Review Article/ Derleme Makalesi

DOI: 10.61845/agrimedical.1471854

Experimental Models in Parkinson's Disease: Advantages and Disadvantages

Parkinson Hastalığında Deneysel Modeller: Avantajlar ve Dezavantajlar

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ABSTRACT

Parkinson's disease is a complex neurodegenerative disease that affects millions of people worldwide. The incidence and prevalence of Parkinson's disease, the second most common neurodegenerative disease after Alzheimer's disease, is gradually increasing. Although it is an important public health concern, the mechanisms related to Parkinson's disease have not been fully elucidated. One of the main approaches to research on mechanisms and treatment related to Parkinson's disease is the use of experimental models. In vitro and in vivo models enable the investigation of disease-related molecular and cellular processes and the testing of potential treatments. A variety of experimental models are used in Parkinson's disease research, including toxin-induced models, genetic models, and transgenic models, each with their strengths and limitations. Experimental models come to the fore in research on Parkinson's disease, which does not yet have a radical treatment. However, it is important to recognize that no experimental model truly represents all aspects of human Parkinson's disease. For this reason, the findings obtained from the studies need to be supported by different test systems and interpreted carefully. Experimental models are invaluable in the quest to elucidate the mechanism of Parkinson's disease and develop effective treatments.

Keywords: 6-OHDA, Haloperidol, MPTP, Paraquat, Reserpine, Rotenone

ÖZ

Parkinson hastalığı dünya çapında milyonlarca insanı etkileyen kompleks nörodejeneratif bir hastalıktır. Alzheimer hastalığından sonra en sık görülen ikinci nörodejeneratif hastalık olan Parkinson hastalığının insidansı ve prevalansı giderek artmaktadır. Önemli bir halk sağlığı problemi olmasına rağmen, Parkinson hastalığına ilişkin mekanizmalar tam olarak aydınlatılamamıştır. Parkinson hastalığıyla ilişkili mekanizmaların ve tedaviye yönelik araştırmaların temel yaklaşımlarından biri deneysel modellerin kullanılmasıdır. İn vitro ve in vivo modeller, hastalıkla ilişkili moleküler ve hücresel süreçlerin araştırılmasına ve potansiyel tedavilerin test edilmesine olanak sağlamaktadır. Toksin kaynaklı modeller, genetik modeller ve transgenik modeller de dahil olmak üzere, Parkinson hastalığı araştırmalarında her birinin güçlü ve sınırlayıcı yönleri bulunan çeşitli deneysel modeller kullanılmaktadır. Henüz radikal bir tedavisi bulunmayan Parkinson hastalığı araştırmalarında deneysel modeller ön plana çıkmaktadır. Ancak hiçbir deneysel modelin insandaki Parkinson hastalığının tüm yönlerini, tam anlamıyla temsil etmediğini kabul etmek önemlidir. Bu nedenle çalışmalardan elde edilen bulguların farklı test sistemleriyle desteklenmesi ve dikkatle yorumlanması gerekmektedir. Deneysel modeller, Parkinson hastalığının mekanizmasının aydınlatılması ve etkili tedaviler geliştirme arayışında paha biçilmez yöntemlerdir.

Anahtar Kelimeler: 6-OHDA, Haloperidol, MPTP, Parakuat, Rezerpin, Rotenon

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Gönderilme Tarihi: 25/04/2024
Kabul Tarihi: 29/05/2024
Yayınlanma Tarihi: 30/06/2024

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Cite this article: Altunlu Ö, Topatan E, Al-yaqoobi Z, Burul F, Bayram C, Sezen S, Ferah Okkay I, Okkay U, Hacimuftuoglu A. Experimental Models in Parkinson's Disease: Advantages and Disadvantages. Ağrı Med J. 2024; 2(2): 80-87

1.Introduction

Parkinson's disease (PD) is a progressive and chronic illness that was first described as "shaking palsy" by Dr. James Parkinson in 1817 (1). According to data from the World Health Organization (WHO), the incidence of PD has increased by 81% in the last 25 years, resulting in 329,000 deaths since the year 2000 (2). It is a neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the accumulation of cytoplasmic protein inclusions called Lewy bodies (3). Symptoms of PD include motor impairments such as bradykinesia, rigidity, resting tremor and postural instability, as well as non-motor impairments such as constipation, orthostatic hypotension, sleep disturbances, anxiety, depression and dementia (4).

Although PD is rare in individuals under the age of 40, its incidence increases with the aging of populations. It is reported to affect around 3% of individuals aged 80 and above (5). With advances in medical care leading to longer lifespans and increased exposure to environmental pollutants, it is expected that the incidence of PD will surpass 12 million by the year 2040. This is likely to result in a significant rise in healthcare and caregiving expenses (6, 7).

