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Review Article

The Interplay between Traumatic Brain Injury, Cocaine Abuse, and Genetic Mutations in the Development of Parkinsons Disease: A Review

Mohamad Qutboddin[1,2], Syed Sagheer Ahmed[1,*], Nahid Abbas[3], Mohammad Ali[1], Bharathi Doddla Raghunathanaidu[1]

[1]Depatment of Pharmacology, Faculty of Pharmacy, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B. G. Nagara, Karnataka, INDIA.
[2]Department of Pharmacology, Akshaya Institute of Pharmacy, Tumkur, affiliated to Rajiv Gandhi University of Health Science, Bengaluru, Karnataka, INDIA.
[3]Department of Chemistry, Akshaya Institute of Pharmacy, Tumkur, affiliated to Rajiv Gandhi University of Health Science, Bengaluru, Karnataka, INDIA.

ABSTRACT

Parkinson's Disease (PD) is a neurodegenerative disorder characterized by the depletion of dopamine neurotransmitters and receptors. Although the etiology of PD is multifactorial, emerging evidence suggests that Traumatic Brain Injury (TBI), cocaine abuse, and genetic mutations may contribute to the development and progression of PD. This review summarizes the current understanding of the interplay between TBI, cocaine abuse, and genetic mutations in DA homeostasis in PD. Here, we discuss the molecular mechanisms underlying DA depletion and receptor dysfunction in PD, and how TBI, cocaine abuse, and genetic mutations may exacerbate these processes. Ultimately, a complex relationship between TBI, cocaine abuse, genetic mutations in dopamine, and PD has been identified.

Keywords: Cocaine abuse, Dopamine, Genetic mutation, Parkinson's disease, Traumatic brain injury.

Correspondence:
Dr. Syed Sagheer Ahmed
Department of Pharmacology, Faculty of Pharmacy, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B. G Nagara-571448, Karnataka, INDIA.
Email: sysaha6835@gmail.com

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INTRODUCTION

Parkinson's Disease (PD) is a chronic and progressively debilitating condition that impacts the nervous system. The Reduced in dopamine levels in the basal ganglia results in symptoms such as Involuntary shaking, increased muscle tone, and impaired balance control as the disease advances.

The global rise in PD cases mirrors many aspects of the pandemic, except for the absence of an infectious cause. Only about 3-5% of Parkinson's cases are linked to mutations in identified Parkinson's-related genes, which are classified as genetically inherited Parkinson's disease. Parkinson's has a profound societal impact. Parkinson's is a prevalent disorder, affecting approximately 6.1 million people worldwide in 2016.[1] The incidence of Parkinson's increases sharply with age. Especially in the age group between 50-59; 17.4 cases were reported in the 100,000 population. Whereas 93.1 cases were reported for the age group of 70 to 79 years. The lifetime probability of developing the disease is estimated to be 1.5%.[2] Parkinson's disease is more prevalent in North America and Europe than in Asia and Africa. The underlying causes of these geographic variations remain unclear, but exposure to environmental factors, is the leading cause of this disease.[3] Unlike in the general population, mortality rates in individuals with Parkinson's do not rise within the first five years of disease onset. However, after ten years, the risk of death increases by 3.5 times, according to the reported data. Drug abuse, pesticides, and head trauma are also associated with PD. Parkinson's happens because of genes, the environment, and how people live.[4] An excess of dopamine can accumulate in the cytoplasm, triggering dopamine auto-oxidation and the production of toxic by-products, which ultimately contribute to neurodegeneration. To prevent this, neurons employ protective mechanisms such as converting cytosolic dopamine into neuromelanin or breaking it down through Monoamine Oxidase (MAO) and Catechol-O-Methyltransferase (COMT) to produce homovanillic acid.[5] This review describes the interplay between traumatic brain injury, cocaine abuse, and genetic mutations in the development of Parkinson's disease.

