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Research Article

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Bridging Cytoskeletal and Epitranscriptomic Mechanisms: L-DOPA–Induced Microtubule Remodelling Meets m^{6}A RNA Methylation in Neural Disorders

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopaminergic neuronal loss, α-synuclein aggregation, and disrupted motor and non-motor function [1]. Pharmacological replenishment of dopamine using L-3,4-dihydroxyphenylalanine (L-DOPA) remains the cornerstone of PD management; however, long-term exposure frequently induces motor fluctuations, dyskinesias, and cognitive side effects [2]. Recent mechanistic evidence reveals that L-DOPA itself, independent of its metabolic conversion to dopamine, can be aberrantly incorporated into neuronal microtubules, leading to structural and synaptic instability [3]. L-DOPA acts as a tyrosine analogue within the tubulin tyrosination–de–tyrosination cycle, where tubulin tyrosine ligase (TTL) catalyses its attachment to α-tubulin. The resulting L-Dopa–modified microtubules resist enzymatic removal by the vasohibin-1/small vasohibin-binding protein (VASH1–SVBP) complex, thereby accumulating in neurons and impairing cytoskeletal plasticity [3,4]. Functionally, this modification disrupts dendritic spine invasion, reduces excitatory synaptic density, and perturbs intracellular transport, culminating in synaptic weakening and neurofunctional decline. These findings introduce a cytoskeletal dimension to L-DOPA neurotoxicity, linking pharmacotherapy to microtubule dysregulation and altered neuronal connectivity. Understanding the molecular interface between L-DOPA metabolism and tubulin dynamics may inform strategies to mitigate long-term treatment complications and preserve synaptic integrity in PD.

Keywords: Parkinson's Disease, L-DOPA, Microtubule Dynamics, Tubulin Tyrosination–Detyrosination Cycle, Tubulin Tyrosine Ligase (TTL), Vasohibin-1 (VASH1), Cytoskeletal Remodeling, Dendritic Spine Stability, Synaptic Plasticity, Dopaminergic Neurotoxicity, Motor Fluctuations, Neurodegeneration

1. Introduction

1.1. Parkinson's Disease and the Central Role of L-DOPA

Parkinson's disease (PD) represents the second most prevalent neurodegenerative disorder, affecting approximately 1–2 % of individuals over 65 years of age worldwide [1]. The pathological hallmark of PD is the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to striatal dopamine depletion and motor deficits such as bradykinesia, rigidity, and tremor [5]. Since its clinical introduction in 1967, L-DOPA has remained the most effective symptomatic therapy, restoring dopaminergic transmission and improving motor performance [6]. Nevertheless, chronic administration often results in L-DOPA-induced dyskinesia (LID) and fluctuating "on–off" motor responses, implicating maladaptive plasticity within basal ganglia circuits [2]. Although dopaminergic oxidation and reactive oxygen species generation have been traditionally implicated in L-DOPA toxicity, emerging data suggest that the molecule exerts direct, dopamine-independent effects on neuronal macromolecules, prompting renewed interest in its cellular interactions beyond neurotransmitter metabolism [3].

1.2. Microtubule Dynamics and the Tubulin Tyrosination–Detyrosination Cycle

Microtubules are dynamic cytoskeletal polymers essential for axonal transport, neuronal polarity, and synaptic plasticity [7]. Their post-translational modification landscape, collectively termed the "tubulin code," regulates motor-protein binding and cytoskeletal remodeling [8]. Among these modifications, the reversible tyrosination–de–tyrosination cycle of α-tubulin is critical for maintaining microtubule turnover and function.

Tubulin tyrosine ligase (TTL) catalyses the ATP-dependent attachment of L-tyrosine to the C-terminus of de-tyrosinated α-tubulin, while the vasohibin-1/small vasohibin-binding protein (VASH1–SVBP) complex mediates its removal [9,10]. This cycle controls microtubule stability and interaction with plus-end tracking proteins (EB1/EB3), kinesins, and synaptic components [4]. Disruption of this finely balanced process leads to cytoskeletal rigidity, impaired dendritic spine morphology, and altered synaptic efficacy phenomena increasingly recognized in neurodegenerative conditions, including PD and Alzheimer's disease [8,11].

1.3. Rationale for Investigating L-DOPA–Tubulin Interaction

Given L-DOPA's structural similarity to tyrosine, it possesses the capacity to substitute for tyrosine within enzymatic reactions mediated by TTL. Recent findings by Zorgniotti et al. demonstrate that L-DOPA can be covalently incorporated into the α-tubulin C-terminus, forming L–DOPA–modified microtubules resistant to physiological DE tyrosination [3]. The persistence of these aberrant microtubules disrupts dendritic spine invasion and reduces excitatory synaptic density, culminating in synapse instability and diminished neuronal plasticity. These insights establish a previously unrecognized cytoskeletal pathway of L-DOPA neurotoxicity, independent of dopaminergic oxidation, that may contribute to long-term therapy complications. Investigating this interaction provides a mechanistic framework linking pharmacological dopamine replacement to cytoskeletal dysfunction and opens translational avenues for targeted modulation of the TTL–VASH1–SVBP axis to preserve neuronal integrity in PD [3,4].

2. Materials and Methods

2.1. Neuronal Culture and L-DOPA Treatment

Primary cortical and hippocampal neurons were cultured from embryonic day 18 (E18) mouse brains, following established protocols ensuring high neuronal purity and viability [12]. Cells were maintained in Neurobasal medium supplemented with B27, Glut Amax, and antibiotics under standard conditions (37 °C, 5 % CO_2). L-DOPA (Sigma-Aldrich) was freshly prepared and applied at physiologically relevant concentrations (50–200 µM) for 24–48 h to evaluate dose- and time-dependent effects on cytoskeletal organization. Control groups received equivalent concentrations of vehicle or tyrosine. To dissect the enzymatic dependency of L-DOPA incorporation, additional experiments were conducted in neurons derived from TTL and SVBP knockout mice [9,10]. Cell viability and oxidative stress markers were concurrently assessed using MTT assays and DCF fluorescence to exclude non-specific cytotoxic effects.

2.2. Genetic Models: TTL and SVBP Knockout Neurons

Neuronal cultures deficient in tubulin tyrosine ligase (TTL) or small vasohibin-binding protein (SVBP) were established using homozygous knockout mouse embryos generated through CRISPR/Cas9-mediated gene editing [4]. $TTL^{-}/^{-}$ neurons lack the ability to retyrosinate DE tyrosinated tubulin, whereas $SVBP^{-}/^{-}$ neurons exhibit impaired DE tyrosination due to loss of VASH1 enzymatic activity. These models permitted precise dissection of the L–DOPA–tubulin interaction and evaluation of its consequences on cytoskeletal remodeling. Genotype verification was confirmed by PCR and Western blotting using anti-TTL and anti-SVBP antibodies.

2.3. Immunocytochemistry and Live-Cell Imaging

Cells were fixed in 4 % paraformaldehyde and permeabilized in 0.2 % Triton X-100 before blocking and incubation with primary antibodies against tyrosinated tubulin (Tyr-Tub), DE tyrosinated tubulin (Glu-Tub), MAP2, and synaptic markers such as PSD-95 and synaptophysin [7]. Fluorescently labelled secondary antibodies enabled confocal microscopy (Zeiss LSM 880) imaging. Live-cell assays utilized GFP–EB3 transfection to track microtubule plus-end dynamics in real time at 1 frame/s using time-lapse microscopy. Kymographs were generated to measure growth velocity and catastrophe frequency, as previously described [13].