The most significant risk factor for PD is age. However, there is also notable attention given to the association between the disease and exposure to environmental pollutants such as industrial chemicals, pesticides, solvents and metals. Although evidence has been reported suggesting that smoking may lead to a decreased risk of developing PD, whether this causal relationship remains controversial (8). Furthermore, it has been observed that death rates attributed to PD in men are significantly higher than in women, across all age groups and in various countries (9).

Although the exact mechanisms underlying the pathogenesis of the disease are not fully understood, factors such as oxidative stress, mitochondrial dysfunction, neuronal excitotoxicity, and neuroinflammation have been reported to play a role in the development of PD (10). Additionally, similar to other neurodegenerative diseases, age-related biological dysfunctions, including telomere dysfunction, genomic instability, epigenetic changes, ubiquitin-proteasome and autophagy-lysosomal system impairments, have been proposed to accelerate neuronal death in PD (11). One distinctive cytological feature of PD is the Lewy body, which involves the misfolding of α-synuclein protein. Lewy bodies are believed to be influenced by various factors in their formation, and the accumulation of the same protein is observed in related disorders such as multiple system atrophy and Lewy body dementia, which are collectively referred to as "synucleinopathies" (12).

Understanding the pathogenesis of PD also involves a key strategy of exploring the underlying genetic basis. Approximately 5-10% of PD cases can be attributed to monogenic forms. For monogenic forms, genes such as synuclein alpha (SNCA), leucine-rich repeat kinase 2 (LRRK2), vacuolar protein sorting ortholog 35 (VPS35), parkin RBR E3 ubiquitin protein ligase (PRKN), PTEN-induced kinase 1 (PINK1), park-7 (DJ1), as well as a recently reported multitude of genes including coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2), LDL receptor related protein 10 (LRP10), transmembrane protein 230 (TMEM230), ubiquinol-cytochrome C reductase core protein 1 (UQCRC1) and vacuolar protein sorting 13 homolog C (VPS13C) are believed to play a role in the development of PD (13).

Currently, the treatment of PD is primarily symptomatic, focusing on slowing down the progression of degeneration, providing neuroprotection, and improving the patient's quality of life. Therefore, an integrative treatment strategy for PD is described, encompassing pharmacotherapy, rehabilitation, supportive care, and surgical options (14). Pharmacological treatment includes agents such as levodopa, carbidopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, amantadine and glial cell-derived neurotrophic factor (GDNF). Surgical treatment involves deep brain stimulation (DBS), while speech therapy, physical therapy, and cognitive-behavioral therapy (15). However, the medications used are not capable of reducing the damage caused by PD. Additionally, high doses of levodopa may lead to uncontrollable movements. Dopamine agonists are not as effective as levodopa in treating the symptoms of PD (16).

One of the primary barriers in the development of neuroprotective drugs is the incomplete understanding of specific molecular mechanisms that trigger neurodegeneration in PD. Although recent discoveries have provided information about molecular pathways likely to be crucial in the pathogenesis of PD, these advancements have not significantly contributed to comprehending other important aspects of the disease (17). For this purpose, experimental animal models are used to understand biological processes in diseases, conduct drug research for specific conditions, prevent drug toxicity, and comprehend drug effects (18). PD can be modeled using both in vitro and in vivo methods. Each experimental model has its advantages and limitations, which determine its suitability for a specific experiment. The harmful effect of chronic exposure to agricultural chemicals on neurons is well-known. Studies have reported that prolonged exposure to agricultural agents can lead to neurotoxicity and an increased risk of PD. These findings have allowed researchers to create various PD models using different neurotoxins (19, 20).

Among the commonly used neurotoxins to induce dopaminergic neurodegeneration, 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat, and rotenone are included. It is believed that all these toxins trigger the formation of reactive oxygen species (ROS). Despite exhibiting significant differences, including ease of use in animals, rotenone and MPTP are similar in their strong ability to inhibit complex I. Only MPTP is clearly associated with a type of human Parkinsonism and therefore, it is the most extensively studied model (17).

6-OHDA is used to induce monoaminergic neuronal toxicity. Injection of 6-OHDA into the striatum causes degeneration of axon terminals in the striatum and subsequently dopaminergic neurons in the substantia nigra (SN). Since 6-OHDA cannot cross the blood-brain barrier, it requires direct application to the SN using stereotaxic procedures. Due to the ease of toxin transmission in a relatively wide brain area, this application is generally preferred in rats rather than mice (21, 22). While 6-OHDA cannot mimic all aspects of the disease, it appears to be a replica of PD in humans. This animal model created with the neurotoxin has been reported to be useful in evaluating the effects of candidate drugs on motor skills (23).