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Traumatic brain injury

According to Graybiel (1990), Dopaminergic neurons in the brain arise from the Ventral Tegmental Area (VTA) and the Substantia Nigra (SN), projecting their axons to the striatum and cortex, limbic system, and hypothalamus.[6] DA affects hormone secretion, motor control, motivation, emotion, and cognitive processing, among other physiological processes.[7] Dopaminergic cell death and biochemical disruption of the dopaminergic system have been observed in animal models of TBI.[8] The Figure 1 explain about the TBI leading to PD.

Injuries with acute, subacute, and chronic pathologies comprise a diverse and complicated disorder, known as traumatic brain injury.[9,10] There are two separate sequential phases of brain trauma injury: the first phase and the second phase. Direct physical damage to neurons, glial cells, and vascular structures is linked to instantaneous biomechanical damage known as primary injury. The integrity of the brain parenchyma and Blood-Brain Barrier (BBB) is disrupted by the impact of damage. Chains of events that disrupt brain function cause further structural damage and accelerate cell death. These are manifestations of the secondary phase, which involves cortical impact injury, Drop-weight injury, Fluid Percussion Injury (FPI) and Blast-induced head injury. Twenty-three different injury processes have been developed using various animal injury models.[11] Changes in DA activity in TBI may lead to long-lasting cognitive impairment. Numerous animal studies have examined the pathophysiology of DA changes following TBI. Axonal damage leads to Wallerian degeneration, structural impairment, tissue edema, and disruption of the BBB. Disintegration can be caused by the original insult. Ischaemia, excitotoxicity, neuroinflammatory reactions, and the aftereffects of alterations in epigenetic and/or genetic expression are examples of secondary damage.[12-14] Severe head trauma damage results in the loss of neurons and white matter, as well as the destruction of anatomical structures in the brain. Neurological deficits associated with permanent neuronal circuit damage are also associated with severe injury. Although direct anatomical damage is a major cause of many neurological deficits resulting from brain injury, inhibition of both electrical and chemical signalling also plays a crucial role. Both behavioral and epigenetic studies have examined these changes.[15,16] All neurotransmitter systems, including Dopaminergic Systems (DAergic), are affected by extensive disruption of neural projections and physical damage to neuronal pathways, such as the nigrostriatal and mesolimbic circuits.[17] In the striatum and FC, synaptic structure and dendritic complexity are altered by the loss of DAergic innervating fibers from the substantia nigra and ventral tegmental region.[18,19] Reduced substantia nigra volume was linked to anomalies in the caudate DaT, and there was evidence of nigrostriatal tract injury, specifically impairing caudate projections. When combine these findings indicate that TBI frequently affects the dopaminergic system.[20] The cytoskeletal protein that stabilizes microtubules is synthesis by Microtubule-Associated Protein Tau (MAPT), which is present on the chromosome-17.[21] Tau proteins are involved in axonal transport regulation, membrane binding, and microtubule stabilisation.[22,23] Tau proteins change shape and can no longer dissolve properly in pathological situations due to alterations in isoforms or phosphorylation patterns, neuronal damage, and axonal transport.[24,25] In India, the incidence of TBI in both sexes was 7464800 (6383800-8667 200), in males was 4673 100 (3987400-5492900), and in females 2 791 700 (2 368100-3 273 300) were reported 2·1 times variation was observed in all states. Figure 2 illustrating the number of Traumatic Brain Injury (TBI) patients by age groups.

In India in 2019, in both males and females 770800 (635 100-919400) people had Parkinson's disease. Approximately 421800 (348300-502 100) males suffered from PD. Whereas the female count was 349000 (287 200-416500). An estimated 45 300 (95% UI 38 600-52 800) deaths were due to PD. However, a 2·3 times variation between the states was observed. Current data analysis reports that PD was uncommon in younger individuals, with prevalence rising significantly among older age groups, especially in those over 50 years of age in both men and women. The Figure 3 represents this data graphically. Note: Values in parentheses represent 95% uncertainty intervals. Prevalence or incidence is reported according to the metric most commonly applied in clinical practice for each disease.

