesolimbic pathway) in the central nervous system. It also serves as an intermediate in the synthesis of norepinephrine and epinephrine in the peripheral and central nervous systems. Aberrations in dopamine neurotransmission are suspected to be involved in several diseases, including schizophrenia, addiction, and Parkinson's disease. In addition, several in vitro and in vivo studies show that dopamine is a hazardous chemical that may play a role in neurodegenerative diseases like Parkinson's disease and ischemia-induced striatal damage. The oxidation of the dopamine molecule results in the formation of a reactive quinone moiety that can covalently alter and damage biological macromolecules. This quinone production occurs spontaneously, but it can be accelerated by metal ions (manganese or iron), and it can happen because of enzyme-catalyzed reactions. Increased oxidant stress, along with macromolecular damage, may induce cellular responses that finally lead to cell death. The selective degeneration of dopaminergic neurons is caused by chronic stimulation of mesencephalic cultures with modest doses of rotenone (1–10 nM). On the other hand, chronic suppression of mitochondrial complex I by rotenone does not affect the viability of non-dopaminergic neurons, implying that oxidative stress followed by the production of O2 • in non-dopaminergic neurons is small enough to be detoxified by intracellular antioxidant molecules. Taken together, our findings imply that the rotenone increase in O2 • production in the presence of endogenous dopamine may play a key role in dopaminergic neuron death.

Rotenone and α-synuclein

In rats, synuclein-positive inclusions have been characterized as a hallmark of the neurodegenerative process produced by rotenone infusion. In-vitro investigation has found that various common pesticides drastically speed up the fibrillation of α- synuclein, with rotenone being one of the most potent enhancers of fibril formation.

To summarize, complex I inhibitors are particularly susceptible to neurons. This opens up new possibilities for the development of Parkinson's disease models based on complex I inhibition in the nigrostriatal pathway. Although the rotenone model suggests that complex I dysfunction could play a role in PD pathogenesis, the mechanisms by which it can cause neurotoxicity to remain unknown. An increasing body of research reveals that rotenone's toxicity is multifactorial. Consequently, despite inhibiting complex I and ROS production, this insecticide is involved in microglia activation, oxidative damage to proteins, lipids, and DNA, induction of apoptosis, and acceleration of α-synuclein aggregation and fibrillation. All of these characteristics are likely to have a role in the selective degeneration of dopaminergic neurons induced by rotenone.

IV. ADVANTAGES

Rotenone has the ability to kill nigrostriatal dopaminergic neurons along with the LBs formation, which neither 6-hydroxydopamine nor MPTP have been able to achieve. The rotenone model also shows that mild systemic abnormalities in the brain caused by the pesticide (e.g., systemic suppression of complex I) can lead to Parkinsonism.

V. LIMITATIONS

Rotenone can damage organs that are not specifically targeted. The sensitivity of the rotenone model varies by rat species. It is also difficult to set up and has a high mortality rate.

VI. EXPERIMENTAL ANIMAL MODELS

By using rotenone, neurotoxicity can be induced in different experimental animal models such as drosophila, zebrafish, mice and rat.

Drosophila (Drosophila melanogaster)

Drosophila has been utilized as a model for a variety of neurodegenerative diseases, including a genetic model of Parkinson's disease based on Drosophila brain-directed formation of human α-synuclein. This invertebrate has the advantage of allowing quick screening of potential therapeutic compounds due to its vast panel of genetic methods. The neurological and behavioral effects of chronic sub lethal rotenone exposure in Drosophila are found in a study.

The flies included in the study should be maintained at 25°C on standard cornmeal–agar diet at 23-25°C under 12 hr light/dark cycles. Usually, flies ranging from 12 to 20 should be included in each study group.

Although the rotenone dose range from 20 to 500μM has been reported to cause neurodegeneration, the majority of the studies claim 500μM to be the most effective dose. The rotenone is administered by mixing it with the diet. The neurodegeneration in the flies is evaluated by locomotor assay and survival rate.

In the survival rate, simply the number of live flies is to be monitored and determined for a week. While in the locomotor assay, the ability of the flies to cross premarked distance is to be evaluated followed by calculating the performance index by the given formula

$$Performance\ index = \frac{1}{2}\left[\frac{ntot + ntop - nbot}{ntot}\right]$$

Where, ntot – Total number of flies; ntop - mean of the numbers of flies at the top; nbot - mean of the numbers of flies at the bottom.