MPTP is one of the neurotoxins that destroys dopaminergic neurons and has been commonly used to create animal models for PD research. Its high lipophilic property allows it to easily cross the blood-brain barrier and it is oxidized in glial cells through the use of MAO-B to form 1-methyl-4-phenylpyridinium ion (MPP+) (Figure 1). MPP+ enters dopaminergic neurons via the dopamine transporter (DAT) and induces apoptotic factors in the SN such as cytochrome C and caspases (24). While rodents are less sensitive to MPTP toxicity compared to primates, mice are frequently used as a model due to their ease of use, cost-effectiveness, and high repeatability. The rapid and transient neurodegeneration observed in animal models using MPTP poses a significant challenge in PD research. Considering the gradual emergence of MPTP-induced symptoms, alternative solutions can be considered (22). MPTP is commonly used in experimental animals

to create PD models due to its ability to induce tremor, rigidity, akinesia, and postural instability in non-human primates. Its cost-effectiveness, ease of use, and lower ethical concerns compared to other toxin-induced animal models make it a preferred choice. However, MPTP-induced Parkinsonism does not lead to the formation of typical Lewy bodies. Moreover, MPTP may not fully replicate the behavioral symptoms of PD in humans (25).

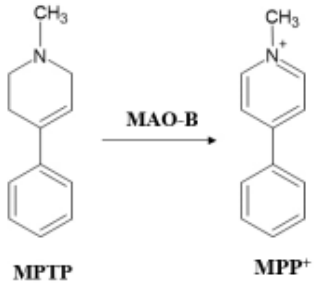

Figure 1. Oxidation of MPTP

Rotenone is a natural neurotoxin found in the roots of certain plants and is currently used as an insecticide, piscicide, and pesticide. It acts as a complex I inhibitor of mitochondrial NADH-dehydrogenase, blocking the use of oxygen during oxidative phosphorylation and driving the cell towards glycolysis and energy reserve depletion. Studies have shown that rotenone induces α-synuclein aggregation (26, 27). Due to its high mortality rate at high doses, the use of rotenone to create PD animal models poses a risk factor (26). However, because of its effects on various pathogenic pathways involved in dopaminergic cell death, such as oxidative stress, α-synuclein phosphorylation and aggregation, and Lewy pathology, as well as its lipophilic nature, rotenone is still used in PD animal models (28).

Paraquat is a pesticide with a chemical structure similar to MPP+ and causes dopaminergic neuron loss in animals. Despite its structural similarity to MPP+, it does not affect mitochondrial respiratory chain complexes like other neurotoxins that induce PD symptoms. As the PD phenotype develops chronically, using paraquat-induced models can be beneficial for examining early stages of the disease compared to other models (19). It enters dopaminergic neurons through DAT and exerts its toxic effects through high ROS levels, such as hydrogen peroxide, hydroxyl radicals, and superoxide radicals. Rodent models induced with paraquat are used to investigate Lewy body pathology in dopaminergic neurons. The use of paraquat-induced models has been reported to be advantageous for studying early stages of the disease due to the chronic development of the PD phenotype, compared to other models (21).

Reserpine is an alkaloid extracted from Rauwolfia serpentina and is used as an antihypertensive drug. By inhibiting the vesicular monoamine transporter 2 (VMAT2), it leads to a decrease in the levels of brain and peripheral monoamines, including noradrenaline and dopamine. Behaviorally, reserpine induces akinesia and hind limb rigidity in rats, rabbits, guinea pigs, cats, and monkeys (29). Although it mimics PD behaviors, it has been reported that reserpine is not a useful model compared to other neurotoxin and genetic models due to its inability to induce neurodegeneration and protein aggregation, lack of specificity for dopaminergic neurotransmission, and rapid decline in its levels in the organism after maintenance (30).

Haloperidol is an antipsychotic that acts primarily as a D2 receptor antagonist and is mainly used to control agitation and aggression in the acute phase of schizophrenia. Extrapyramidal side effects such as dystonia, rigidity, tremor, and akathisia can be observed with haloperidol administration (31). Catalepsy induced by systemic haloperidol administration in rodents is attributed to the blockade of D2 dopaminergic receptors in the nigrostriatal pathway, making it a useful animal model for studying motor disturbances observed in PD and screening potential antiParkinsonian compounds (32). However, it fails to trigger any other specific feature of PD and therefore its use is limited (29).

Genetic models of PD are created through transgenic expression of α-synuclein and LRRK2 or through knockout/knockdown of genes such as PARKIN, DJ-1, and PINK1, which play a role in PD pathology, to investigate the molecular mechanisms of genes involved in PD (19). These models generally do not encompass significant specific features of PD, including degeneration of dopaminergic neurons and motor symptoms (29). However, only a few of these models exhibit all the characteristics of the disease and are often quite different from the human condition. In support of this, most genetic models have been reported to fail in inducing the main pathological feature of PD, which is the loss of dopaminergic neurons (19). While PD is not considered a strongly genetic disease due to genetic variations accounting for only about 5% of all cases, these genetic models are thought to be useful for studying idiopathic PD (22).

