Vol. 12 (2026): Proceedings of the 2026 International Conference on Life Sciences and Health Engineering (IC-LSHE 2026)
E-ISSN: 3105-0522 P-ISSN：3105-0514
DOI: https://doi.org/10.70267/lshe.20260116

Parkinson's Disease: Calcium Dysregulation as a Multilevel Mechanism of Selective Neuronal Vulnerability, with Implications for Therapeutic Strategy

Weijie Lai*

ZJU-UoE Institute, Zhejiang University, Haining, China

**Corresponding author: Weijie Lai*

Abstract

Parkinson's disease (PD) is a prevalent neurodegenerative disorder characterised by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta. Despite extensive investigation into genetic and environmental risk factors, the mechanisms underlying this selective neuronal vulnerability remain incompletely understood. Increasing evidence suggests that calcium dysregulation represents a unifying pathogenic mechanism linking molecular, cellular, and systems-level processes in PD. This review synthesises evidence demonstrating how the intrinsic reliance of substantia nigra dopaminergic neurons on calcium-dependent autonomous pacemaking imposes a sustained metabolic burden that predisposes these neurons to degeneration. It examines how genetically diverse PD-associated mutations, including those affecting PINK1/Parkin, LRRK2, and GBA, converge on disrupted calcium homeostasis through distinct cellular pathways involving mitochondrial buffering, lysosomal calcium signalling, and organelle quality control. At the cellular level, chronic calcium dysregulation drives oxidative stress, α-synuclein aggregation, and impaired autophagy, forming a self-reinforcing cycle of neuronal dysfunction. These processes extend beyond individual neurons, promoting neuroinflammation and basal ganglia circuit reorganisation that ultimately underlie motor symptom expression. The review further discusses the therapeutic implications of this multilevel framework, highlighting why broad calcium channel blockade has shown limited clinical efficacy. It argues that future disease-modifying strategies will require greater molecular and temporal precision, as well as integration with systems-level neuromodulation approaches that reduce activity-dependent calcium and metabolic burden. Overall, calcium dysregulation emerges as a central integrator of vulnerability across biological scales in Parkinson's disease, offering a coherent framework for understanding pathogenesis and guiding therapeutic innovation.

Keywords

Parkinson's disease, calcium dysregulation, selective neuronal vulnerability, dopaminergic neurons, α-synuclein pathology

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by both motor dysfunction and selective neuronal loss. Clinically, it presents with bradykinesia, rigidity, resting tremor, and postural instability, while pathologically it is defined by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) [1]. As one of the most prevalent neurodegenerative diseases worldwide, PD represents a growing biomedical and societal challenge in ageing populations [2]. Despite extensive research into genetic, molecular, and environmental contributors, the mechanisms underlying the selective vulnerability of SNc dopaminergic neurons relative to neighbouring neuronal populations remain poorly understood [3-5].

Recent advances suggest that this selective vulnerability cannot be explained by a single genetic mutation or toxic insult [3, 5]. Instead, accumulating evidence points towards calcium dysregulation as a unifying mechanistic framework linking genetic susceptibility, cellular stress, and systems-level dysfunction in PD [6-8]. SNc dopaminergic neurons exhibit a distinctive form of autonomous pacemaking that is tightly coupled to sustained calcium entry via L-type calcium channels, particularly those containing the Cav1.3 subunit [9, 10]. Although physiologically essential for tonic dopamine release, this calcium-dependent firing strategy places these neurons under chronic metabolic stress, increasing their vulnerability to mitochondrial dysfunction, oxidative stress, and protein aggregation [3, 11]. Importantly, this calcium burden coincides with the intrinsic metabolic liability of dopamine itself: its cytosolic metabolism and oxidation generate reactive oxygen species and quinone intermediates, thereby imposing an additional oxidative load [12, 13]. The convergence of sustained calcium influx and dopamine-related oxidative stress therefore creates a uniquely hostile intracellular environment in SNc neurons, helping to explain their disproportionate susceptibility to degeneration [11, 14, 15].

Under physiological conditions, intracellular calcium levels in dopaminergic neurons are tightly regulated through coordinated buffering, active transport, and sequestration by intracellular organelles, particularly the endoplasmic reticulum and mitochondria [16, 17]. Activity-dependent calcium entry couples neuronal firing to neurotransmitter release and mitochondrial ATP production, aligning metabolic output with energetic demand [10]. However, the reliance of SNc dopaminergic neurons on sustained calcium influx renders this homeostatic balance especially fragile. Even modest perturbations in calcium handling, mitochondrial efficiency, or buffering capacity can shift calcium signalling from a physiological regulator to a chronic source of cellular stress, providing a critical baseline for understanding pathological calcium dysregulation in PD [11, 17].

Consistent with this framework, genetic, iPSC-based, and imaging studies have demonstrated how disruptions in calcium homeostasis interact with PD-associated pathways, including those involving PINK1, Parkin, LRRK2, and α-synuclein, to drive neurodegeneration [7, 18, 19]. These findings indicate that calcium dysregulation does not act as an isolated molecular defect, but rather as a central integrator that amplifies diverse genetic and cellular stressors.

Building on this perspective, this review argues that calcium dysregulation operates across genetic, cellular, and systems levels to shape Parkinson's disease pathogenesis, providing a coherent framework for selective neuronal vulnerability. Unlike previous reviews that have primarily focused on intracellular calcium channels or single-cell calcium signalling, this article adopts a multiscale approach to examine how calcium-dependent stress propagates from subcellular organelles to neural circuits and ultimately contributes to motor dysfunction. It further examines how insights into calcium-dependent mechanisms have both informed and constrained therapeutic development, highlighting the limitations of calcium-targeted pharmacological interventions. Finally, the review considers how, at later disease stages marked by substantial neuronal loss, therapeutic focus increasingly shifts toward systems-level neuromodulation aimed at reducing activity-dependent calcium and metabolic burden rather than correcting underlying cellular pathology.

2. Calcium Dysregulation as a Mechanism of Selective Neuronal Vulnerability

Increasing evidence suggests that calcium dysregulation represents a critical mechanistic convergence point through which diverse genetic and cellular risk factors drive selective neuronal vulnerability in Parkinson's disease [3, 6, 7]. Rather than acting as isolated causes, mutations associated with both familial and sporadic PD appear to compromise dopaminergic neurons' capacity to maintain calcium homeostasis, thereby amplifying metabolic stress and lowering the threshold for neurodegeneration.

2.1 Genetic risk factors converging on calcium homeostasis

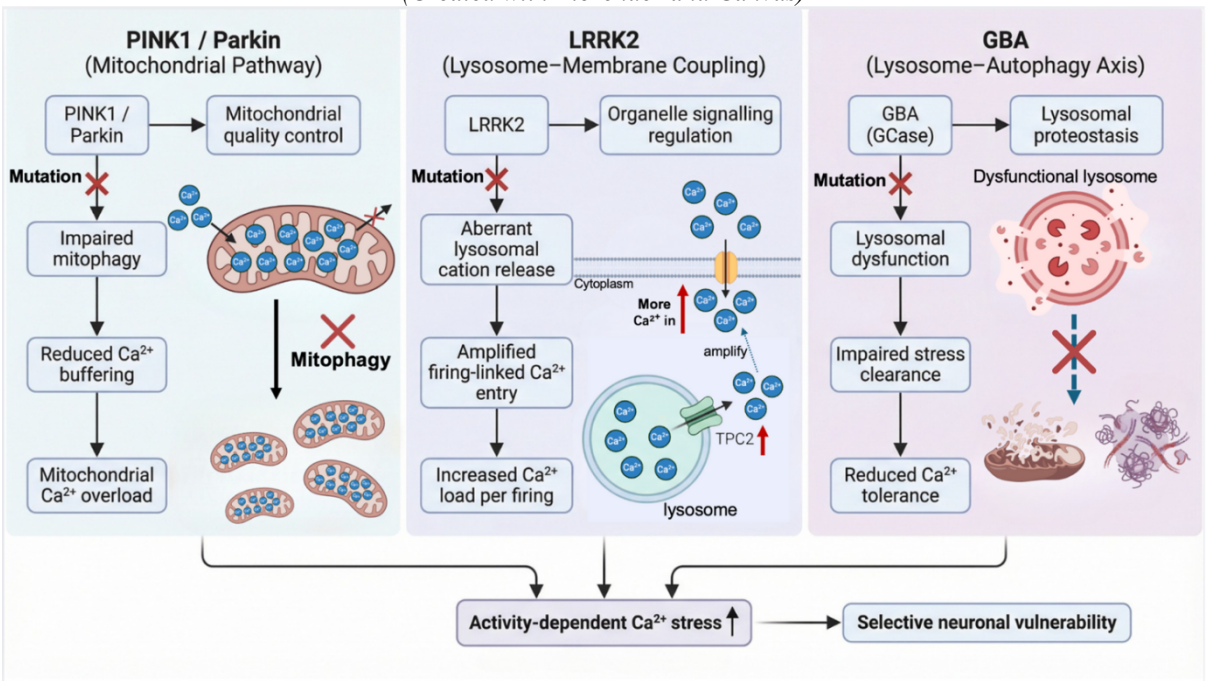
To illustrate how genetically diverse forms of Parkinson's disease converge on calcium dysregulation, this section focuses on three representative genetic risk factors: PINK1/Parkin, LRRK2, and GBA. Pathogenic mutations in these genes can disrupt calcium homeostasis at distinct cellular control points, including mitochondrial calcium buffering, lysosomal calcium signalling, and organelle quality control (Figure 1), thereby linking genetic heterogeneity to selective neuronal vulnerability [20-22].

Mutations in PINK1 and Parkin, key regulators of mitochondrial quality control, provide direct genetic evidence that impaired mitochondrial calcium handling can drive neurodegeneration [3]. Under physiological conditions, mitochondria transiently sequester cytosolic calcium during neuronal activity to support ATP production while limiting toxic calcium accumulation [17]. Calcium imaging studies demonstrate that PINK1-deficient neurons exhibit defective mitochondrial calcium efflux, leading to sustained intramitochondrial calcium accumulation and reduced buffering capacity (Figure 1) [18]. Notably, neuronal death can be triggered by physiological calcium loads rather than excessive calcium entry, reflecting a reduced tolerance to activity-dependent calcium stress. Parkin dysfunction further exacerbates this vulnerability by impairing mitophagy, allowing calcium-intolerant mitochondria to persist [21].

In contrast, LRRK2 mutations disrupt calcium homeostasis primarily through lysosome-associated mechanisms [23]. A recent study combining human neuronal models, in vivo Drosophila assays, and calcium imaging demonstrates that pathogenic LRRK2 exaggerates depolarisation-induced calcium entry via aberrant activation of the lysosomal cation channel TPC2 [22]. This maladaptive coupling between lysosomal cation release and plasma membrane calcium influx increases calcium load during neuronal firing, thereby lowering the threshold for cellular stress (Figure 1) [23]. Importantly, pharmacological modulation of TPC2 ion selectivity was sufficient to normalise calcium entry and rescue behavioural deficits, highlighting dysregulated calcium signalling dynamics rather than acute cytotoxicity as the key pathogenic mechanism [24].

GBA mutations, which impair the lysosomal enzyme glucocerebrosidase and represent the most common genetic risk factor for Parkinson's disease, further reinforce this convergence on calcium stress [20]. Although GBA does not directly regulate calcium flux, loss of glucocerebrosidase activity disrupts lysosomal function and TFEB-mediated autophagy, secondarily reducing the cell's capacity to cope with sustained calcium stress (Figure 1) [25-27]. In dopaminergic neurons operating near the limits of calcium tolerance, such secondary destabilisation may further lower the threshold for calcium-induced toxicity.

Figure 1. Genetically distinct Parkinson's disease risk factors converge on activity-dependent calcium stress. (Created with Biorender and Canvas)

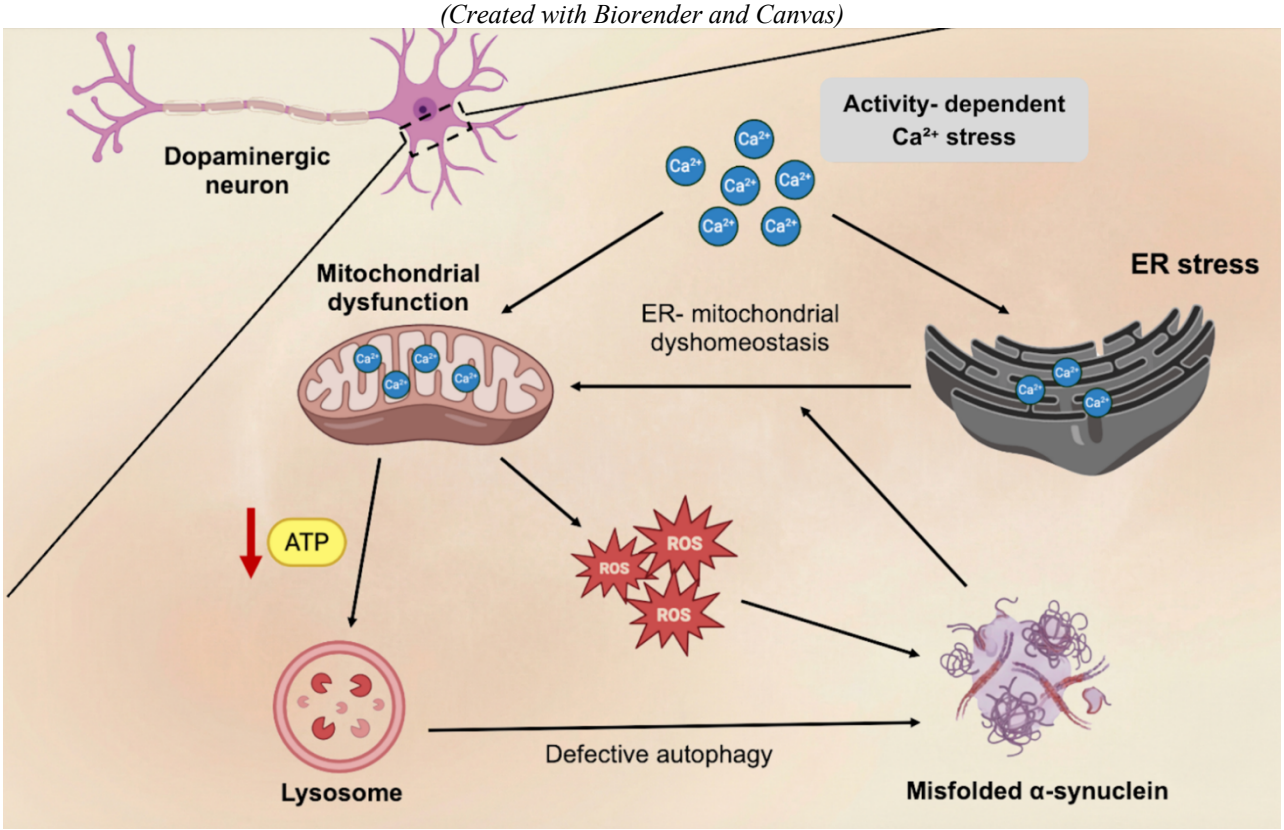


2.2 Cellular Pathways Linking Calcium Dysregulation to Neurodegeneration

At the cellular level, sustained calcium dysregulation initiates a cascade of pathological processes that amplify neuronal vulnerability [28]. The endoplasmic reticulum (ER), the major intracellular calcium store, normally ensures precise calcium release for physiological signalling. Under sustained calcium dysregulation, chronic calcium overload drives excessive ER-to-mitochondria calcium transfer, leading to mitochondrial calcium accumulation and metabolic overstimulation [29]. This metabolic strain increases the production of reactive oxygen species (ROS), which progressively compromises mitochondrial function and reduces the capacity of mitochondria to buffer subsequent calcium influx [28].

Apart from directly damaging mitochondria, excessive ROS production promotes the misfolding and aggregation of α-synuclein, a presynaptic protein involved in synaptic vesicle dynamics and a central pathological hallmark of Parkinson's disease [28]. Aggregated α-synuclein, in turn, interferes with the recovery of mitochondrial calcium dynamics following calcium release from the endoplasmic reticulum, prolonging mitochondrial calcium burden and thereby increasing oxidative stress and mitochondrial dysfunction [30]. In parallel, misfolded and aggregated α-synuclein is inefficiently degraded by lysosomes, placing a substantial burden on the autophagic system and contributing to defective autophagic flux [31]. Because lysosomal function is energetically demanding and depends on ATP supplied by mitochondria, mitochondrial dysfunction further impairs lysosomal homeostasis [28]. Together, these processes establish a self-reinforcing vicious cycle linking calcium stress, ER stress, mitochondrial dysfunction, lysosomal impairment, and α-synuclein pathology, ultimately rendering dopaminergic neurons functionally compromised and progressively vulnerable to degeneration (Figure 2).

Figure 2. Cellular network linking activity-dependent calcium stress to dopaminergic neuronal vulnerability. (Created with Biorender and Canvas)



Although substantial progress has been made in describing these pathways, the precise causal relationships among calcium dysregulation, mitochondrial failure, α-synuclein aggregation, and lysosomal dysfunction remain incompletely resolved [32]. Whether calcium overload acts as an initiating trigger or a downstream amplifier likely depends on disease stage, genetic background, and neuronal context, underscoring that selective neuronal vulnerability in Parkinson's disease emerges from the dynamic convergence of multiple calcium-dependent stressors.

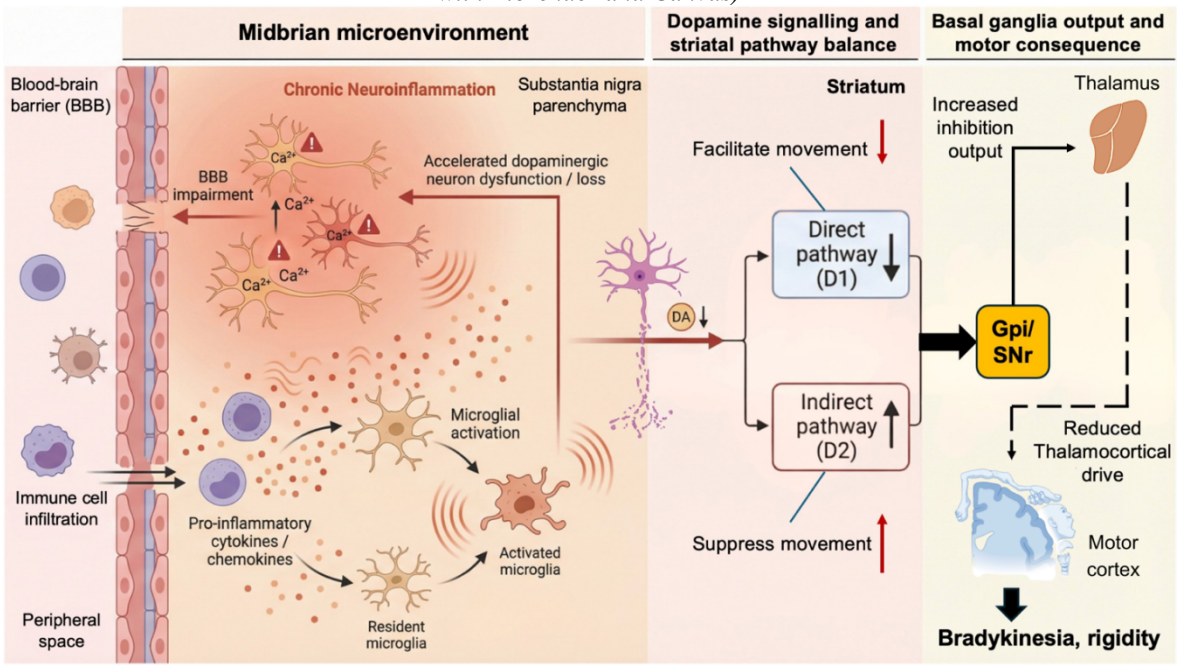
3. From Cellular Pathology to Network Dysfunction: A Systems-Level Perspective

Although calcium-driven stress originates within individual substantia nigra dopaminergic neurons, it propagates across tissue and circuit levels (Figure 3). Excessive calcium signalling also contributes to the disruption of the blood–brain barrier (BBB) [33]. BBB impairment permits increased infiltration of peripheral immune cells and facilitates sustained activation of resident microglia within the midbrain [34, 35]. Activated microglia and infiltrating immune cells release pro-inflammatory cytokines and chemokines, thereby promoting a chronic neuroinflammatory environment that accelerates dopaminergic neuronal dysfunction and degeneration [33].

As dopaminergic neurons progressively lose function or degenerate, dopamine levels in their projection targets, such as the striatum, decrease. This dopamine deficit has direct consequences for basal ganglia circuit organisation. Dopamine normally maintains a balance between the direct pathway, which facilitates movement, and the indirect pathway, which suppresses movement [36]. Dopamine depletion weakens direct pathway activity while relatively enhancing indirect pathway influence [37]. The net effect is excessive inhibitory output from basal ganglia output nuclei to thalamocortical motor circuits, leading to reduced cortical motor drive and the emergence of cardinal motor features such as bradykinesia and rigidity [38].

Evidence for this multilevel transition from cellular pathology to circuit dysfunction comes from complementary experimental approaches. In animal models, genetic or toxin-induced disruption of dopaminergic neurons reproduces both dopamine loss and characteristic motor deficits [37]. Electrophysiological studies demonstrate widespread reorganisation of firing patterns across basal ganglia circuits following dopamine depletion, indicating network-level adaptation rather than isolated neuronal failure [39, 40]. In humans, PET imaging consistently links reduced striatal dopaminergic signalling with motor symptom severity [41]. Together, these findings illustrate how calcium-driven cellular stress is amplified through neuroinflammatory and circuit-level mechanisms, ultimately transforming local neuronal vulnerability into systems-level dysfunction in Parkinson's disease [37].

Figure 3. System-level amplification of calcium-driven dopaminergic vulnerability in Parkinson's disease. (Created with Biorender and Canvas)



4. Therapeutic Implications: Calcium-Targeted Interventions and Neuromodulation

Given growing evidence that calcium dysregulation contributes to selective dopaminergic vulnerability in Parkinson's disease, targeting calcium signalling has been considered a logical therapeutic approach [42]. Cav1.3-containing L-type calcium channels were therefore targeted as a major source of calcium entry in substantia nigra dopaminergic neurons. Epidemiological and preclinical studies suggested that blocking these

channels could reduce cumulative calcium stress, leading to clinical testing of the calcium channel blocker isradipine [43, 44]

Despite encouraging epidemiological and preclinical data, the phase III STEADY-PD trial failed to demonstrate disease-modifying efficacy [45]. Rather than refuting the role of calcium dysregulation, this outcome can be hypothesised to reflect key limitations of current pharmacological strategies. First, isradipine lacks cell-type and subcellular specificity, resulting in broad suppression of calcium influx across neuronal populations [46]. Given the indispensable role of calcium signalling in neuronal metabolism, synaptic transmission, and gene regulation, such global inhibition likely disrupts physiological function and severely constrains the therapeutic window. Second, although intervention occurred at an early clinical stage [42], key pathological processes, such as dopaminergic axonal loss and organellar dysfunction, may already have been established, limiting the capacity of calcium modulation to meaningfully alter disease progression.

These clinical and mechanistic outcomes highlight the need for therapeutic precision rather than broad calcium suppression. Future strategies aim to preserve physiological signalling while mitigating pathogenic overload through Cav1.3-selective inhibitors, mitochondria-targeted antioxidants, and enhancement of PINK1/Parkin-mediated mitochondrial quality control [19, 45]. Although still at early translational stages, these approaches represent a shift toward mechanism-informed interventions that balance calcium homeostasis without compromising neuronal function [46].

As Parkinson's disease progresses, the therapeutic impact of pharmacological calcium modulation becomes increasingly limited, as substantial dopaminergic neuronal loss and circuit reorganisation have already occurred [47]. Under these conditions, restoring function requires strategies that address established network-level dysfunction rather than solely correcting cellular calcium dysregulation [48]. Deep brain stimulation (DBS) exemplifies this systems-level approach by modulating pathological basal ganglia output and alleviating motor symptoms independently of ongoing neurodegeneration [49]. Clinically, DBS has demonstrated significant improvements in motor symptoms, with meta-analyses reporting reductions in UPDRS-III motor scores comparable to medical therapy [50]. Studies show an average improvement of 60.7% to 66% in UPDRS-motor scores after DBS implantation, sustained for several years [51]. This includes substantial decreases in tremor and rigidity, with some patients experiencing as high as 85% improvement in tremor and 66% improvement in rigidity at 5 years post-DBS [52]. However, conventional DBS relies on continuous open-loop stimulation, which can impose additional metabolic demand and activity-dependent calcium influx, potentially aggravating calcium and energy stress in vulnerable neural circuits [47, 48].

These limitations have driven the development of adaptive DBS and brain–computer interface (BCI)–based neuromodulation. By adjusting stimulation in real time and delivering it only when pathological activity emerges, adaptive systems reduce unnecessary neural activation, lower cumulative energy expenditure, and minimise stimulation-induced calcium influx [53]. Adaptive DBS (aDBS), also known as closed-loop DBS, has been shown to be equally or even more effective than conventional continuous DBS in alleviating motor symptoms such as rigidity, while significantly reducing stimulation time and energy consumption by up to 56% [54, 55]. Some reports indicate that aDBS can lead to motor score improvements that are 27% to 29% higher than open-loop DBS and provides better control of symptoms and dyskinesias, particularly improving bradykinesia without additional side effects [55, 56]. Rather than directly suppressing calcium signalling, this approach limits activity-driven calcium and metabolic burden, representing a mechanism-informed evolution of system-level intervention for Parkinson's disease [49].

5. Conclusion

Parkinson's disease is best understood not as the consequence of a single genetic defect or isolated molecular pathway, but as the outcome of multilevel processes converging on calcium dysregulation. The intrinsic reliance of substantia nigra dopaminergic neurons on sustained calcium-dependent pacemaking creates a physiological vulnerability that, when combined with genetic and cellular stressors, predisposes these neurons to degeneration.

Genetically diverse risk factors, including PINK1/Parkin, LRRK2, and GBA, disrupt calcium handling at distinct cellular sites yet converge functionally to impair mitochondrial buffering, lysosomal clearance, and organelle quality control. These disturbances reinforce one another through calcium-driven oxidative stress,

α-synuclein aggregation, and defective autophagy, forming a self-sustaining cycle of neuronal dysfunction. Importantly, calcium-associated pathology extends beyond individual neurons, promoting neuroinflammation and network-level reorganisation that ultimately manifests as basal ganglia circuit dysfunction and motor impairment.

This integrated framework helps explain the limited clinical success of calcium-targeted pharmacological interventions, as global calcium inhibition risks disrupting essential physiological signalling and is unlikely to reverse established pathology. Future disease-modifying strategies will therefore require greater molecular and temporal precision and will likely need to be integrated with systems-level approaches. In this context, adaptive neuromodulation strategies that reduce activity-dependent calcium and metabolic burden offer a promising, mechanism-informed direction for therapeutic development.

References

[1] Bloem, B. R., Okun, M. S. and Klein, C. Parkinson's disease. Lancet. 2021, 397(10291), pp. 2284-2303. https://doi.org/10.1016/s0140-6736(21)00218-x.

[2] Ben-Shlomo, Y., Darweesh, S., Llibre-Guerra, J., Marras, C., San Luciano, M. and Tanner, C. The epidemiology of Parkinson's disease. Lancet. 2024, 403(10423), pp. 283-292. https://doi.org/10.1016/s0140-6736(23)01419-8.

[3] Michel, P. P., Hirsch, E. C. and Hunot, S. Understanding Dopaminergic Cell Death Pathways in Parkinson Disease. Neuron. 2016, 90(4), pp. 675-91. https://doi.org/10.1016/j.neuron.2016.03.038.

[4] Verma, A. and Ravindranath, V. Ca(V)1.3 L-Type Calcium Channels Increase the Vulnerability of Substantia Nigra Dopaminergic Neurons in MPTP Mouse Model of Parkinson's Disease. Frontiers in Aging Neuroscience. 2019, 11, p. 382. https://doi.org/10.3389/fnagi.2019.00382.

[5] Filimontseva, A., Fu, Y., Vila, M. and Halliday, G. M. Neuromelanin and selective neuronal vulnerability to Parkinson's disease. Trends in Neurosciences. 2025, 48(6), pp. 445-459. https://doi.org/10.1016/j.tins.2025.04.005.

[6] Benkert, J., Hess, S., Roy, S., Beccano-Kelly, D., Wiederspohn, N., Duda, J., Simons, C., Patil, K., Gaifullina, A., Mannal, N., et al. Cav2.3 channels contribute to dopaminergic neuron loss in a model of Parkinson's disease. Nature Communications. 2019, 10(1), p. 5094. https://doi.org/10.1038/s41467-019-12834-x.

[7] Beccano-Kelly, D. A., Cherubini, M., Mousba, Y., Cramb, K. M. L., Giussani, S., Caiazza, M. C., Rai, P., Vingill, S., Bengoa-Vergniory, N., Ng, B., et al. Calcium dysregulation combined with mitochondrial failure and electrophysiological maturity converge in Parkinson's iPSC-dopamine neurons. iScience. 2023, 26(7), p. 107044. https://doi.org/10.1016/j.isci.2023.107044.

[8] Lin, J., Pang, D., Li, C., Ou, R., Yu, Y., Cui, Y., Huang, J. and Shang, H. Calcium channel blockers and Parkinson's disease: a systematic review and meta-analysis. Therapeutic Advances in Neurological Disorders. 2024, 17, p. 17562864241252713. https://doi.org/10.1177/17562864241252713.

[9] Guzman, J. N., Sánchez-Padilla, J., Chan, C. S. and Surmeier, D. J. Robust pacemaking in substantia nigra dopaminergic neurons. Journal of Neuroscience. 2009, 29(35), pp. 11011-9. https://doi.org/10.1523/jneurosci.2519-09.2009.

[10] Guzman, J. N., Sanchez-Padilla, J., Wokosin, D., Kondapalli, J., Ilijic, E., Schumacker, P. T. and Surmeier, D. J. Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. Nature. 2010, 468(7324), pp. 696-700. https://doi.org/10.1038/nature09536.

[11] Surmeier, D. J., Guzman, J. N., Sanchez-Padilla, J. and Schumacker, P. T. The role of calcium and mitochondrial oxidant stress in the loss of substantia nigra pars compacta dopaminergic neurons in

Parkinson's disease. Neuroscience. 2011, 198, pp. 221-31. https://doi.org/10.1016/j.neuroscience.2011.08.045.

[12] Zucca, F. A., Segura-Aguilar, J., Ferrari, E., Muñoz, P., Paris, I., Sulzer, D., Sarna, T., Casella, L. and Zecca, L. Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. Progress in Neurobiology. 2017, 155, pp. 96-119. https://doi.org/10.1016/j.pneurobio.2015.09.012.

[13] Zhou, Z. D., Yi, L. X., Wang, D. Q., Lim, T. M. and Tan, E. K. Role of dopamine in the pathophysiology of Parkinson's disease. Translational Neurodegeneration. 2023, 12(1), p. 44. https://doi.org/10.1186/s40035-023-00378-6.

[14] Dryanovski, D. I., Guzman, J. N., Xie, Z., Galteri, D. J., Volpicelli-Daley, L. A., Lee, V. M., Miller, R. J., Schumacker, P. T. and Surmeier, D. J. Calcium entry and α-synuclein inclusions elevate dendritic mitochondrial oxidant stress in dopaminergic neurons. Journal of Neuroscience. 2013, 33(24), pp. 10154-64. https://doi.org/10.1523/jneurosci.5311-12.2013.

[15] Ricke, K. M., Paß, T., Kimoloi, S., