ISSN : 2319-2607 (Print); 2583-0856 (Online) IISUniv.J.Sc.Tech. Vol.12(1), 1-13 (2023)
REVIEW ARTICLE

MPTP-Induced Parkinson's Disease Mice Model: Insights into Pathology, Mechanisms, and Therapeutic Interventions

Kanika Bhardwaj, Neelu Kanwar Rajawat *
Department of Zoology, IIS (Deemed to be University), Jaipur, Rajasthan - 302020 India.

Abstract

Parkinson's disease (PD) is a debilitating neurodegenerative disease characterized by motor impairments such as tremor, bradykinesia, akinesia, rigor, postural unstableness, and microphagia. The development of animal models has been fundamental to studying sustaining mechanisms and assessing possible restorative interventions. The 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP)-induced mouse model of Parkinson`s disease has arisen as a precious implement for concluding the pathophysiology of the disorder. This paper provides a detailed review of the MPTP-induced Parkinson`s Disease mouse model, entailing its methodology, behavioral phenotypes, neuropathological changes, and molecular mechanisms. Moreover, it explores the utility of this model in testing new medicinal avenues and highlights its limitations. Therefore, the MPTP-induced PD mice model remains essential for improving our understanding of the pathophysiology of PD and for developing novel treatments targeted at reducing the crippling symptoms and eventually curing Parkinson's disease.

Keywords: Behavior, MPTP, Pathophysiology, Parkinson`s disease, Rodents

Introduction

Millions of people globally have been affected by the complex and devastating neurological condition known as Parkinson's disease. Parkinson's disease, which is characterized by the gradual degeneration of some nerve cells in the brain, has been named after Dr. James Parkinson, who first wrote about the ailment in his book "An Essay on the Shaking Palsy" published in 1817 (Parkinson, 2002). Dopamine, a neurotransmitter that is produced by these cells and referred to as dopaminergic neurons, is vital for regulating movement and coordination.

Clinical Features

Parkinson's disease (PD) is a neurodegenerative complication that initially affects the motor complex (Yarnall *et al.,* 2012). It's portrayed by a progressive loss of dopamine-producing cells in the substantia nigra area of the brain. While the accurate reason for Parkinson's disease isn't completely reasoned, both inheritable and environmental factors are credited to play a part in its progression (Fife, 2016). The clinical features of Parkinson's disease can differ among individualities, but the upcoming are some of the most usual signs and symptoms:

Tremor: One of the hallmark symptoms of Parkinson's disease is a rep temblor, generally starting in one hand and frequently described as a" capsule-rolling" temblor. Temblors can likewise happen in the legs, chin, or other regions of the body (Sveinbjornsdottir, 2016).

Bradykinesia: This refers to slowness of motion and is another vital characteristic of Parkinson's disease. It can indicate hardship in beginning movements, distracted facial expression (mask-alike face), and diminished winking (Sveinbjornsdottir, 2016).

Rigor: Stiffness or rigidness in the muscles is frequent in Parkinson's disease. It can route to muscle throes, limited range of movement, and a feeling of muscle solidity.

Postural unstableness: As Parkinson's disease progresses, individualities may endure problems with equilibrium and collaboration. This can accelerate the threat of cascade and frame walking or turning difficult (Sveinbjornsdottir, 2016).

Akinesia: This refers to a deduction or misplacement of voluntary muscle movements. It can evince a general sense of reduced movement or a feeling of being" firmed " in place (Sveinbjornsdottir, 2016).

Micrographia: Various people with Parkinson's disease evolve small, confined handwriting, known as micrographia (Letanneux *et al.,* 2014).

Speech and swallowing asperities: Parkinson's disease can affect the muscles affected in speech work and

*Corresponding Author Email: neelukanwar.rajawat@iisuniv.ac.in

swallowing, routing to fluctuations in voice grade, downgraded volume, harmonized speech, and rigors ingesting (Sveinbjornsdottir, 2016).

Non-motor symptoms: In extension to motor symptoms, Parkinson's disease can also offer a range of non-motor symptoms. These may involve depression, anxiety, sleep disturbances, constipation, loss of sense of smell (anosmia), cognitive changes, and autonomic dysfunction (similar to changes in blood pressure and bladder control) (Pfeiffer, 2016).

It's important to note that the present and sequence of Parkinson's disease can vary extensively from person to person. Some individuals may witness a slower complication progression and moderate symptoms, while others may progress more fleetly and have too severe symptoms. It's recommended to consult with a healthcare professional for an accurate opinion and proper guidance on parkinson's condition.

Pathology

The pathology of Parkinson's disease (PD) involves the progressive degeneration of specific brain regions and the cumulation of aberrant protein oligomers. The initial pathological features of Parkinson's disease involve:

Loss of Dopamine: Producing Neurons Parkinson's disease is portrayed by the particular loss of dopaminergic neurons in the substantia nigra, a region of the brain involved in movement control. These neurons produce dopamine, a neurotransmitter that plays a vital part in coordinating movement (Damier *et al.,* 1999).

Lewy Bodies: Lewy bodies are abnormal protein oligomers that begin in the brain of individuals with Parkinson's disease. They're initially composed of a protein called alpha-synuclein. These protein clumps accumulate within the remaining neurons in the substantia nigra and other brain regions associated with Parkinson's disease (Wakabayashi *et al.,* 2013).

Neuroinflammation: Inflammation in the brain, known as neuroinflammation, is believed to contribute to the progression of Parkinson's disease. Triggered resistant cells, like microglia, discharge inflammatory intermediaries that can invoke affliction to neurons and complicate the neuro degenerative process (Hirsch *et al.,* 2012).

Loss of Other Neurotransmitters: Although dopamine reduction is the hallmark trait of Parkinson's disease, the degeneration of other neurotransmitter systems also occurs. These involve the noradrenergic, serotonergic, and cholinergic complexes, which can contribute to non-motor symptoms observed in PD (Muñoz *et al.,* 2020).

Disturbance of Brain Circuits: The loss of dopamine-producing neurons and other neurotransmitter imbalances disrupt the intricate network of brain circuits involved in motor control and cooperation. The basal ganglia is a group of structures responsible for regulating movement, is particularly affected. This disturbance leads to the characteristic motor symptoms seen in Parkinson's disease, alike bradykinesia, temblor, and rigorousness (Lewis *et al.,* 2003).

While the exact cause of Parkinson's disease is still not completely understood, several factors have been intertwined, including inherited mutations, environmental toxic, oxidative stress, mitochondrial dysfunction, and damaged protein degeneration pathways. These factors contribute to the cumulation of alpha-synuclein and the later degeneration of dopaminergic neurons.

Challenges Associated with PD

Parkinson's disease (PD) poses several challenges for individuals affected by the condition, as well as for their families, caregivers, and healthcare systems. Some of the main challenges associated with Parkinson's disease include:

Motor Symptoms: The motor symptoms of Parkinson's disease, like temblors, bradykinesia (slowness of movement), rigor, and postural shakiness, can significantly impact a being's capability to perform diurnal conditioning. Simple tasks like dressing, eating, and bathing may get challenging, leading to a loss of independence and a downscaled quality of life (Moustafa *et al.,* 2016).