Cocaine abuse

Cocaine attaches to the dopamine transporter, blocking dopamine reuptake. The extent of this binding is closely associated with self-administration of various stimulants.[26] Prolonged cocaine use may lead to the depletion of neurotransmitter reserves, which could explain the 'crash' and craving experience when the drug is discontinued. Supporting this hypothesis, a study of 20 chronic cocaine users found significantly higher prolactin levels (35.4±26.9 ng/mL) compared to the control group (7.0±5.0 ng/mL). Prolactin levels in cocaine users ranged from 5 to 96 ng/mL, with a median of 23 ng/mL. Notably, these increased levels did not fully return to normal within two weeks. This evidence has given rise to the 'dopamine depletion' hypothesis of cocaine addiction.[27] In a study involving 21 cocaine-dependent individuals seeking inpatient treatment, Ten patients showed high HDRS scores upon admission, which decreased by 50% or more during their hospital stay, despite the absence of targeted treatment.[28] This study revealed dopamine depletion occurrence was observed in cocaine addicts. In individuals who abused cocaine, a notable decline in dopamine D2 receptors was observed, which was linked to reduced metabolic activity in the cingulate gyrus and orbitofrontal cortex. This mechanism contributes to Cocaine disrupts the brain's dopamine system, leading to uncontrollable drug use. Additionally, cocaine users exhibit a significant decrease in dopamine secretion which, when combined with the reduction in D2 receptors, further exacerbates the condition.[29]

Chronic cocaine use can lead to dopamine depletion due to the prolonged inhibition of dopamine reuptake. Normally, after reabsorption, dopamine is stored in secretory vesicles for reuse. However, when the reuptake is blocked, this recycling process is disrupted, causing the released dopamine to break down in the synapse. Evidence for this is the elevated levels of the synaptic dopamine metabolite, 3-methoxytyramine, observed after cocaine use.[30] Additionally, increased tyrosine hydroxylase activity indicates increased dopamine synthesis. However, if this synthesis is insufficient to offset the loss of dopamine in the synapse, dopamine depletion becomes inevitable.[31] In contrast to the observed decrease dopamine levels in nucleus.[32] Phasic dopamine levels declined in both regions as the cocaine intake rate increased. Notably, the reduction in dopamine levels within the ventral medial striatum was significantly correlated with the rate of escalation.[33]

Genetic mutation

In Parkinson's, several genes are associated with mutations that contribute to disease development. They are classified into two types based on their mutations.

Autosomal Dominant Mutations

a) *SNCA* (α-Synuclein),

b) *LRRK2* (Leucine-Rich Repeat Kinase 2),

Autosomal Recessive Mutations

a) *PARK2* (Parkin),

b) *PINK1* (PTEN-Induced Putative Kinase 1),

c) *DJ-1* (PARK7).

SNCA (A-Synuclein)

Deficient dopamine retention resulting from a-synuclein mutations may play a role in pathogenesis of PD.[34] Polymeropoulos *et al.*,[35] discovered a missense mutation in the α-synuclein gene on chromosome 4q21-23, which led to the replacement of alanine with threonine at position 53. α-Synuclein mutations follow an autosomal dominant inheritance pattern and lead to an earlier onset of PD compared to idiopathic cases 52 and 56. Mutations associated with PD accelerate α-synuclein oligomerization, and the development of non-fibrillar oligomers may be crucial for disease progression.[36] The presence of α-synuclein as the main element in Parkinson's disease.[37] Parkin ubiquitinates a higher-molecular-weight variant of α-synuclein, a role that is lost because of disease-related mutations in parkin.[38] A later study revealed that parkin targets synphilin-1, a protein that interacts with α-synuclein, rather than α-synuclein itself.[39] The ubiquitination of synphilin-1 is impaired by familial parkin mutations. The toxic buildup of abnormal α-synuclein forms can occur, as oxidative stress has been shown to trigger α-synuclein aggregation.[40,41] This implies that inadequate removal of oxidatively modified α-synuclein may contribute to the development of Parkinson's.