In addition to the mentioned models, as a new approach for PD, in vitro studies using organoids derived from induced pluripotent stem cells (iPSCs) of PD patients can potentially reflect the progression of the disease in humans (19).

In this review, in vitro and in vivo PD models have been examined with their advantages and disadvantages, aiming to shed light on the mechanisms underlying dopaminergic neuron death and potential drug treatments, as well as exploring new therapeutic approaches.

2. Experimental PD Models

2.1. PD Model Using 6-Hydroxydopamine (6-OHDA)

6-OHDA is a compound that an analog of dopamine (Figure 2). The neurotoxic effects of 6-OHDA have been substantiated in studies (33, 34). It is taken up by presynaptic catecholaminergic neurons primarily through transporters such as DAT and noradrenaline membrane transporter (NAT). Once inside these neurons, it induces toxic effects by generating free radicals like superoxide, hydrogen peroxide, hydroxyl radicals, and initiating mitochondrial damage. As a consequence, it leads to cell death in catecholaminergic neurons (21).

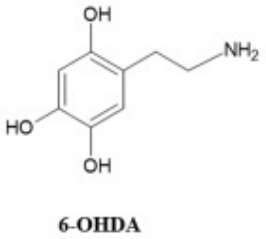

Figure 2. Chemical Structure of 6-OHDA

Although the intracellular toxicity mechanism in both peripheral and central catecholaminergic neurons is the same, the toxic effects of 6-OHDA show significant differences depending on the administration method, allowing its utilization in various studies. Unable to cross the blood-brain barrier, systemic administration of 6-OHDA damages neurons in the sympathetic nervous system, leading to a chemical sympathectomy effect and affecting the function of many autonomic organs. Due to this effect, it is frequently used to create a sympathectomy model in several investigations (35-37). Moreover, intracerebral applications of 6-OHDA, such as hippocampal infusion, result in spatial and memory impairments, while infusion to the medial preoptic area or cortex leads to disruptions in the sleep-wake cycle and attention abilities. Infusions into the striatum, SN,

and medial forebrain bundle (MFB) induce physiological and motor disorders resembling human PD (38, 39). For this reason, 6-OHDA was initially used in the first animal model of PD (22, 40). In in vivo models, Caenorhabditis elegans, non-human primates, and rodents can be used, but rodents are preferred more due to their mammalian nature and cost-effectiveness (23). Rats are often favored over mice because the small size of mice poses challenges in localizing stereotactic applications. Stereotactic applications are usually performed unilaterally to ensure each animal has a lesion-free hemisphere as its own control (41). Although bilateral applications induce bilateral motor deficits, severe bradykinesia, aphasia, and adipsia, these symptoms may not be well tolerated by the subjects. To create bilateral motor deficits, a study using repeated intraventricular administrations was conducted to increase the animals' tolerance by gradually transitioning symptoms from unilateral to bilateral (42).

6-OHDA is used to model both early and late stages of PD, depending on the injection site and concentration (43). The application of this toxin induces not only motor deficits but also non-motor PD symptoms such as cognitive impairments, depression/anxiety, pain, and sleep disturbances in a dose-dependent manner (44). For instance, low doses may lead to motor deficits, while high doses may cause depression (45). This helps researchers to focus on the specific aspect they want to study. Additionally, in vitro studies using various cell lines such as mouse dopaminergic neuronal cell line (MN9D), rat pheochromocytoma cell line (PC12), rat dopaminergic neural cell line (N27), human neuroblastoma cell line (SH-SY5Y), and lund human mesencephalic (LUHMES) are widely employed to investigate the potential intracellular pathways involved in 6-OHDA-induced PD, including oxygen radicals and mitochondrial damage, as well as to test potential therapeutic agents (46-49). However, the model created by 6-OHDA does not fully replicate the pathology of PD as seen in MPTP, as it does not affect the locus coeruleus, does not lead to the reported norepinephrine depletion in PD, and does not form Lewy bodies (21). On the other hand, the fact that 6-OHDA cannot cross the blood-brain barrier in the Parkinson's model necessitates intracerebral administration, leading to serious ethical concerns. However, these local applications are widely used because they allow precise targeting of the desired region with much lower doses, avoiding systemic side effects caused by the toxin (50).