Non-Motor Symptoms: Parkinson's disease isn't exclusively limited to motor symptoms. Non-motor symptoms, like depression, anxiety, cognitive changes, sleep disturbances, constipation, and autonomic dysfunction, can be evenly devitalizing and impact multiple aspects of a person's well-being. These symptoms may not admit the same status of attention as the motor symptoms but can significantly affect the overall quality of life for beings with PD (Pfeiffer, 2016).

Mutating Symptoms: Parkinson's disease is a progressive condition, and its symptoms can change throughout the day. Some beings experience" on" eras with better mobility and symptom control, while others have" off" eras with worsening symptoms. These changes can make it onerous to plan diurnal conditioning, maintain social engagements, and stick to a compatible cure schedule (McNeill *et al.,* 2012).

Medication Management: Parkinson's disease is generally managed with drugs that help replenish dopamine situations or enhance its effectiveness in the brain. Yet, chancing the right drug regime and managing the timing and dose can be complex. Moreover, long-term use of certain drugs can lead to side effects or complications, needing ongoing monitoring and adaptations by healthcare professionals (Manning *et al.*, 2012).

Emotional and mental Impact: Parkinson's disease can have a significant emotional and mental impact on individuals and their families. Managing a confirmed progressive condition, dealing with changes in physical capacities, and facing doubt about the future can lead to sensibilities of anxiety, depression, frustration, and solitude. Support from healthcare professionals, support groups, and psychological health services are pivotal in addressing these challenges (Rodrigues *et al.*, 2006).

Caregiver Burden: Parkinson's disease frequently requires substantial caregiving support as the condition progresses. Caregivers may need help with diurnal conditioning, drug administration, mobility support, and emotional support. The physical and emotional demands of caregiving can be overpowering and may impact the caregiver's own well-being and quality of life (Martínez Martín *et al.*, 2007).

Access to Specialized Care: Parkinson's disease management frequently requires a multidisciplinary approach involving neurologists, movement condition specialists, physical and occupational therapists, speech-language pathologists, and other healthcare professionals. Yet, access to technical care and comprehensive Parkinson's disease centers can be limited, particularly in pastoral or underserved areas, leading to a contrast in healthcare delivery (Pearson *et al.*, 2023).

Research and Treatment Gaps: Despite significant advancements in understanding Parkinson's disease, there's still important to learn about its causes, progression, and implicit treatments. Exploration gaps in areas like disorder alteration, non-motor symptom care, and substantiated approaches to care. Bridging these gaps and rephrasing scientific discoveries into practical treatments remains a challenge.

Addressing the challenges associated with Parkinson's disease requires a comprehensive approach involving medical interventions, recuperation curatives, social support, and ongoing research. Works to enhance access to care, enhance caregiver support, and advance scientific understanding are essential in amending the lives of individuals living with Parkinson's disease.

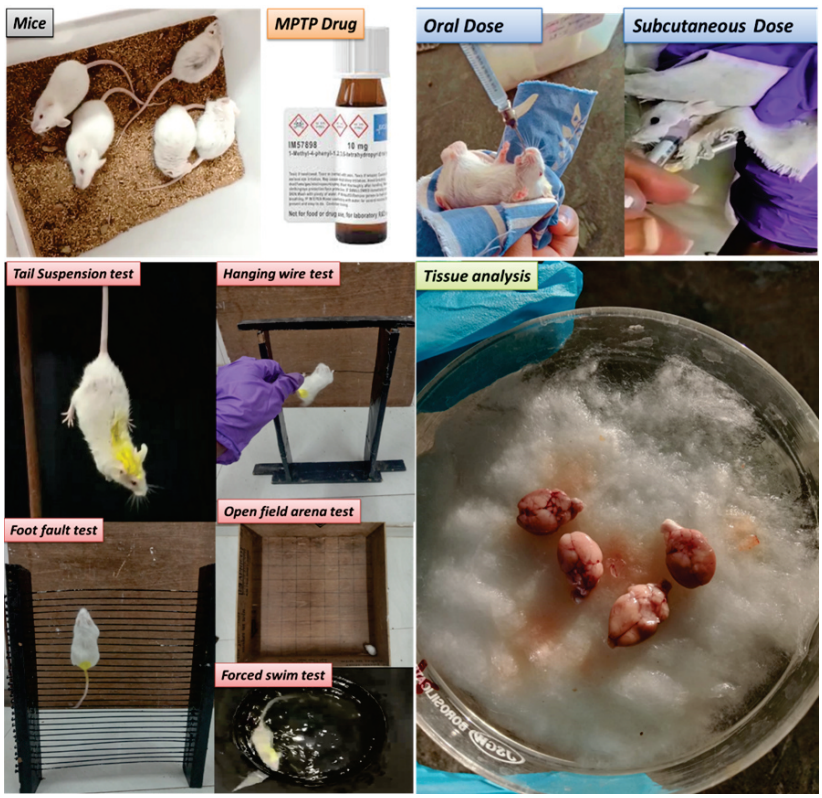

Fig 1. How to induce Parkinson disease in animal model using MPTP?

MPTP-Induced Parkinson's Disease Mice Model

Methodology to Induce Parkinson`s Disease via MPTP

The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model is extensively used to induce Parkinson's disease- similar symptoms in mice. MPTP is a neurotoxin that especially targets and damages dopaminergic neurons in the brain, leading to motor impairments like those observed in human Parkinson's disease. The methodology for prevailing Parkinson's disease using MPTP in mice (Jackson-Lewis and Przedborski, 2007) involves several ways (Fig 1.):

Model Selection: Mice of the applicable strain and age are named for the study. Generally used strains include C57BL/ 6 and BALB/ c mice.

MPTP Preparation: MPTP is generally prepared as a result of saline or other applicable vehicle. It's important to handle MPTP with caution as it's poisonous. Investigators should follow safety guidelines and take necessary preventives while handling and preparing MPTP (Jackson-Lewis and Przedborski, 2007).

Administration Route: MPTP can be administered to mice via different routes, including systemic injection, intraperitoneal (IP) injection, subcutaneous (SC) injection, or intravenous (IV) injection. The specific route depends on the study design and aims (Jackson-Lewis and Przedborski, 2007).

Dosing and Treatment Administration: The dosing and treatment regime of MPTP depend on the desired effect and the experimental design. Investigators generally use multiple injections of MPTP over successive days to induce progressive and sustained dopaminergic neurodegeneration (Jackson-Lewis and Przedborski, 2007).

Stereotactic Injection **(Optional)*:*** In some studies, MPTP may be administered directly into specific brain regions using stereotactic injection ways. This allows for precise targeting of dopaminergic areas, like the substantia nigra or striatum (Jackson-Lewis and Przedborski, 2007).

Observation and Behavioral Assessments: After MPTP administration, mice are nearly observed for the development of Parkinson's disease- similar symptoms. Behavioral assessments are performed to assess motor dearth, like bradykinesia, temblor, and distorted coordination. Common tests include the pole test, rotarod test, open field test, and gait analysis (Luchtman *et al.,* 2009).