DRD2 Gene

This gene does not follow a clear autosomal dominant or recessive inheritance pattern, like *SNCA, LRRK2, PINK1, or PARK2*. This gene is mainly regarded as a risk factor for Parkinson's disease rather than a direct cause. *DRD2* comprises six introns. Alternative splicing gives rise to two primary variants: *D2S* and *D2L*.[42] Over 200 polymorphisms have been discovered in DRD2, primarily located in introns and regions flanking downstream.[43] Disorders of mood, schizophrenia, movement-related conditions, and variations in drug response.[44,45] A common single nucleotide polymorphism which involves a C-to-T substitution at position 957 in exon 7. The minor T allele is present in approximately 50% of the Caucasian population. This SNP has been linked to reduced mRNA stability and translation, diminished dopamine-induced upregulation of *DRD2* membrane expression *in vitro*, and reduced *DRD2* expression in the cortex and striatum of healthy individuals.[46-48] The syndrome has been associated with the impairment of Dopamine (DA) receptors, which exhibit numerous mutations. To clarify the role of mesolimbic DA systems, three primary competing explanations "liking," "learning," and "wanting" were assessed in patients having symptoms of PD.[49] Certain genetic factors and environmental influences.[50] may lead to a deficiency in D2 receptors, increasing individuals' susceptibility to engaging in various addictive, impulsive, and compulsive behaviors.[51,52] DAT1 is located on chromosome *5p15.3*, the *DAT1* gene (also known as *SLC6A3*) contains a *VNTR* polymorphism in its 3' non-coding region.[53,54] Two significant alleles within this polymorphism may independently increase the risk of developing Reward Deficiency Syndrome (RDS) behaviours.

LRRK2 Gene

The *LRRK2* (Leucine-Rich Repeat Kinase 2) gene mutation is a major genetic factor in Parkinson's Disease (PD). It produces a kinase enzyme that plays a crucial role in neuronal signalling, autophagy, and mitochondrial processes. Variants of *LRRK2*, particularly the *G2019S* mutation, have been linked to both hereditary and sporadic forms of PD. The expression of *LRRK2* results in an age-related decline in dopamine (DA)-responsive motor activity and the degeneration of DA neurons.[55-59] *LRRK2* is functional in the brain and comprises 51 exons. Dardarin contains five functional domains in its C-terminal region.[60,61] A portion of this protein is known as the leucine-rich region because of its high concentration of the amino acid leucine, which serves as a building block of proteins. To assess the impact of *LRRK2* on tau phosphorylation, a SH-SY5Y cell clone was used that overexpressed *LRRK2*. The results showed a notable increase in tau phosphorylation at *Thr181* and *Ser396* in the cells with elevated *LRRK2* expression. This increase was mitigated when *LRRK2* was knocked down.[62] Oxidative stress is a condition in