2.2. PD Model Using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

MPTP is a synthetic analogue of the narcotic agent meperidine (51). Due to its ability to induce symptoms similar to PD and the positive response of PD patients with MPTP usage to levodopa treatment, it has been defined as a ''Parkinson-related substance'' (52). MPTP possesses a lipophilic structure that allows it to easily cross the blood-brain barrier and exhibit specific toxicity to dopaminergic neurons (40). Following systemic administration, MPTP is oxidized by MAO-B in glial cells to form a toxic metabolite called MPP+, which cannot cross the blood-brain barrier but can be easily taken up by dopaminergic neurons via norepinephrine and dopamine transporters due to its structural similarity to dopamine. This metabolite accumulates in the synaptic vesicles and mitochondria of dopaminergic and noradrenergic neurons through DAT and NAT. It enters the vesicles via VMAT2 and reduces the entry of dopamine into the vesicles, leading to its degradation in the cytoplasm and an increase in dopamine-associated oxidative stress. MPP+ further inhibits the uptake of dopamine into synaptic vesicles and its release, resulting in a decrease in dopamine levels. In mitochondria, it binds to NADH dehydrogenase and inhibits complex 1, causing a decrease in ATP production and accumulation of reactive oxygen species. Consequently, pathways such as the mitochondrial apoptotic pathway, inflammatory pathway, and induction of oxidative stress in the locus coeruleus, striatum, and SNpc regions lead to cell damage in dopaminergic and noradrenergic neurons (41, 53). Moreover, MPTP can mimic other known biochemical features of PD, such as decreased levels of striatal dopamine and tyrosine hydroxylase, increased levels of both striatal precursor proteins preproenkephalin and acetylcholine (ACh), elevated extracellular glutamate levels, and decreased glutathione (GSH) in the basal ganglia (54). In vitro studies using various cell lines, including MN9D, PC12, N27, SH-SY5Y, and LUHMES, utilize MPTP to induce PD models and shed light on potential intracellular pathways associated with PD pathology and test therapeutic agents (55-58).

In vivo models induced by MPTP allow the development of both bilateral motor and non-motor symptoms of PD, but there are conflicting results regarding whether it induces memory impairment (59-61). In MPTP modeling, repeated intraperitoneal injections are commonly used. Some studies argue that systemic injections fail to induce the formation of Lewy body-like cytoplasmic inclusions, while others suggest that high doses of MPTP do lead to the formation of α-synuclein, the main component of Lewy bodies (41, 62).

While zebrafish, Caenorhabditis elegans, and non-human primates can be used in MPTP-induced PD models, rodents are more commonly used due to their mammalian nature and cost-effectiveness. However, despite MPTP fails to induce significant dopaminergic neurodegeneration in rats, rats are preferred over mice for modeling (41, 63). Although MPTP can be easily administered intraperitoneally, mice are less sensitive to MPTP compared to primates, and high doses are required to induce α-synuclein formation, which increases the risk of mortality and toxicity (54).

The most significant disadvantage of this model is the rarity of Lewy body formation and the difficulty in replicating the behavioral features observed in PD (19, 25). However, due to its cost-effectiveness, ease of use, and fewer ethical concerns, it is still widely employed in the generation of PD models (52).

2.3. PD Model Using Reserpine

Reserpine is one of the first anti-hypertensive agents developed for human use. It irreversibly binds to VMAT1 and VMAT2 in adrenergic vesicles in neurons, inhibiting the storage of monoamines within the vesicles. This leads to the breakdown of monoamines in the cytoplasm, increasing oxidative stress and causing cell damage (64-66). Chronic clinical use of reserpine has been observed to cause drowsiness, depression, and motor disturbances in patients, leading to its use in modeling motor and non-motor disorders in rodents (30). In in vivo studies, reserpine administration has been shown to rapidly reduce extracellular dopamine concentration in the SNpc and striatum to undetectable levels. Animal studies have reported that reserpine induces motor disorders such as akinesia, hypokinesia, catalepsy, limb rigidity, and oral tremor, as well as anxiety and depressive disorders (30, 67). Although some studies suggest that reserpine could be used in a PD dementia model, others claim that it does not lead to memory impairment (68, 69). In vivo models are conducted in rodents, cats, monkeys, Caenorhabditis elegans, and even Drosophila through repeated subcutaneous injections or oral administration (70, 71). Many studies have shown that reserpine induces □-synuclein formation in in vivo and in vitro models (64, 72, 73). Despite studies linking the induced pathology to movement disorders, the molecular etiology remains uncertain (67). Therefore, numerous in vitro studies are being conducted to elucidate the intracellular pathways responsible for these pathologies and to test potential therapeutic agents (64, 74).

Indeed, while reserpine can successfully induce motor and sensory disorders similar to the main biochemical components

of PD, it is no longer considered a popular choice as a PD model due to its temporary effects and lack of sufficient selectivity for dopamine (29).