Tissue Analysis: At the end of the study, mice are euthanized, and their brain tissue is collected for more analysis. This may involve histological examination to assess dopaminergic neuron loss, neuroinflammation, and the presence of protein oligomers, like Lewy bodies or alpha-synuclein (Jackson-Lewis and Przedborski, 2007).

It's important to note that the MPTP-induced model in mice represents an acute model of Parkinson's disease and doesn't completely brief the progressive nature of the complication in humans. Yet, it serves as a precious tool for studying the earliest neurodegenerative processes and assessing implicit remedial interventions. Investigators can stick to ethical guidelines and institutional regulations while conducting trials involving creatures.

Behavioral Assessment

Behavioral phenotypes and motor assessments play a vital purpose in studying Parkinson's disease (PD) in animal models. One generally utilized model to induce PD-similar symptoms in mice is the 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP) model. MPTP is a neurotoxin that widely damages dopaminergic neurons in the substantia nigra, leading to motor impairments analogous to those observed in PD cases. In this ambient, experimenters lean on behavioral phenotypes and motor assessments to estimate the effectiveness of implicit remedial interventions and consolidate our understanding of the disorder (Meredith and Rademacher, (2011). Behavioral phenotypes pertain to observable traits or characteristics displayed by animals that give perception into their neurological and physiological states. In the ambient PD examination using the MPTP-induced mouse model, behavioral phenotypes are used to assess varied motor deaths and non-motor symptoms associated with the disorder. These assessments generally involve a battery of tests that can estimate locomotor condition, balance, coordination, gait, and other relative behaviors (Brooks and Dunnett, 2009).

Pole climbing Test: In this test assessment of balance, motor coordination, and bradykinesia (slowed movement) occurred. Usually, a vertical pole is positioned within the home cage or another enclosed area. The mouse is initially trained to slide down the pole, and the time it takes for it to turn and drop to the ground is timed. It is timed how long it takes the mouse to go down the pole, and any obstacles or hesitancy in the movement are noted. Turning difficulties, prolonged descent times, and increased hesitations are common signs of motor coordination impairments, such as bradykinesia (Taylor *et al.,* 2010).

Open Field Test : One of the most used behavioral tests is the open-field test, which measures locomotor conditions and exploratory actions. Mice are placed in an open arena, and their movement is watched and recorded. In the MPTP model, PD mice frequently show reduced locomotor condition and depleted exploration compared to healthy control mice. These changes reflect the motor impairments observed in PD cases, similar to bradykinesia (slowness of movement) and akinesia (absence of voluntary movement) (Rodriguez-Oroz *et al.,* 2009).

Rotarod Test: Another important assessment is the rotarod test, which evaluates motor activity and balance. In this test, mice are placed on a rotating rod, and the time they can maintain their balance is recorded. PD mice induced by MPTP generally show a dropped dormancy to fall compared to control mice, indicating compromised motor activity and balance (Meredith and Kang, 2006).

Gait Analysis: Gait analysis is another precious tool for assessing motor deaths in PD mouse models. It involves the dimension of varied parameters related to the animal's walking pattern, like as stride length, base of support, and gait speed. PD mice frequently display changes in these parameters, including reduced stride length and irregular gait patterns, mimicking the gait abnormalities seen in PD cases (Taylor *et al.,* 2010).

In addition to these motor assessments, experimenters may also delve into non- motor symptoms associated with PD, like anxiety, depression, and cognitive impairments. These symptoms can be estimated through varied behavioral paradigms, including the elevated plus maze, forced swim test, and Morris water maze, among others (Zohar *et al.,* 2011).

Overall, behavioral phenotypes and motor assessments in the MPTP-induced PD mouse model are critical for understanding the pathophysiology of PD, assessing implicit remedial interventions, and developing new treatment strategies. These assessments give a high perception of the disorder mechanisms and help bridge the gap between preclinical exploration and clinical employment for Parkinson's disease.

Neuropathological Changes in Parkinson's Disease

Dopaminergic Changes

The MPTP-induced Parkinson's disease (PD) mouse model has been extensively used to study the neuropathological changes associated with the disorder. MPTP is a neurotoxin that widely damages dopaminergic neurons in the substantia nigra, leading to motor dearths and other PD- such symptoms. By prevailing these neurodegenerative changes, experimenters can examine the underpinning neuropathology and research implicit remedial interventions. Further some of the vital neuropathological changes observed in the MPTP-induced PD mouse model:

Dopaminergic neuron loss: One of the hallmark features of PD is the progressive loss of dopaminergic neurons in the substantia nigra. In the MPTP model, MPTP administration leads to the destruction of these neurons, mimicking the dopaminergic cell loss observed in human PD. This loss of dopaminergic neurons results in a reduction of dopamine situations in the striatum, contributing to motor impairments (Damier *et al.,* 1999).

Lewy body pathology: Lewy bodies are abnormal protein oligomerizations that are characteristic neuropathological symbols of PD. In the MPTP- induced PD mouse model, the conformation of Lewy body-alike accruals can be observed in the surviving dopaminergic neurons of the substantia nigra. These accruals contain primarily the protein alpha-synuclein and are supposed to play a function in neuronal dysfunction and cell death (Wakabayashi *et al.*, 2013).

Inflammation and glial activation: Neuroinflammation and activation of glial cells, particularly microglia, and astrocytes are prominent features in PD. In the MPTP model, there's an increase in inflaming tags and activation of microglia and astrocytes in the substantia nigra and other brain regions. This neuroinflammatory response may contribute to the progressive neurodegeneration observed in PD (Hirsch *et al.*, 2012).

Oxidative stress: Oxidative stress, characterized by an imbalance between the yield of reactive oxygen species (ROS) and the antioxidant defense system, is indicated in PD pathology. MPTP administration leads to increased ROS exhibition and diminished antioxidant mechanisms, influencing oxidative damage to neurons and other cellular constituents (Wang *et al.,* 2022).

Mitochondrial dysfunction: Mitochondrial dysfunction is nearly associated with PD pathology. In the MPTP-induced PD mouse model, MPTP impairs mitochondrial function in dopaminergic neurons, leading to energy deficiencies and increased vulnerability to oxidative stress. These mitochondrial abnormalities contribute to neuronal dysfunction and cell death (Wang *et al.,* 2022).

Neurochemical modifications: Apart from dopamine reduction, the MPTP model also exhibits modifications in other neurotransmitter systems. For illustration, there may be changes in serotonin, noradrenaline, and

glutamate levels, which can contribute to non-motor symptoms observed in PD (Muñoz *et al.,* 2020).

These neuropathological changes observed in the MPTP-induced PD mouse model give a high perception of the underpinning mechanisms of PD. They reflect vital aspects of human complications, including dopaminergic cell loss, Lewy body pathology, inflammation, oxidative stress, and mitochondrial dysfunction. Understanding these neuropathological changes in the ambient of the MPTP model allows experimenters to develop and test new remedial strategies targeting specific aspects of PD pathology.

Inflammatory Response and Oxidative Stress

In the MPTP-induced Parkinson's disease (PD) mice model, there are notable inflammatory and oxidative stress responses that contribute to the pathogenesis and progression of the disorder. The administration of the neurotoxin MPTP widely damages dopaminergic neurons in the substantia nigra, influencing motor impairments and PD- suchlike symptoms. Further, we will discuss the inflammatory and oxidative stress responses observed in this model.

Inflammatory responses: Inflammation plays a significant function in the neurodegenerative process in PD. Following MPTP administration, there's an activation of vulnerable cells, specifically microglia, which are the resident vulnerable cells of the central nervous system. Microglia get initiated and release pro-inflammatory atoms, including cytokines (like tumor necrosis factor-alpha, interleukin- 1β) and chemokines (like monocyte chemoattractant protein- 1), aggravating the inflammatory response. The activation of microglia and the later release of inflammatory intermediates contribute to the progressive degeneration of dopaminergic neurons in the substantia nigra. The severe activation of microglia and the sustained release of pro-inflammatory atoms cause envenomed surroundings for neurons, leading to their dysfunction and demise (Joglar *et al.,* 2009).

Oxidative stress responses: Oxidative stress is a state of imbalance between the yield of reactive oxygen species (ROS) and the antioxidant defense mechanisms. MPTP administration leads to an increase in ROS generation and a loss in the condition of antioxidant enzymes, like superoxide dismutase, catalase, and glutathione peroxidase. The elevated ROS situations create damage to cellular building blocks, including lipids, proteins, and DNA. This oxidative damage leads to the impairment of mitochondrial function, aggravating the yield of ROS and creating an acute cycle of oxidative stress. Dopaminergic neurons are particularly vulnerable to oxidative stress due to their high metabolic condition and limited antioxidant capacity. The interplay between inflammation and oxidative stress further contributes to neurodegeneration in the MPTP-convinced PD mice model. Inflammatory intermediaries released by sparked microglia can induce the yield of ROS in adjoining cells, worsening oxidative damage and amplifying the inflammatory response. This complementary relationship between inflammation and oxidative stress creates a self-eternalizing cycle of neuronal injury (Hwang, 2013).

The seditious and oxidative stress responses observed in the MPTP-induced PD mice model give perception into the complex mechanisms underpinning PD pathology. Understanding these responses is vital for developing remedial strategies that target inflammation and oxidative stress to relieve neurodegeneration and improve PD symptoms.

Experimenters have explored varied approaches to modulate these responses, similar anti-inflammatory medicines, antioxidants, and neuroprotective agents, to alleviate the adverse problem of inflammation and oxidative stress. These interventions aim to suppress microglial activation, reduce pro-inflammatory cytokine release, and enhance the antioxidant defense system to restore cellular homeostasis and shield dopaminergic neurons from further damage.

In summary, the MPTP-induced PD mice model demonstrates prominent inflammatory and oxidative stress responses that contribute to neurodegeneration and disorder progression. Targeting these pathways represents an implicit remedial avenue for developing new interventions to retard or halt the progression of PD.

Other Neuropathological Changes

Protein aggregation (e.g., alpha-synuclein): One of the hallmark neuropathological features of PD is the accumulation of abnormal protein oligomerization, primarily composed of alpha-synuclein, within neurons. These oligomers are known as Lewy bodies and Lewy neuritis. Alpha-synuclein is a typically resolvable protein that, in PD, undergoes misfolding and aggregation, leading to its accumulation in affected brain regions, including the substantia nigra. The presence of alpha-synuclein oligomers is believed to contribute to neuronal dysfunction and cell death. They intrude with cellular processes, disrupt protein degeneration pathways, and damage normal synaptic function. Likewise, alpha-synuclein oligomers can propagate from one neuron to another, spreading pathology

throughout the brain, and are supposed to play a critical part in disorder progression (Kalia *et al.,* 2013).

Mitochondrial dysfunction: Mitochondria, the energy-producing organelles within cells, are nearly intertwined in PD pathology. Dysfunction in mitochondrial processes, including disabled energy yield, increased oxidative stress and compromised quality control mechanisms, contribute to neuronal vulnerability in PD. In PD, mitochondrial dysfunction is characterized by a reduced condition of complex I of the electron transport chain, leading to disabled ATP production and increased yield of reactive oxygen species (ROS). The accumulation of ROS can affect oxidative damage to cellular factors, including lipids, proteins, and DNA, thus worsening neurodegeneration. Also, dysfunctional mitochondria release pro-apoptotic factors, promoting cell death (Wang *et al.,* 2022).

Synaptic modifications: Synapses, the junctions between neurons, play a critical part in neuronal communication and are affected in PD. The loss of dopaminergic neurons in the substantia nigra leads to a reduction in dopamine amount in target regions, alike the striatum. This dopamine reduction results in differences in synaptic transmission and malleability, contributing to motor and non-motor symptoms of PD. In addition to dopamine reduction, synaptic dysfunction in PD involves differences in other neurotransmitter systems, alike glutamate, and GABA. Excitatory and inhibitory synaptic imbalances can disrupt normal circuitry and contribute to the motor and non-motor incarnations of the disorder (Picconi *et al.,* 2012).

These neuropathological changes — protein aggregation (e.g., alpha-synuclein), mitochondrial dysfunction, and synaptic differences — interact and contribute to the progressive neurodegeneration observed in PD. They're nearly intertwined, affecting each other and amplifying the pathological processes underpinning the disorder. Understanding these neuropathological changes is vital for developing remedial strategies that can target specific mechanisms intertwined in PD pathology. Varied approaches, including alpha-synuclein-targeted curatives, mitochondrial defensive agents, and strategies to restore synaptic function, are being explored to alleviate these pathological changes and potentially retard or halt the progression of PD.

Overall, the neuropathological changes observed in PD, particularly protein aggregation, mitochondrial dysfunction, and synaptic modifications, give the critical perception of the complex molecular and cellular mechanisms driving the disorder. Advancements in our understanding of these changes hold word for the development of new remedial interventions and enhanced regulation of PD.

Molecular Mechanisms and their Pathways

The MPTP-induced Parkinson's disease (PD) mice model provides precious perception into the molecular mechanisms and pathways underpinning the disorder. MPTP is a neurotoxin that widely damages dopaminergic neurons in the substantia nigra, leading to motor dearths and PD- like symptoms. Currently, we will explore the detailed molecular mechanisms and pathways intertwined in the MPTP-induced PD mice model.

Dopaminergic neurodegeneration: MPTP administration results in the conversion of MPTP to its active metabolite, 1- methyl-4-phenyl pyridinium (MPP), which widely accumulates in dopaminergic neurons via the dopamine transporter (DAT). MPP interferes with the mitochondrial complex I serve, leading to disabled ATP yield, amplified oxidative stress, and subsequent dopaminergic neurodegeneration (Damier *et al.,* 1999).

Mitochondrial dysfunction: Mitochondrial dysfunction is a crucial contributor to PD pathology. MPTP-induced oxidative stress and impairment of mitochondrial complex I act lead to dropped ATP yield and amplified yield of reactive oxygen species (ROS). ROS accumulation causes oxidative damage to cellular factors, including lipids, proteins, and DNA, further worsening neurodegeneration (Wang *et al.,* 2022).

Protein aggregation: In the MPTP-induced PD mice model, alpha-synuclein plays a vital part in the development of protein oligomers. Alpha-synuclein is prone to misfolding and aggregation, leading to the development of Lewy bodies and Lewy neurites. The accumulation of alpha-synuclein oligomers disrupts protein homeostasis, impairs cellular function, and contributes to neurodegeneration (Kalia *et al.,* 2013).

Inflammation and immune responses: Inflammatory processes and immune system activation are intertwined in the pathogenesis of PD. MPTP-induced neuronal damage triggers the activation of microglia, the resident immune cells of the brain. Actuated microglia release pro-inflammatory cytokines, like tumor necrosis factor-alpha (TNF- α) and interleukin- 1β (IL- 1β), aggravate the inflammatory response and contribute to neuroinflammation and neurodegeneration (Joglar *et al.,* 2009).

Excitotoxicity and synaptic dysfunction: The loss of dopaminergic neurons in the MPTP model leads to

imbalances in excitatory and inhibitory neurotransmission. Reduced dopamine amount affect in altered synaptic plasticity and disintegrated communication within neuronal circuits. Excitotoxicity, caused by extreme glutamate release and successive over-activation of glutamate receptors, further contributes to neuronal damage and cell death (Picconi *et al.,* 2012).

Oxidative stress and antioxidant defense: MPTP-induced PD mice show increased oxidative stress due to mitochondrial dysfunction and extreme ROS yield. The imbalance between ROS generation and antioxidant defense mechanisms leads to cellular damage and neuronal death. Antioxidant enzymes, like superoxide dismutase (SOD) and glutathione peroxidase, are involved in neutralizing oxidative stress, and their action is disrupted in PD (Wang *et al.,* 2022).

Autophagy and protein degeneration pathways: Impairments in autophagy and protein degeneration pathways contribute to the accumulation of misfolded proteins, including alpha-synuclein, in PD. MPTP-induced PD mice show dysregulation of these pathways, influencing reduced consent of oligomerized proteins and worsening neurodegeneration (Lu *et al.,* 2020).

Understanding these molecular mechanisms and pathways in the MPTP-induced PD mice model provides a critical perception of the complex nature of the disorder. It allows experimenters to develop and test restorative interventions targeting specific factors of these pathways. Experimental strategies aimed at restoring mitochondrial function, modulating protein aggregation, suppressing neuroinflammation, enhancing antioxidant defenses, and promoting proper protein degeneration have shown vow in alleviating neurodegeneration and enhancing PD symptoms in preclinical studies using the MPTP-induced PD mice model.

Inflammatory Response and Immune Activity

Microglial activation: Microglia, the resident immune cells of the central nervous system, plays a vital part in the inflammatory response in PD. Following MPTP administration, microglia get triggered in the substantia nigra and other affected brain regions. Activation of microglia is characterized by changes in morphology, increased expression of cell surface tags, and the yield of pro- inflammatory atoms.

Release of pro-inflammatory cytokines: Triggered microglia release varied pro- inflammatory cytokines, involving tumor necrosis factor-alpha (TNF- α), interleukin- 1β (IL- 1β), interleukin- 6 (IL- 6), and interleukin- 12 (IL- 12). These cytokines contribute to the modification of the inflammatory response and can induce neurotoxicity, leading to further damage to dopaminergic neurons (Członkowska *et al.,* 1996).

Reclamation of peripheral immune cells: In addition to microglial activation, the MPTP-induced PD mice model exhibits infiltration of peripheral immune cells into the brain. Immune cells, alike monocytes, and T-cells, are engaged in the place of injury in response to chemotactic signals. The infiltration of supplemental vulnerable cells contributes to the neuroinflammatory response and amplifies the immune-mediated damage to dopaminergic neurons (Chung *et al.,* 2016).

Activation of astrocytes: Astrocytes, another type of glial cell, are also involved in the inflammatory response in PD. MPTP administration leads to the activation of astrocytes, characterized by hypertrophy and increased expression of glial fibrillary acidic protein (GFAP). Actuated astrocytes can release pro- inflammatory cytokines and chemokines, aggravating the inflammatory response and contributing to neuronal damage (Chen *et al.,* 2009).

Nuclear factor- kappa B (NF- κB) signaling: NF- κB is a vital transcript factor involved in the regulation of immune and inflammatory responses. In the MPTP-induced PD mouse model, the activation of microglia and astrocytes leads to the activation of the NF- κB signaling pathway. NF- κB activation results in the upregulation of pro-inflammatory cytokines, chemokines, and inducible nitric oxide synthase (iNOS), further promoting neuroinflammation and neurotoxicity (Dolatshahi *et al.,* 2021).

Inflammasome activation: Inflammasomes are multi-protein complexes involved in the built-in immune response. In the MPTP-induced PD mouse model, Inflammasome activation has been observed. The NLRP3 inflammasome, in particular, is intertwined with PD pathology. Activation of the inflammasome leads to the processing and release of pro-inflammatory cytokines, alike IL- 1β and IL- 18, contributing to neuroinflammation and dopaminergic neurodegeneration (Wen *et al.,* 2018).

The seditious and vulnerable-affiliated mechanisms observed in the MPTP- induced PD mouse model emphasize the part of neuroinflammation in disorder progression. The sustained activation of microglia, infiltration of supplemental vulnerable cells, release of pro-inflammatory cytokines, and activation of astrocytes inclusively contribute to the neuroinflammatory response and subsequent neurodegeneration. Targeting these inflammatory and immune- affiliated pathways

represents an implicit remedial approach for PD, with the intent of degrading neuroinflammation and guarding dopaminergic neurons against damage.

Alpha-Synuclein Protein Pathology

In the MPTP-induced Parkinson's disease (PD) mouse model, alpha-synuclein plays a significant part in the pathogenesis and progression of the disorder. Alpha-synuclein is a protein that's abundantly expressed in neurons and is primarily localized in presynaptic terminals. In PD, alpha-synuclein undergoes misfolding and aggregation, leading to the development of abnormal protein deposits known as Lewy bodies and Lewy neurites. Currently, we will consider the function of alpha-synuclein in the MPTP-induced PD mouse model and its counteraccusations for PD pathology:

Aggregation of alpha-synuclein: MPTP administration in PD mouse models leads to the aggregation of alpha-synuclein in affected brain regions, including the substantia nigra. The accumulation of combined alpha-synuclein is a characteristic neuropathological hallmark of PD. These protein oligomers are allowed to disrupt cellular function and contribute to the neuro degenerative process (Kalia *et al.,* 2013).

Dopaminergic neurodegeneration: Alpha-synuclein aggregation is nearly associated with the loss of dopaminergic neurons observed in PD. In the MPTP-induced PD mouse model, combined alpha-synuclein is set up within the dopaminergic neurons of the substantia nigra, where it contributes to neuronal dysfunction and cell death. The presence of alpha-synuclein oligomers in these neurons is believed to damage cellular processes and activate toxins cascades that finally lead to neurodegeneration (Damier *et al.,* 1999).