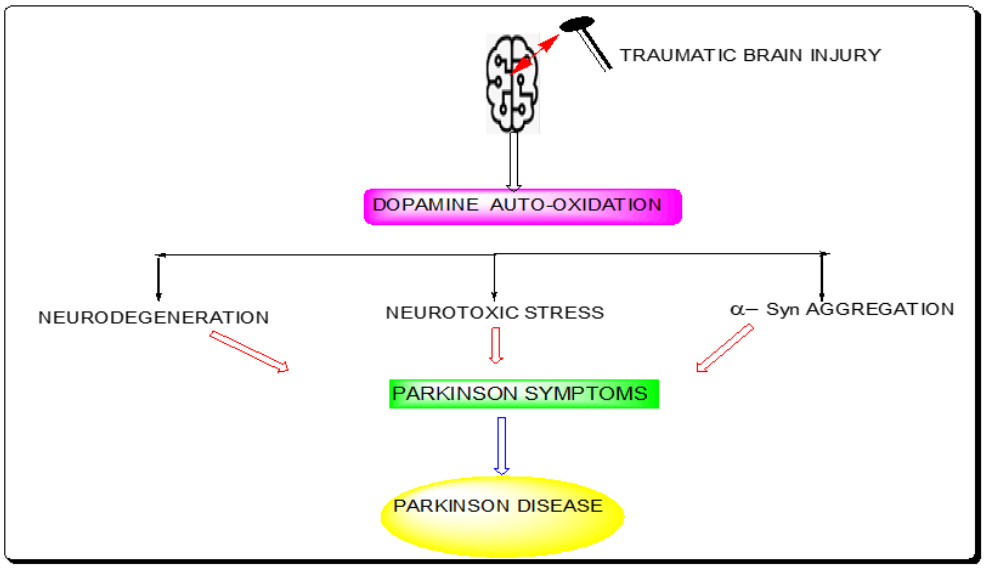

Figure 1: Neurodegeneration pathway caused due to TBI leading to PD.

which the body's antioxidant defenses fail to maintain normal levels of Reactive Oxygen Species (ROS) at normal levels.[63] Under such conditions, cells overexpressing either *LRRK2 WT* or the *p.G2019S* variant experience significantly increased cell death rates compared to those not under oxidative stress. This indicates that the expression of *LRRK2 WT* or *p.G2019S*, combined with oxidative stress, synergistically enhanced cell death, with the most pronounced effect observed in cells overexpressing the *p.G2019S* variant.[64] *LRRK2* may play a role in the progression of Parkinson's disease by directly impairing immune cell function. Where it is involved in immune responses to pathogens.[65,66]

A significant increase in *LRRK2* protein levels has been detected in microglial cells within the Substantia Nigra Pars Compacta (SNpc) and striatum of mice following inflammation induced by Lipopolysaccharide (LPS).[67]

PINK1 Gene

Alteration in PINK1 Gene Cause Parkinson's disease (PD), resulting from either homozygous or compound heterozygous alterations. However, some studies have identified heterozygous *PINK1* mutations in patients with PD and in healthy controls. The presence of heterozygous mutations in healthy individuals suggests that other genetic or environmental factors may influence penetrance and expression of the disease. Additionally, the functional impact of these mutations can vary, with some leading to partial loss of kinase activity or mitochondrial dysfunction, which are central to *PINK1's* role in mitochondrial quality control and protection against oxidative stress.[68-70] The mutation results in the replacement of the amino acids arginine and glycine at a particular protein site, which contributes to the onset of parkinsonism in the population. This mutation was initially discovered in 2001 in a large Italian family pedigree located on chromosome 1 (*PARK* 6 locus).[71,72] It is hypothesized that a mutation in *PINK1* may increase vulnerability to reactive oxygen species and other cellular stressors, ultimately contributing to the development of Parkinson's disease.[73]

ATP13A2 Gene

ATP13A2, also known as *PARK9*, is a P-type ATPase that functions primarily as an ion pump. It is involved in the transport of polyamines such as spermidine and spermine, which are crucial for cellular homeostasis. *ATP13A2* is essential for maintaining lysosomal function and protecting against oxidative stress and neurodegeneration.[74] When *ATP13A2* function is compromised, lysosomal degradation is impaired, leading to accumulation of α-synuclein aggregates. This contributes to PD pathogenesis by promoting neuronal toxicity and degeneration. Additionally, *ATP13A2* has been shown to regulates autophagy, which is crucial for clearing damaged proteins and organelles.[75] *ATPase13A2*, which consists of 29 exons, encodes a protein composed of 1,180 amino acids. *ATP13A2* is typically located in the lysosomal membrane and features an ATPase domain along with ten transmembrane domains. This protein plays a role in preventing α-synuclein clumping, maintaining proper mitochondrial and lysosomal activities, and protecting against neurodegeneration. Mutations in *ATP13A2* have been identified in patients with juvenile-onset Parkinson's disease.[76]

DJ-1 Gene

DJ-1 serves a vital function as a sensor for oxidative stress and a defender Against Reactive Oxygen Species (ROS). It engages in numerous cellular activities, including antioxidant defense, mitochondrial operations, and protein breakdown. Alteration in the DJ-1 gene are associated with juvenile Parkinson's disease, which is inherited in an autosomal recessive pattern, highlighting its crucial role in promoting neuronal survival and protecting against oxidative damage.[77] *DJ-1*, also referred to as protein *DJ-1*,

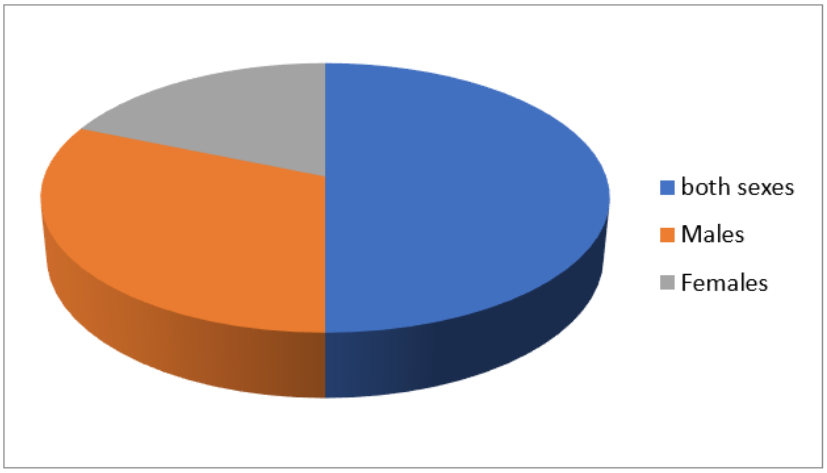

Figure 2: TBI cases reported in India.

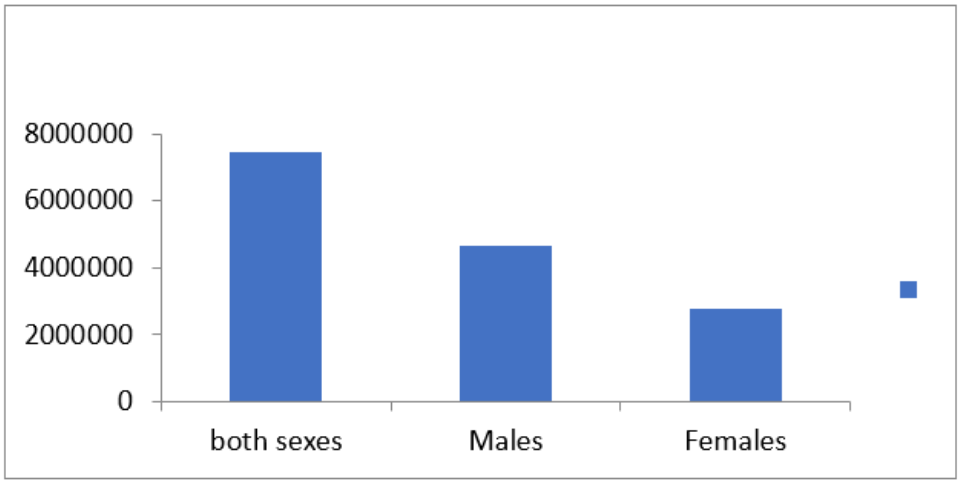

Figure 3: PD cases reported in India.

is composed of seven coding exons that generate a189-amino acid protein referred to as Parkinson's protein 7. This protein is widely expressed and acts as a cellular sensor for oxidative stress.[78,79] *DJ-1* functions as a chaperone in the protein-folding process, assisting newly formed proteins in attaining the correct three-dimensional shape, refolding damaged proteins, conveying specific proteins to proteasomes, and aiding RNA production and regulation. *DJ-1* gene mutations account for approximately 1-2% of autosomal recessive early onset Parkinson's disease cases.[80] The identification of *DJ-1* mutations in consanguineous families from secluded European areas is crucial for understanding the genetic foundation of Parkinson's. *DJ-1*, located on chromosome *1p36 (PARK7 locus)*.[81] The *p.Arg610Gly* mutation is collocated in the GYF domain of the protein it encodes and is considered pathogenic because it disrupts ligand-binding function. This mutation leads to abnormalities in *GIGYF2*, resulting in insulin dysregulation and impaired signalling in the Insulin/IGF-1 Receptor (IGF-1R) pathway, which serves as an equilibrium maintenance of brain function. This disruption is regarded as a key mechanism underlying LOPD.[82,83]

CONCLUSION

PD is characterized by the depletion of dopamine neurotransmitters and receptors. The evidence reviewed here suggests that traumatic brain injury, cocaine abuse, and genetic Alteration may contribute to the development and progression of Parkinson's disease by exacerbating dopamine depletion and receptor dysfunction**.** An increasing number of cases of injuries and genetic or abuse-related neurological disorders have been reported in India. Substantial state-level variations. These neurological disorders, especially Parkinson's disease, emphasize the importance of tailored, state-specific healthcare system responses. These gaps in neurology services-spanning awareness, early detection, treatment, and rehabilitation-should be addressed to improve the prevention and management of PD.

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ABBREVIATIONS

PD: Parkinson's Disease; **LOPD:** Late-Onset Parkinson's Disease; **PARK7:** Parkinson's Disease Protein 7; **ROS:** Reactive Oxygen Species; **LPS:** Lipopolysaccharide; **LRRK2:** Leucine-Rich Repeat Kinase 2; **DA:** Dopamine; **SNP:** Single Nucleotide Polymorphism; **PINK1:** PTEN-Induced Putative Kinase 1; **MAO:** Monoamine Oxidase; **COMT:** Catechol-O-Methyltransferase; **FPI:** Fluid Percussion Impact; **BBB:** Blood-Brain Barrier; **HVA:** Homovanillic Acid; **MHPG:** 3-Methoxy-4-Hydroxyphenylglycol; **HDRS:** Hamilton Depression Rating Scale; **MAPT:** Microtubule-Associated Protein Tau; **SNpc:** Substantia Nigra Pars Compacta.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies. While aging is the strongest risk factor, growing evidence suggests that environmental, lifestyle, and genetic factors interact to influence disease onset and progression. This review examines the interplay between three critical factors-Traumatic Brain Injury (TBI), cocaine abuse, and genetic mutations-and their combined contribution to the development of PD.

TBI induces oxidative stress, neuroinflammation, mitochondrial dysfunction, and blood–brain barrier disruption, all of which can accelerate dopaminergic neuronal loss. Cocaine abuse, through repeated dopaminergic overstimulation, vascular injury, and neurotoxic metabolites, may further sensitize nigrostriatal pathways to degeneration. Meanwhile, pathogenic mutations in genes such as *LRRK2, SNCA, PINK1, DJ-1*, and *Parkin* increase vulnerability to cellular stress and protein aggregation.

When combined, these insults may act synergistically: TBI and cocaine exposure may unmask or amplify the effects of underlying genetic susceptibility, leading to earlier onset or faster progression of PD. Understanding this multifactorial interaction highlights the need for integrated research and preventive strategies, including targeted screening of at-risk individuals, neuroprotective interventions after brain injury, and harm reduction approaches for substance abuse.

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