2.4. PD Model Using Haloperidol

Haloperidol is an antipsychotic that acts as a dopamine type 2 receptor antagonist and is commonly used in the treatment of acute and chronic psychoses, as well as various neuropsychiatric disorders (75). Antipsychotics, including haloperidol, are the most common cause of drug-induced Parkinsonism, leading to motor function disorders such as tardive dyskinesia, tardive dystonia, akathisia, myoclonus, and tremor, especially after their use by patients. Therefore, many patients using antipsychotics have been misdiagnosed with PD and treated with antiParkinsonian drugs (76). Haloperidol usage can also lead to extrapyramidal side effects such as akinesia and rigidity. These observed motor disturbances have led to the use of haloperidol to create animal models for studying and screening potential antiParkinsonian compounds. In in vivo studies, haloperidol is commonly administered intraperitoneally, but subcutaneous and intramuscular routes are also used to create the model. Systemic administration of haloperidol in rodents blocks D2 dopaminergic receptors in the nigrostriatal pathway, inducing catalepsy characterized by bradykinesia and rigidity, which are important symptoms of PD (32, 77, 78). However, the use of haloperidol to create in vivo models is limited as it fails to trigger any other specific features of PD apart from catalepsy and rigidity (29). Additionally, our literature search did not find any studies related to in vitro investigations involving haloperidol.

2.5. PD Model Using Rotenon

In PD pathophysiology, chemicals, particularly pesticides, are believed to play a significant role. However, the examination of toxicological and epidemiological studies related to pesticides is inconclusive in establishing a causal relationship with any specific pesticide (79). A meta-analysis of studies on PD and environmental factors by Priyadarshi et al. noted that due to the presence of uncertain data and heterogeneity among the reported studies, a significant dose-response relationship could not be established (80).

Rotenone is a natural insecticide and pesticide extracted from the roots of plants belonging to the Lonchocarpus and Derris genera. Due to its lipophilic nature, it easily crosses all biological barriers, including the blood-brain barrier. The lipophilic property of rotenone allows for its systematic administration, making it technically less challenging compared to models that require stereotactic injection into the brain (81). Rotenone is classified as a ''moderately hazardous'' pesticide by the WHO. It is widely used to model PD in animals through its inhibition of mitochondrial complex I (82). Rotenone was first used in 1985 by Heikkila et al. for modeling PD. Another attempt to model PD using rotenone was made in 1997 by Ferrante et al. who administered 18 mg/kg/day intravenously to rats (28). Since 2000, various species such as rats, mice, fish, and Drosophila have been used in in vivo PD models using rotenone (83).

Studies have shown that chronic oral administration of rotenone induces dopaminergic neurodegeneration and motor impairments, leading to behavioral symptoms of PD in C57BL/6 mice. At high concentrations, rotenone affects peroxisome morphology and distribution in COS-7 cells, which can influence the peroxisome-mitochondria redox relationship and contribute to PD pathogenesis. Similarly, rotenone has been demonstrated to cause degeneration in human dopaminergic SH-SY5Y cells through the PI3K/Akt/GSK-3β/CREB signaling pathway by reducing phospho-CREB levels. Other studies have shown that rotenone application in SH-SY5Y cells reduces PARKIN expression, increases PINK1 expression, and leads to mitochondrial dysfunction, oxidative stress, and cell death. Rotenone-induced neurotoxicity can also result from microglial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-derived superoxide release. Additionally, rotenone activates calcium/calmodulin-dependent protein kinase II, increasing intracellular free Ca2+ ions and inducing neuronal apoptosis. In another study, rotenone exposure was shown to cause dysbiosis of the gut microbiota, which may play a significant role in the development of PD. Advantages of using rotenone in PD modeling include its ability to produce complex systemic inhibition, unlike MPTP, which only inhibits catecholaminergic neurons' complex I. Even at low doses, rotenone induces dopaminergic neurodegeneration, and compared to other animal models, it more prominently produces and accumulates α-synuclein. However, some drawbacks of using rotenone in PD modeling include the lack of well-documented cases of rotenone-induced PD in humans. Rotenone is less specific to dopaminergic neurons compared to the MPTP-induced model, and the motor impairment induced by rotenone is not highly specific to nigrostriatal neurodegeneration (86).

2.6. PD Model Using Paraquat

Paraquat is widely used as an herbicide in many parts of the world. Human exposure to paraquat occurs through inhalation and dermal absorption (87). In experimental models, paraquat, which induces oxidative stress, and rotenone, which inhibits mitochondrial complex I, lead to the loss of nigral dopaminergic neurons and behavior disorders associated with human PD. Since the 1980s, an association between PD and various pesticides, including paraquat, has been recorded (88). However, although there is a possibility of a link between PD and pesticides, many studies have not definitively linked any specific pesticide to PD in humans (89, 90). The results of previous studies associating paraquat with PD are also controversial (91). Compared to other studies on paraquat use in PD, a study by Mandel et al. supports the findings of Tanner et al. it highlights the importance of focusing on pesticides in studies with a well-defined population exposed to pesticides, considering complex 1 inhibition or oxidative stress (79).