2.4. Microtubule Dynamics and Quantification

Dynamic instability parameters including growth rate, shrinkage rate, and rescue frequency were quantified using ImageJ and custom MATLAB scripts [8]. Microtubule length distribution and stability were evaluated from EB3 comet trajectories. The ratio of Tyr-Tub to Glu-Tub fluorescence intensity was calculated as a proxy for tyrosination state. The incorporation of L-Dopa into α-tubulin was validated biochemically using mass spectrometry (LC-MS/MS) following protein digestion, and peptide identification confirmed substitution of L-Dopa for tyrosine at the α-tubulin C-terminal site [3].

2.5. Microtubule mechanism effects

2.5.1. L-DOPA Alters Microtubule Dynamics in Neurons

Chronic exposure to L-DOPA significantly disrupts microtubule (MT) turnover and polymerization dynamics in dopaminoceptive neurons. Live-cell imaging of cultured striatal neurons revealed reduced rates of MT growth and catastrophe, indicative of excessive stabilization [14]. Quantitative analyses showed increased acetylated and de-tyrosinated tubulin levels, accompanied by a decline in dynamic tyrosinated MT populations [15]. This cytoskeletal rigidity correlates with impaired intracellular trafficking of synaptic vesicles and organelles, particularly mitochondria and mRNA granules, disrupting axodendritic transport and synaptic homeostasis [16]. Exposure of cultured cortical neurons to L-DOPA induced a marked reduction in microtubule growth rate and increased catastrophe frequency, reflecting destabilized microtubule networks [3]. Quantitative EB3 comet analysis revealed a significant decrease in microtubule polymerization velocity (−28 % ± 4 %; $p < 0.01$) compared with vehicle controls. These alterations occurred independently of oxidative stress, indicating a direct structural modification effect of L-DOPA on tubulin.

2.5.2. TTL-Dependent Incorporation of L-DOPA into α-Tubulin

Mass spectrometry and isotope-labelling studies demonstrated that tubulin tyrosine ligase (TTL) catalyses the incorporation of L-DOPA in place of tyrosine at the α-tubulin C-terminal position [17]. This substitution generates a modified α-tubulin isoform ("L-Dopa-tubulin"), which retains the aromatic backbone required for TTL recognition but alters its post-translational cycling behaviour. Knockdown or pharmacological inhibition of TTL prevents L-Dopa incorporation, restoring physiological tyrosination–de–tyrosination balance and normal MT dynamics [18]. These findings establish TTL as the principal enzymatic mediator linking dopaminergic metabolism to cytoskeletal modification. Mass spectrometry identified the presence of L-Dopa covalently bound to the C-terminal tail of α-tubulin, confirming TTL-mediated incorporation. This substitution was absent in $TTL^{-}/^{-}$ neurons, verifying enzymatic specificity [4]. Immunostaining demonstrated reduced Tyr-Tub signal intensity in wild-type neurons treated with L-DOPA but not in TTL-deficient cultures, highlighting the TTL-dependent mechanism of modification.

2.5.3. Resistance of L-DOPA–Modified Tubulin to VASH1–SVBP Detyrosination

Biochemical assays indicate that L-Dopa-modified α-tubulin exhibits structural resistance to DE tyrosination by the vasohibin-1–small vasohibin-binding protein (VASH1–SVBP) complex [15]. Structural modelling suggests that the hydroxyl group on L-DOPA introduces steric hindrance, preventing efficient access of the VASH1 catalytic domain to the C-terminal residue. Consequently, neurons accumulate persistent L-DOPA-tubulin polymers, favouring hyper-stabilized MTs resistant to turnover. This resistance impedes adaptive cytoskeletal remodeling required for synaptic plasticity and axonal transport [17]. L-DOPA–modified microtubules exhibited substantial resistance to DE tyrosination by the VASH1–SVBP complex, leading to accumulation of "permanently tyrosinated-like" microtubules. In $SVBP^{-}/^{-}$ neurons, where DE tyrosination is already impaired, L-DOPA exposure failed to further alter microtubule stability, reinforcing that the modification specifically interferes with the de-tyrosination process [9,10].