Propagation of alpha-synuclein pathology: Alpha-synuclein oligomers have the capability to propagate from one neuron to another, contributing to the spread of pathology in the brain. In the MPTP-induced PD mouse model, combined alpha- synuclein can be transmitted from affected dopaminergic neurons to adjoining cells, leading to the progressive involvement of added brain regions. This propagation of alpha-synuclein pathology is allowed to contribute to the phased spread of neurodegeneration throughout the brain, mirroring the progressive nature of PD in humans (Kalia *et al.,* 2013).

Disabled protein homeostasis: Oligomerized alpha-synuclein interferes with protein homeostasis and cellular quality control mechanisms. It disrupts the normal functioning of the ubiquitin-proteasome system and autophagy pathways, which are responsible for the concurrence of misfolded proteins and cellular debris. Disabled protein degeneration and the accumulation of venomous protein species, including combined alpha-synuclein, contribute to cellular dysfunction and neurodegeneration (Kalia *et al.,* 2013).

Neurotoxicity and cellular dysfunction: Oligomerized alpha-synuclein exhibits neurotoxic effects, leading to synaptic dysfunction, disrupted neurotransmitter release, and mitochondrial dysfunction. It has been suggested that soluble oligomeric forms of alpha-synuclein may be particularly venomous to neurons, causing mitochondrial damage, oxidative stress, and disturbance of calcium homeostasis. These cellular dysfunctions further contribute to the progressive neurodegeneration observed in PD (Fukuda, 2001).

The function of alpha-synuclein in the MPTP-induced PD mouse model highlights its involvement in the pathological processes underpinning the disorder. The aggregation and accumulation of alpha-synuclein disintegrate cellular function, disfigure protein degeneration mechanisms, and promote neurotoxicity, leading to dopaminergic neurodegeneration and the incarnation of PD- such symptoms. Understanding the function of alpha-synuclein in this model contributes to our knowledge of PD pathology and provides chances for the development of new remedial strategies targeting alpha-synuclein and its pathological upshots.

Therapeutic Aspects

Pharmacological Amelioration

Pharmacological interventions in the MPTP-induced Parkinson's disease (PD) mouse model have been considerably explored to develop new remedial strategies and estimate implicit treatments for the disorder. The MPTP model is an extensively used preclinical model that mimics crucial aspects of PD, including dopaminergic neurodegeneration and motor dearths. Currently, we will give a detailed account of some pharmacological interventions that have been tested in the MPTP-induced PD mouse model:

Dopaminergic relief therapeutics: One of the primary strategies in PD treatment involves replacing the lost dopamine. In the MPTP-induced PD mouse model, pharmacological interventions with levodopa, a precursor of dopamine, have been shown to palliate motor symptoms and rejuvenate dopaminergic function. Levodopa is generally administered in combination with an accessory dopa- decarboxylase inhibitor (like carbidopa) to enhance its efficiency and minimize accessory side effects (Vaidya *et al.,* 2023).

Dopamine agonists: Dopamine agonists, like pramipexole and ropinirole, directly stimulate

dopamine receptors and can be used as monotherapy or in combination with levodopa. These agents have been tested in the MPTP model and shown to ameliorate motor symptoms and give long-term benefits (Vaidya *et al.,* 2023).

Anticholinergics: In some cases, anticholinergic medicines, like as trihexyphenidyl and benztropine, are used to palliate tremors and other motor symptoms associated with PD. These drugs block the action of acetylcholine, a neurotransmitter involved in motor control (Vaidya *et al.,* 2023).

Monoamine oxidase- B (MAO- B) inhibitors: MAO- B inhibitors, like selegiline and rasagiline, increase the amount of dopamine in the brain by blocking the enzyme responsible for dopamine breakdown. These cures have been tested in the MPTP model and demonstrated neuroprotective results, conserving dopaminergic neurons and ameliorating motor function (Vaidya *et al.,* 2023).

Anti-inflammatory agents: Inflammation plays a significant part in PD pathology, and anti-inflammatory agents have been probed as implicit remedial interventions. Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase- 2 (COX- 2) inhibitors, like as ibuprofen and celecoxib, have been tested in the MPTP model and shown to reduce neuroinflammation and give neuroprotection (Vaidya *et al.,* 2023).

Antioxidants: Oxidative stress is a vital contributor to PD pathology, and antioxidant composites have been studied for their possible neuroprotective result. For instance, coenzyme Q10, vitamin E, and N-acetylcysteine (NAC). These antioxidants have been shown to downgrade oxidative stress, preserve dopaminergic neurons, and ameliorate motor function in the MPTP model (Vaidya *et al.,* 2023).

Neurotrophic factors: Neurotrophic factors, like glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), have been probed for their capability to promote neuronal survival and growth. These factors have shown promising results in the MPTP model, screening dopaminergic neurons, enhancing their survival, and ameliorating motor function (Vaidya *et al.,* 2023).

Other experimental interventions: Varied other pharmacological interventions have been explored in the MPTP model, including calcium channel blockers, anti-apoptotic agents, and anti-aggregation composites targeting alpha-synuclein. These interventions aim to alleviate specific aspects of PD pathology, like calcium dysregulation, apoptosis, and protein aggregation (Vaidya *et al.,* 2023).

It's important to note that while the MPTP- induced PD mouse model provides precious perception into possible remedial interventions, not all findings from animal studies rephrase directly to human clinical trials. yet, these preclinical studies help identify promising applicants for further exploration and give a base for understanding the mechanisms underpinning PD pathophysiology.

In conclusion, the MPTP- induced PD mouse model has been considerably applied to test varied pharmacological interventions targeting different aspects of the disorder. These interventions encompass dopaminergic relief remedies, dopamine agonists, anticholinergics, MAO- B inhibitors, anti-inflammatory agents, antioxidants, neurotrophic factors, and experimental interventions targeting specific mechanisms. The findings from these studies contribute to our understanding of PD pathophysiology and offer implicit avenues for the development of new treatments for this devitalizing neurodegenerative disease.

Gene and Cell-Predicated Amelioration

Gene-predicated and cell-predicated remedies hold great promising effects for the treatment of Parkinson's disease (PD), including in the MPTP- induced PD mouse model. These innovative approaches aim to restore the loss of dopaminergic neurons and ameliorate motor function by targeting specific genes or using cell transplantation. Currently, we will give a detailed account of gene-predicated and cell-predicated remedies tested in the MPTP- induced PD mouse model.

Gene-predicated Remedies

Gene remedy using viral vectors: Viral vectors, similar as adeno- associated viruses (AAV) and lentiviruses, have been used to deliver remedial genes to the brain. In the MPTP- induced PD mouse model, these vectors can be finagled to deliver genes coding neurotrophic factors, like as glial cell line-derived neurotrophic factor (GDNF) or brain-derived neurotrophic factor (BDNF). This gene transfer promotes the survival and growth of dopaminergic neurons, leading to bettered motor function.

Alpha-synuclein gene silencing: As an abnormal accumulation of alpha- synuclein is a vital role of PD, gene-predicated curatives that target alpha- synuclein expression have been delved. Ways similar to RNA hindrance (RNAi) or antisense oligonucleotides can be employed to widely silence alpha-synuclein gene

expression, reducing its aggregation and toxicity. In the MPTP- induced PD mouse model, this approach has shown promising results in relieving alpha- synuclein pathology and enhancing motor symptoms (Buttery and Barker, 2020).

CRISPR/ Cas9 intermediated genome editing: The CRISPR/ Cas9 system enables precise variation of the genome, offering implicit remedial usages. In the MPTP-induced PD mouse model, CRISPR/ Cas9 technology can be used to correct inheritable mutations associated with PD or modify genes involved in the disorder process. This approach holds a pledge for addressing specific inheritable factors contributing to PD pathology (Buttery and Barker, 2020).

Cell-predicated Remedies

Dopaminergic cell transplantation: Cell-predicated remedies involving transplantation of dopaminergic cells into the brain have been considerably studied in the MPTP- induced PD mouse model. Different cell sources, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and fetal ventral mesencephalic (VM) tissue, have been used to bring dopamine-producing cells. These transplanted cells can integrate into the host brain, restore dopamine release, and ameliorate motor function.

Gene-modified cell transplantation: Transplantation of genetically modified cells can enhance the remedial possibility of cell-predicated remedies. For example, cells can be manipulated to overexpress neurotrophic factors or release atoms that support dopaminergic neuron survival and function. In the MPTP- induced PD mouse model, this approach has shown enhanced transplantation results and enhanced neuroprotection (Buttery and Barker, 2020).

Reprogramming strategies: Reprogramming strategies involve converting other cell types, like fibroblasts, into dopaminergic-like neurons. strategies like induced pluripotent stem cell (iPSC) reprogramming or direct lineage conversion can induce patient-specific cells for transplantation. In the MPTP- induced PD mouse model, reprogrammed cells have demonstrated integration, survival, and functional enhancement (Buttery and Barker, 2020).

Probative cell curatives: Alongside dopaminergic cell transplantation, probative cell curatives have been explored. These involve transplanting cells that release neurotrophic factors or retain anti-inflammatory effects, promoting neuroprotection and enhancing the survival of endogenous dopaminergic neurons. Mesenchymal stem cells (MSCs) and neural stem cells (NSCs) are illustrations of supporting cell types tested in the MPTP model (Buttery and Barker, 2020).

Gene-predicated and cell-predicated remedies in the MPTP- induced PD mouse model give an important perception of their implicit clinical usages. These approaches aim to restore dopaminergic function, cover remaining neurons, and ameliorate motor symptoms. Although further exploration is demanded to optimize their safety and efficiency, these innovative strategies hold significant pledges for unborn remedial interventions in PD cases.

Conclusion

The MPTP-induced Parkinson`s Disease mice model has delivered premium perception into the pathophysiology of Parkinson's condition, permitting the examination of upholding mechanisms and assessment of possible remedial interventions. Despite its limits, this model remains a precious implement in the field of Parkinson`s Disease examination. By additional understanding of the MPTP-induced Parkinson`s Disease mice model, we can advance our knowledge of the disorder and elaborate more efficient strategies for its regulation and treatment.

Future Aspect

Future research utilizing this model and modern technology could significantly improve our knowledge of Parkinson's disease and lead to the development of novel therapeutics.

Acknowledgments

The infrastructural financial support under CURIE programme from the WISE-KIRAN division of Department of Science and Technology, New Delhi, India to IIS (deemed to be University), Jaipur, India (File No. DST/CURIE-02/2023/IISU) is gratefully acknowledged.

Conflict of Interest

The Authors declare no conflict of interest.

References

Brooks, S. P., Dunnett, S. B. 2009. Tests to assess motor phenotype in mice: a user's guide. Nat. Rev. Neurosci. 10(7), 519-529. https://doi.org/10.1038/nrn2652.

Buttery, P. C., Barker, R. A. 2020. Gene and cell-based therapies for Parkinson's disease: Where are we?

Neurotherapeutics. 17(4), 1539-1562. https://doi.org/10.1007%2Fs13311-020-00940-4.

Chen, P. C., Vargas, M. R., Pani, A. K., Smeyne, R. J., Johnson, D. A., Kan, Y. W., Johnson, J. A. 2009. Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease: Critical role for the astrocyte. PNAS. 106(8), 2933-2938. https://doi.org/10.1073/pnas.0813361106.

Chung, Y. C., Shin, W. H., Baek, J. Y., Cho, E. J., Baik, H. H., Kim, S. R., Jin, B. K. 2016. CB2 receptor activation prevents glial-derived neurotoxic mediator production, BBB leakage and peripheral immune cell infiltration and rescues dopamine neurons in the MPTP model of Parkinson's disease. Exp. Mol. Med. 48(1), e205-e205. https://doi.org/10.1038/emm.2015.100.

Członkowska, A., Kohutnicka, M., Kurkowska-Jastrzębska, I., & Członkowski, A. 1996. Microglial reaction in MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) induced Parkinson's disease mice model. Neurodegener. 5(2):137-143. https://doi.org/10.1006/neur.1996.0020.

Damier, P., Hirsch, E. C., Agid, Y., Graybiel, A. 1999. The substantia nigra of the human brain: II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain. 122(8), 1437-1448. https://doi.org/10.1093/brain/122.8.1437.

Dolatshahi, M., Ranjbar Hameghavandi, M. H., Sabahi, M., & Rostamkhani, S. 2021. Nuclear factor kappa B (NF κB) in pathophysiology of Parkinson disease: Diverse patterns and mechanisms contributing to neuro degeneration. Eur. J. Neurosci. 54(1), 4101-4123. https://doi.org/10.1111/ejn.15242.

Fife, B. 2016. Stop Alzheimer's Now!: How to Prevent and Reverse Dementia, Parkinson's, ALS, Multiple Sclerosis, and Other Neuro degenerative Disorders.

Fukuda, T. 2001. Neurotoxicity of MPTP. J. Neuropathol. 21(4). 323-332. 10.1046/j.1440-1789.2001.00402.x

Hirsch, E. C., Vyas, S., Hunot, S. 2012. Neuroinflammation in Parkinson's disease. Parkinsonism Relat. Disord. 18, S210-S212. 10.1016/S1353-8020(11)70065-7

Hwang, O. 2013. Role of oxidative stress in Parkinson's disease. Exp. Neurobiol. 22(1), 11-17. 10.5607/en.2013.22.1.11

Jackson-Lewis, V., & Przedborski, S. 2007. Protocol for the MPTP mouse model of Parkinson's disease. Nat. Protoc. 2(1), 141-151. 10.1038/nprot.2006.342

Joglar, B., Rodriguez Pallares, J., Rodriguez Perez, A. I., Rey, P., Guerra, M. J., Labandeira Garcia, J. L. 2009. The inflammatory response in the MPTP model of Parkinson's disease is mediated by brain angiotensin: relevance to progression of the disease. J. Neurochem. 109(2), 656-669. 10.1111/j.1471-4159.2009.05999.x

Kalia, L. V., Kalia, S. K., McLean, P. J., Lozano, A. M., Lang, A. E. 2013. α Synuclein oligomers and clinical implications for Parkinson disease. Ann. Neurol. 73(2), 155-169. 10.1002/ana.23746

Letanneux, A., Danna, J., Velay, J. L., Viallet, F., Pinto, S. 2014. From micrographia to Parkinson's disease dysgraphia. Mov. Disord. 29(12), 1467-1475. 10.1002/mds.25990

Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., Owen, A. M. 2003. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. J. Neurosci. 23(15), 6351-6356. 10.1523/JNEUROSCI.23-15-06351.2003

Lu, J., Wu, M., & Yue, Z. 2020. Autophagy and Parkinson's disease. Autophagy: biology and diseases: clinical science, 21-51. 10.1007/978-981-15-4272-5_2

Luchtman, D. W., Shao, D. I., Song, C. 2009. Behavior, neurotransmitters and inflammation in three regimens of the MPTP mouse model of Parkinson's disease. Physiol. Behav. 98(1-2), 130-138. 10.1016/j.physbeh.2009.04.021

Manning, K. J., Clarke, C., Lorry, A., Weintraub, D., Wilkinson, J. R., Duda, J. E., Moberg, P. J. 2012. Medication management and neuropsychological performance in Parkinson's disease. J. Clin. Neuropsychol. 26(1), 45-58. 10.1080/13854046.2011.639312

Martínez Martín, P., Forjaz, M. J., Frades Payo, B., Rusinol, A. B., Fernández García, J. M., Benito León, J. Catalán, M. J. 2007. Caregiver burden in Parkinson's disease. Mov. Disord. 22(7), 924-931. 10.1002/mds.21355

McNeill, A., Duran, R., Hughes, D. A., Mehta, A., & Schapira, A. H. 2012. A clinical and family history study of Parkinson's disease in heterozygous glucocerebrosidase mutation

carriers. JNNP. 83(8), 853-854. 10.1136/jnnp-2012-302402

Meredith, G. E., Kang, U. J. 2006. Behavioral models of Parkinson's disease in rodents: a new look at an old problem. Mov. Disord. 21(10), 1595-1606. 10.1002/mds.21010

Meredith, G. E., Rademacher, D. J. 2011. MPTP mouse models of Parkinson's disease: an update. J. Parkinsons Dis. 1(1), 19-33. 10.3233/JPD-2011-11023

Moustafa, A. A., Chakravarthy, S., Phillips, J. R., Gupta, A., Keri, S., Polner, B., Jahanshahi, M. 2016. Motor symptoms in Parkinson's disease: A unified framework. Neurosci. Biobehav. Rev. 68, 727-740. 10.1016/j.neubiorev.2016.07.010

Muñoz, A., Lopez-Lopez, A., Labandeira, C. M., & Labandeira-Garcia, J. L. 2020. Interactions between the serotonergic and other neuro-transmitter systems in the basal ganglia: Role in Parkinson's disease and adverse effects of L-DOPA. Front. Neuroanat. 14, 26. 10.3389/fnana.2020.00026

Parkinson, J. 2002. An essay on the shaking palsy. JNCN. 14(2), 223-236. 10.1176/jnp.14.2.223

Pearson, C., Hartzman, A., Munevar, D., Feeney, M., Dolhun, R., Todaro, V., & Beck, J. C. 2023. Care access and utilization among medicare beneficiaries living with Parkinson's disease. NPJ Parkinsons Dis. 9(1), 108. 10.1038/s41531-023-00523-y

Pfeiffer, R. F. 2016. Non-motor symptoms in Parkinson's disease. Parkinsonism Relat. Disord. 22, S119-S122. 10.1016/j.parkreldis.2015.09.004

Picconi, B., Piccoli, G., Calabresi, P. 2012. Synaptic dysfunction in Parkinson's disease. Synaptic plasticity: dynamics, development and disease. 553-572. 10.1007/978-3-7091-0932-8_24

Rodrigues de Paula, F., Teixeira Salmela, L. F., Coelho de Morais Faria, C. D., Rocha de Brito, P., Cardoso, F. 2006. Impact of an exercise program on physical, emotional, and social aspects of quality of life of individuals with Parkinson's disease. Mov. Disord. 21(8), 1073-1077. 10.1002/mds.20763

Rodriguez-Oroz, M. C., Jahanshahi, M., Krack, P., Litvan, I., Macias, R., Bezard, E., Obeso, J. A. 2009. Initial clinical manifestations of Parkinson's disease: features and patho physiological mechanisms. Lancet Neurol. 8(12), 1128-1139. 10.1016/S1474-4422(09)70293-5

Sveinbjornsdottir, S. 2016. The clinical symptoms of Parkinson's disease. J. Neurochem. 139, 318-324. 10.1111/jnc.13691

Taylor, T. N., Greene, J. G., Miller, G. W. 2010. Behavioral phenotyping of mouse models of Parkinson's disease. Behav. Brain Res. 211(1), 1-10. 10.1016/j.bbr.2010.03.004

Vaidya, B., Gupta, P., Laha, J. K., Roy, I., & Sharma, S. S. 2023. Amelioration of Parkinson's disease by pharmacological inhibition and knockdown of redox sensitive TRPC5 channels: Focus on mitochondrial health. Life Sci. 121871. 10.1016/j.lfs.2023.121871

Wakabayashi, K., Tanji, K., Odagiri, S., Miki, Y., Mori, F., Takahashi, H. 2013. The Lewy body in Parkinson's disease and related neuro degenerative disorders. Mol Neurobiol. 47, 495-508. 10.1007/s12035-012-8280-y

Wang, L., Zhao, Z., Zhao, L., Zhao, Y., Yang, G., Wang, C., Li, S. 2022. Lactobacillus plantarum DP189 reduces α-SYN aggravation in MPTP-induced parkinson's disease mice via regulating oxidative damage, inflammation, and gut microbiota disorder. J. Agric. Food Chem. 70(4), 1163-1173. 10.1021/acs.jafc.1c07711

Wen, L., Zhang, Q. S., Heng, Y., Chen, Y., Wang, S., Yuan, Y. H., Chen, N. H. 2018. NLRP3 inflammasome activation in the thymus of MPTP-induced Parkinsonian mouse model. Toxicol. Lett. 288, 1-8. 10.1016/j.toxlet.2018.02.003

Yarnall, A., Archibald, N., Burn, D. 2012. Parkinson's disease. J. Med. 40(10), 529- 535. https://doi.org/10.1016/j.mpmed.2012.07.008.

Zohar, O., Rubovitch, V., Milman, A., Schreiber, S., Pick, C. G. 2011. Behavioral consequences of minimal traumatic brain injury in mice. Acta. Neurobiol. Exp. 71(1), 36-45. 10.55782/ane-2011-1821