Paraquat is a pesticide belonging to the family of 1,1'-dimethyl-4,4'-bipyridil (Figure 3). It is structurally similar to MPTP, and this resemblance is the reason for why it is associated with PD. In in vivo rodent models of PD, paraquat has been shown to cause dopaminergic neuron loss. Prolonged exposure to paraquat reduces dopamine levels and/or increases the accumulation of α-synuclein in the brain. However, the mechanisms by which paraquat crosses the blood-brain barrier and its detrimental effects on dopaminergic neurons and astrocytes are not yet fully understood (92).

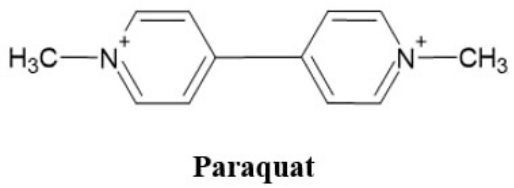

Figure 3. Chemical Structure of Paraquat

The meta-analysis study, which includes twelve reviews based on paraquat, does not conclude that paraquat causes PD (92-94). However, many authors in recent publications have proposed an association between paraquat exposure and PD. Nevertheless, updating these systematic reviews and meta-analyses relies on new studies exploring the potential relationship between paraquat and PD (94). Experimental evidence suggests that paraquat can cause significant damage to mitochondria in a dose-dependent manner, leading to oxidative stress, cytochrome C release, and caspase-9 activation, ultimately leading to

mitophagy and apoptosis (95). Similarly, it has been reported that paraquat produces radicals, including H2O2, O2, and HO-, using complex III of the electron transport chain in rat brains. In human SH-SY5Y neuroblastoma cells, paraquat induces oxidative stress through ROS production, leading to apoptosis and DNA fragmentation by increasing caspase-3 activation. Paraquat enters dopaminergic neurons via DAT and also enters astrocytes through organic cation transporter-3 (OCT3). Paraquat exposure has been associated with variable changes in mRNA levels of DAT and dopamine receptor D3 (DRD3), which are two components of the dopaminergic signaling pathway (84, 85). Paraquat exhibits neurotoxic effects, primarily showing synergistic and potent degeneration of dopaminergic neurons in the basal ganglia. Thus, this toxin-induced upregulation and accumulation of α-synuclein significantly contribute to the PD model. Considering these advantages of paraquat, this modeling provides a valuable contribution to clearly express the progression of PD. However, the disadvantages include the lack of motor impairment observed in the PD model and its limitation mainly to Lewy body pathology (86).

2.7. Genetic Models

It is believed that PD is a combination of genetic and environmental risk factors, making genetics play a significant role in PD pathogenesis (96). Drosophila melanogaster is a powerful organism for modeling human neurodegenerative diseases. Approximately 75% of all human disease genes have homologs in Drosophila. Through various studies conducted in the last 15 years, gene mutations associated with PD have been identified. These mutations can be mainly categorized into autosomal dominant and autosomal recessive mutations. The autosomal dominant mutations include SNCA, LRRK2 (PARK8), HTRA2 (PARK13), and others. On the other hand, the autosomal recessive mutations include PARKIN, DJ-1, PINK1, and others (as shown in the Table 1). In a recent study, it has been reported that mitochondrial dysfunction and oxidative stress play a significant role in PD pathogenesis, and genes like PINK1, PARKIN, and DJ-1 have important roles in mitochondrial function and oxidative stress resistance (97). Therefore, these genes associated with PD are of great importance in the pathophysiology of the disease.

SNCA is the first gene identified in familial PD. The first transgenic mouse model with α-synuclein was generated by Masliah et al. however, this initial transgenic mouse model could not fully replicate the human pathology (98, 99). Subsequently, more α-synuclein models were produced through expression via the tyrosine hydroxylase (TH) promoter. On the other hand, a model containing a double mutant (A30P/A53T) showed a phenotype of motor deficits and neuronal aggregation due to significant neurite dystrophy (100). While these models are useful in shedding light on the neurodegeneration associated with α-synuclein, their clinical relevance to PD can be questioned. LRRK2, specifically the G2019S and R1441C/G mutations, are the most common two LRRK2 mutations. Most LRRK2 transgenic animal models have failed to explain the major distinguishing features of PD. In one published study, BAC-LRRK2-R1441G transgenic mice showed motor impairments and axonal pathology in the striatum, but no significant dopamine cell loss or α-synuclein aggregations were observed (101). Similarly, other LRRK2 models have been created using viral vectors such as herpes simplex virus (HSV) and adenoviral vectors. As a result, HSV-LRRK2-G2019 infection in the mouse striatum was found to induce approximately 50% degeneration of dopaminergic neurons (102). PARKIN, associated with about 50% of familial and 20% of idiopathic cases of early-onset PD, is one of the most common autosomal recessive mutations. PARKIN is an E3 ubiquitin ligase and plays a significant role in proteasomal degradation. Although numerous PARKIN knockout models have been produced, none have successfully summarized the typical PD phenotype. However, in primary midbrain cultures prepared from PARKIN knockout lines, increased sensitivity to rotenone was demonstrated, while overexpression of PARKIN prevented dopaminergic neurodegeneration in rats treated with 6-OHDA and in mice treated with MPTP. From these screenings, it is concluded that the PARKIN model is not yet an ideal animal model for PD, but PARKIN remains a potential therapeutic target. DJ-1 is thought to be an antioxidant protein that is beneficial in protecting dopamine neurons from oxidative stress. It is believed that DJ-1 deficiency can trigger motor dysfunction even in the absence of nigral neurodegeneration. Additionally, DJ-1 has been shown to play a neuroprotective role in our neural system. Therefore, DJ-1 knockout mice could be a valuable tool for investigating the molecular mechanism of PD. PINK1 is a neuroprotective kinase mainly found in mitochondria and cytosolic compartments, and it plays a role in neuronal differentiation. In a study conducted in SH-SY5Y cells, increased PINK1 expression was associated with neurite growth and induction of dendrite length in dopaminergic neurons. Thus, it was noticed that PINK1 and PARKIN mutants have similar phenotypes. Although studies have been conducted on PINK1 knockout mouse models, there is no clear PD pathology observed in the brain. However, the studies have shown that PINK1 knockout mice are sensitive to oxidative stress and ROS production (6, 19, 86, 103).

Table 1. Molecular Models Associated with PD [97, 108].

PD gene/locus	Mutation	Phenotypic Expression in Mammals/ Mice	Trusted PD Gene
SNCA /PARK	Missense or multiplication	Expression of Human α-Syn (A53T, A30P): ↑ Accumulation of α-synuclein, ND and leading to cell death. Progressive motor disorder accompanied by accumulation of α synuclein in the soma and neurite	+++
PARK /PARK2	Missense or loss of function	Motor deficit, nigrostriatal degeneration, α-synuclein accumulation	+++
UCH-L1/PARK5	Missense	Rotenone induced mouse models: ↑ α-synuclein aggregation	+
DJ-1 /PARK7	Missense	Loss of DA neurons in SN of brain	+++
LRRK2 /PARK8	Missense	Progressive motor deficit with immobility by 10-12 months	+++
ATP13A2 /PARK9	Missense or loss of function	Impairment in lysosomal degradation, α-synuclein accumulation and neurotoxicity	+++
GIGYF2/PARK11	Missense	Exhibits motor dysfunction by 12-15 months	+
HTRA2/PARK13	Missense	☒Climbing ability, movement disorders, and tremor	+
PLA2G6/PARK14	Missense or loss of function	Loss of DA neurons in SN	+++
FBOX7/PARK15	Missense	↓ Proteasome activities and early-onset motor deficit	+++
VPS35/PARK17	Missense	Mitochondrial fusion and cellular respiration function impairments and neuronal loss	+++
EIG4G1/PARK18	Missense	Impairment in oxidative stress resistance	+
DNAJC6/PARK19	Missense or loss of function	Early postnatal mortalities, and weight loss of surviving pups	++
SYNJ1/PARK20	Missense or loss of function	Progressive PD-like behavioral alterations and DA neurodegeneration	++

Symbols indicate; +++: Very high, ++: High, and +: Low.

Genetic PD animal models are mostly initially generated in mice due to their practicality and suitability compared to other models. However, most genetic mouse models of PD fail to achieve damage to over 50% of nigral dopaminergic neurons (104). Many behavioral, physiological, and biochemical differences are known between mice and rats. Additionally, there are significant differences in their genetic sequence and expression. For example, rats have lower LRRK2 expression in the SN compared to mice (105). As a result of reviews conducted for PD, 90 independent common genetic risk factors and associated phenotypes have been identified, which could be valuable qualities for future PD biomarker studies (106).

Various software and studies are available in neurodegenerative diseases and genome-wide association studies. Methylation Genome-wide Association Studies (MWAS) methods have emerged to investigate the impact of differentially methylated positions (DMPs) on complex diseases. Recently, the OmicS-based Complex Trait Analysis (OSCA) software has been developed, and both the Mixed linear model-based omics association (MOA) and mixed-linear model method (MOMENT) software are used to test the relationship between each DNA methylation region and traits (107).

3. Conclusion

It is important to acknowledge that no single animal model perfectly replicates all aspects of human PD. In order to carry out the experimental processes successfully, researchers should choose the experimental PD model to be used in accordance with the study design. In candidate drug molecule or active ingredient research, an experimental PD model should be selected for the symptoms or mechanism for which the drug is expected to be indicated. Each model has its limitations, and findings from animal studies must be carefully interpreted and validated in human clinical trials. Nonetheless, animal models remain invaluable tools in the quest to unravel the complexities of PD and develop effective treatments for this challenging condition.

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