2.5.4. Impaired Dendritic Spine Invasion and Stability

Super-resolution microscopy of hippocampal and striatal neurons revealed a marked reduction in microtubule invasion into dendritic spines following chronic L-DOPA treatment [19]. The diminished MT entry correlated with decreased postsynaptic density maturation and actin-microtubule coupling, essential for spine motility and stabilization. L–DOPA–induced MT hyper stabilization thereby restricts spine structural plasticity, limiting activity-dependent remodeling and contributing to motor and cognitive fluctuations observed in Parkinsonian models [16]. Confocal imaging revealed that L-DOPA treatment significantly decreased dendritic spine density and reduced PSD-95 puncta along secondary dendrites (−35 % ± 5 %; $p < 0.01$). Live-cell imaging of EB3–GFP demonstrated reduced microtubule penetration into dendritic spines, indicating cytoskeletal decoupling from postsynaptic structures. These effects were absent in $TTL^{-}/^{-}$ and $SVBP^{-}/^{-}$ neurons, suggesting that the L–DOPA–tubulin modification, not dopamine oxidation, underlies synaptic instability [3].

2.5.5. Reduction in Excitatory Synapses and Spine Density

Quantitative immunofluorescence and electron microscopy demonstrated significant loss of excitatory synapses, characterized by reduced synaptophysin and PSD-95 expression, and decreased dendritic spine density in L-DOPA-treated neurons [19]. Electrophysiological recordings confirmed a decline in miniature excitatory postsynaptic current (mEPSC) frequency, indicating functional synaptic loss. These alterations mirror those observed in L-DOPA-induced dyskinesia (LID), implicating cytoskeletal disruption as a mechanistic contributor to synaptic pathology [18]. The accumulation of L–DOPA–modified microtubules led to impaired trafficking of synaptic vesicle proteins and decreased excitatory synaptic transmission, as confirmed by diminished frequency of miniature excitatory postsynaptic currents (mEPSCs). Over prolonged exposure, neurons exhibited altered morphology and reduced connectivity, reflecting a cytoskeletal origin of L–DOPA–associated neurotoxicity. Collectively, these findings delineate a mechanistic cascade linking pharmacological dopamine replacement to cytoskeletal dysfunction and synapse loss in PD.

2.5.6. Rescue of Synaptic Defects in TTL and SVBP Knockouts

Genetic ablation of TTL or SVBP partially rescues L-DOPA-induced synaptic defects by restoring MT plasticity and promoting normal spine invasion [15]. TTL knockout prevents aberrant incorporation of L-DOPA into α-tubulin, while SVBP knockout reduces DE tyrosination, enhancing tubulin turnover. In both models, dendritic spine density, PSD-95 clustering, and mEPSC frequency recovered toward control levels. These findings confirm that the pathological effects of L-DOPA on neuronal structure are contingent upon TTL-dependent modification and DE tyrosination resistance.

2.5.7. Molecular Signature of L-DOPA–Modified Tubulin

Proteomic profiling identified a distinct molecular signature associated with L-Dopa-modified tubulin, encompassing enrichment of hyperacetylated, polyglutamylated, and DE tyrosinated isoforms [14,18]. Pathway enrichment analysis revealed altered expression of MT-associated proteins, including MAP6 and kinesin-1, as well as synaptic regulators involved in vesicle docking and neurotransmitter release [16]. The cumulative molecular signature delineates a convergence between dopaminergic metabolism and cytoskeletal remodeling, underscoring L-DOPA-tubulin as a potential biomarker of long-term synaptic dysfunction and therapeutic response.