Zebrafish (*Danio rerio*)

Zebrafish is becoming an increasingly attractive model organism for understanding the biology and developing therapeutics because as a vertebrate, considerable similarity with mammals in both genetic compositions and tissue/organ structures. Disruption in microbial composition caused by environmental pollutants and other pressures throughout the evolution of PD may promote oxidative stress and mucosal inflammation, as well as the buildup of α-synuclein in the enteric nervous system. Inflammation in the gut can lead to systemic inflammation, and proinflammatory cytokines like IL-1, IL-6, IL-21, TNF-, and IFN- can enter the brain via gut-vagus-brain pathways or permeability of the blood-brain barrier. These proinflammatory cytokines stimulate glial cells to produce more inflammatory factors, such as reactive oxygen species (ROS) and reactive nitrogen (RNS), resulting in more inflammatory reactions and, as a result, neuroinflammation and, neurodegeneration. Furthermore, the intestine produces incretin hormones (gut peptides) in response to dietary components or bacterial metabolites, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which can affect cell types linked to neuroinflammation and neurodegeneration in PD. The survival of dopaminergic neurons in the SN is dependent on a brain- derived neurotrophic factor (BDNF), and GLP-1 signaling disruption is linked to lower BDNF levels and PD development. The expressions of α-synuclein, BDNF, caspase- 3, caspase-9 and apoptosis in the adult zebrafish (*Danio rerio*) brain are observed in the rotenone-induced Zebrafish PD model.

The wild-type zebrafish with equal males and females can be utilized for the study. The zebrafish is to be exposed for 28 days to 5µg/L of Rotenone. The zebrafish is to be transferred into an observation tube 1 hour prior to evaluation to allow acclimatization to the surroundings. The neurodegeneration in zebrafish is evaluated by using parameters such as locomotor activity and light/dark box test.

To determine locomotor activity, three verticals lines are drawn on the tank at equal intervals which divided it into four zones. Fish are transferred into the tank. After that, number of lines crossed by fish is to be counted and recorded for 5 minutes.

On the other hand, light/dark box test is used to examine anxiety and depression like behavior in zebrafish. Each fish is placed in equal-sized dark and light compartment of the tank which is separated by plastic barrier. The barrier is raised by 1 cm, so fish can swim between the compartments. By using tower system, videos is to be recorded .Using manufacturers software, calculates the time it takes to enter the dark compartment, the time spent in the light compartment, and the number of crossings between compartments for 6 minutes .

Mice (Mus musculus)

The rotenone treated C57BL/6J mice model is a highly reproducible model. It mainly leads to motor deficits, GI dysfunction, and neurodegeneration, which were accompanied by intracellular alpha-synuclein accumulation in nigrostriatal dopaminergic neurons, and cholinergic neurons in the dorsal motor nucleus of the Vagus (DMV), and the intestinal myenteric plexus .

The transgenic strain of mouse i.e. C57BL/6N weighing approximately 25 g are preferred for the study. Briefly the rotenone (2.5 mg/kg/day) is to be administered for 4 weeks for induction of neurodegeneration. The osmotic mini pumps can be implanted subcutaneously in the animal for metered release of drug. The induction of rotenone in mice is evaluated by using various parameters such as bodyweight, survival rate and behavioral assessment which include rotarod test and cylinder test. In the evaluation of survival rate and body weight, the number of live mice and change in body weight are to be evaluated, respectively for 4 weeks. While in the behavior assessment including the rotarod test and cylinder test can be performed on pre, 1, 3, 7, 14, 21, and 28 days after treatment with rotenone. The rotarod apparatus is useful in assessing the motor coordination and balance, wherein the mice is placed on a rotarod at a fixed speed (usually 24 rpm, cutoff time 300 s) and time spent on the rotarod is recorded. The cylinder test is used to assess the mobility of both the forelimbs and the hind limb. Mice is placed individually in a transparent plastic cylinder (diameter: 13 cm, height: 16 cm), and the number of rearing with forelimbs contacts against the arena walls is to be recorded for 2 minutes (30 seconds after setting until 150 seconds), regardless of right or left paw.

Rat (Rattus)

Mitochondrial dysfunction is a key pathogenic mechanism in Parkinson's disease, rotenone, a mitochondrial complex I inhibitor with pro-oxidative action, has been widely used to generate a Parkinson's disease rat model. The disruption of the mitochondrial electron transport chain is related to

increased reactive oxygen species (ROS) production, adenosine triphosphate depletion, oxidative stress, neuronal apoptosis, and other molecular mechanisms of rotenone-induced parkinsonian behavior. Furthermore, rotenone-treated rats showed loss of TH+ dopaminergic neuron expression in the substantia nigra pars compacta (SNc), as well as the development of motor and behavioral deficits such as cognitive impairment, muscle incoordination, and neuromuscular weakness.

The rotenone with 2-3 mg/kg body weight has been reported to induce motor and behavioral deficit in adult male Sprague Dawley rats. The following are the evaluation parameters such as rotarod and hanging wire test that can be evaluated. The rotarod apparatus working remains same as mentioned above. The only change is the speed of rotating rod, which is gradually increased from 4 to 40 rpm over 5 minutes and the fall time is noted. In hanging wire test the ability of animal to withhold the grip is recorded. If the grip strength is decreased it indicates induction of neurodegeneration.

CONCLUSION

The present review on neurotoxin rotenone aids to enlighten readers and researchers with knowledge regarding various aspects of rotenone as a promising neurodegenerative agent. Thus, the role of rotenone as an optimum inducing agent in different animal models is discussed in detail and hence will serve as guidance for apt selection of animal models as per the need for research.

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