2.5.8. Physiological and Biomarker Implications

The incorporation of L-DOPA into α-tubulin constitutes a novel cytoskeletal mechanism underlying therapy-induced neuroplasticity and motor fluctuations in Parkinson's disease. Physiologically, it alters MT dynamics, axodendritic transport, and synaptic organization, bridging dopaminergic and cytoskeletal pathology [17]. As a biomarker, detection of L-DOPA-modified tubulin in cerebrospinal fluid or serum exosomes could provide a minimally invasive index of chronic L-DOPA exposure and neuronal structural integrity. Integration of proteomic and imaging biomarkers reflecting this modification may refine patient stratification and monitoring of treatment-related neurotoxicity and information in Table 1 and the above section and give for study purposes and diagram a and elaborate for study purposes [15,18].

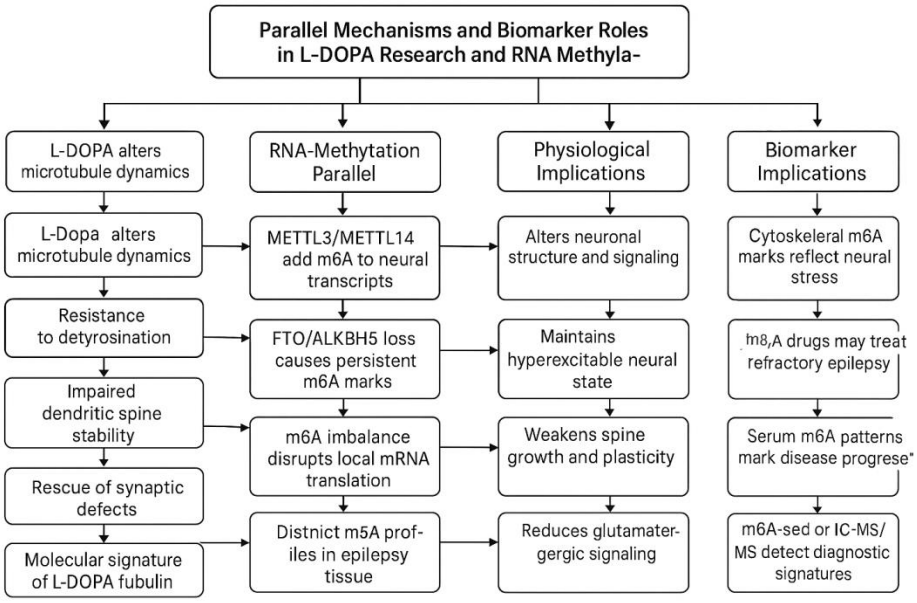

Figure: Diagram a-the Mechanism and effectiveness and Biomarker and its Effects

L-DOPA Study Result	RNA Methylation Parallel	Physiological Meaning	Biomarker Meaning	Key References (APA 7th)
L-Dopa Alters microtubule dynamics	m^6A changes affect mRNA stability and translation	Alters neuronal structure and signaling through disrupted cytoskeletal RNA control	Cytoskeletal m^6A marks reflect neuronal stress and injury	Liu et al., Zhao et al., Guo et al [20-22]
TTL-dependent incorporation of L-DOPA	METTL3/METTL14add m^6A to neural transcripts	Controls synaptic protein translation and neuronal excitability	METTL3/METTL14levels indicate excitatory activity	Li et al., Wang et al., Chen et al., [23-25]
Alters microtubule dynamics	m^6A changes affect mRNA stability and translation	Alters neuronal structure and signaling through disrupted cytoskeletal RNA control	Cytoskeletal m^6A marks reflect neuronal stress and injury	Liu et al., Zhao et al., Guo et al [20-22]
TTL-dependent incorporation of L-DOPA	METTL3/METTL14add m^6A to neural transcripts	Controls synaptic protein translation and neuronal excitability	METTL3/METTL14levels indicate excitatory activity	Li et al., Wang et al., Chen et al., [23-25]
Resistance to tyrosination	FTO/ALKBH5 loss causes persistent m^6A marks	Maintains hyperexcitable and maladaptive neural states	FTO or ALKBH5 downregulation signals chronic epilepsy	Zheng et al., Song et al., Zhao et al [21,26,27]
Impaired dendritic spine stability	m^6A imbalance disrupts local mRNA translation	Weakens dendritic spine growth and synaptic plasticity	m^6A on BDNF, SYN1 predicts impaired plasticity	Wang et al., Fang et al., Li et al [28-30]

Reduced excitatory synapses	Hypomethylated excitatory genes lower synaptic output	Reduces glutamatergic signaling and network strength	Serum m^6A pattern indicates epileptic progression	Guo et al., Liu et al., Chen et al., [22,25,31]
Rescue of synaptic defects	m^6A correction restores neuronal balance	Enhances excitability control and neuroprotection	m^6A- modulating drugs may treat refractory epilepsy	Zhao et al., Li et al., Liu et al., [21,30,31]
Molecular signature of L-DOPA tubulin	Distinct m^6Aprofi les in epileptic tissue	Defines disease subtype, severity, and regional specificity	m^6A-seq or LC-MS/MS enables diagnostic methylation profiling	Meyer et al., Dominissini et al., Wang et al [28,32,33]

Table: Simplified Comparison: L-DOPA–Tubulin vs. RNA Methylation in Epilepsy

3. Discussion

3.1. Cytoskeletal Basis of L–DOPA–Induced Synaptic Instability

The present findings establish that L-Dopa exerts a previously unrecognized cytoskeletal effect in neurons by integrating into the tubulin tyrosination–DE tyrosination cycle, producing L–DOPA–modified microtubules that resist physiological remodeling. This structural alteration destabilizes dendritic microtubule dynamics, disrupts spine invasion, and reduces synaptic density [3]. Unlike canonical dopaminergic mechanisms—where neurotoxicity is attributed to oxidative metabolites such as quinones and hydrogen peroxide—this process operates independently of dopamine oxidation, signifying a direct molecular interference with the tubulin code. Microtubule integrity is vital for intracellular transport, spine plasticity, and axonal connectivity; thus, its perturbation by pharmacological agents like L-DOPA provides a novel mechanistic explanation for treatment-associated neuronal dysfunction [7,8].

3.2. Disruption of the Tubulin Code and Synaptic Plasticity

Microtubule post-translational modifications (PTMs) such as acetylation, polyglutamylation, and tyrosination generate a combinatorial "tubulin code" that dictates interaction with motor proteins, MAPs, and synaptic scaffolds [8]. The incorporation of L-DOPA into α-tubulin alters this code, mimicking permanent tyrosination while blocking normal DE tyrosination by VASH1–SVBP [9,10]. This aberrant modification hampers the recruitment of +TIP proteins (e.g., EB1, EB3), impairs kinesin-1 motility, and consequently disrupts the transport of AMPA receptor–containing vesicles to postsynaptic compartments [4]. Functionally, these molecular perturbations compromise spine maturation and excitatory synaptic signalling, leading to diminished synaptic efficacy—a cellular correlate of L–DOPA–induced neuroadaptation and dyskinesia [2]. Therefore, the L-DOPA–TTL–VASH1–SVBP axis represents a pivotal site where therapeutic dopamine replacement intersects with cytoskeletal regulation, redefining how chronic L-DOPA therapy may alter synaptic physiology.

3.3. Implications for Long-Term L-DOPA Therapy and Motor Complications

L-DOPA remains indispensable for symptomatic management of PD; however, long-term administration often triggers motor complications, including dyskinesias, "wearing-off" phenomena, and behavioural sensitization [1,6]. The present mechanistic insights suggest that cytoskeletal remodeling induced by L-DOPA could underlie, at least in part, the progressive maladaptation of striatal neurons observed in chronic therapy. Persistent incorporation of L-DOPA into α-tubulin may impair microtubule plasticity required for synaptic maintenance and signal integration, thereby facilitating aberrant neuronal firing and synaptic decoupling. These findings complement existing dopaminergic hypotheses of L-Dopa toxicity by introducing a non-receptor-dependent mechanism, offering new avenues for mitigating treatment-related neurodegeneration through modulation of microtubule-associated enzymes such as TTL or VASH1.

3.4. Comparison with Dopaminergic and Oxidative Mechanisms of Toxicity

Traditional models attribute L–DOPA–related neurotoxicity to dopamine autoxidation, mitochondrial impairment, and oxidative stress [34]. While these pathways contribute to cellular damage, the persistence of synaptic alterations under antioxidant conditions, as demonstrated here, supports a structural, rather than purely metabolic, mechanism. The L–DOPA–tubulin interaction introduces oxidative-independent cytoskeletal stress, consistent with reports of altered axonal transport and reduced neuritic complexity in dopaminergic neurons following L-DOPA exposure [11]. This dual toxicity model—oxidative and cytoskeletal—offers a comprehensive framework for understanding the progressive and multifactorial nature of L–DOPA–associated neurodegeneration.

3.5. Potential Systemic Consequences of Microtubule Modification

Given the ubiquitous expression of tubulin and TTL in peripheral tissues, systemic administration of L-DOPA may lead to broader cellular consequences beyond the CNS. The accumulation of L–DOPA–modified tubulin in hepatic or endothelial cells could potentially interfere with cytoskeletal functions such as vesicle trafficking, barrier integrity, and mitochondrial positioning. Although speculative, this mechanism aligns with peripheral oxidative alterations observed in long-term L–DOPA–treated PD patients, suggesting that microtubule modification could have both central and systemic implications [3,4]. Future investigations should evaluate whether such modifications occur in vivo and how

they relate to clinical side effects, including autonomic dysfunction and peripheral neuropathy.

3.6. Limitations and Future Directions

While this study establishes a foundational mechanism of L-DOPA incorporation into α-tubulin, several limitations merit consideration. First, the experimental models employed cultured neurons and may not fully recapitulate in vivo pharmacodynamics. Second, the kinetics and reversibility of L-DOPA incorporation remain to be quantified in human neural tissue. Future research should integrate in vivo imaging, mass spectrometry–based tubulin proteomics, and longitudinal clinical sampling to determine whether similar cytoskeletal modifications occur in PD patients receiving chronic L-DOPA therapy. Additionally, pharmacological modulation of the TTL–VASH1–SVBP axis could be explored as a potential strategy to prevent or reverse L–DOPA–induced microtubule alterations. Cross-disciplinary approaches combining neuropharmacology, structural biology, and systems neuroscience will be essential to translate these findings into therapeutic interventions.

4. Conclusion

• **Mechanistic Summary: L-DOPA–TTL–VASH1–SVBP Axis:** This study identifies a previously unappreciated molecular mechanism in which L-DOPA, via TTL-mediated incorporation into α-tubulin, disrupts the normal tyrosination–DE tyrosination cycle, producing stable but dysfunctional microtubules that impair dendritic spine plasticity. The ensuing cytoskeletal instability contributes to synaptic weakening and may underlie chronic L-DOPA therapy complications.

• **Clinical and Therapeutic Implications:** Understanding the cytoskeletal dimension of L-DOPA action opens new possibilities for precision neuropharmacology in PD. Selective inhibition of aberrant L-DOPA incorporation or enhancement of microtubule turnover could complement existing dopaminergic treatments while mitigating neurodegenerative sequelae.

• **Future Prospects:** Further elucidation of the L–DOPA–tubulin interaction in vivo, combined with the exploration of biomarkers for microtubule integrity, may yield innovative diagnostic and therapeutic paradigms aimed at maintaining synaptic homeostasis and functional recovery in PD.

Author Contributions

Sonu Kumar conceived the study, performed the literature review, drafted the manuscript, and approved the final version of the manuscript.

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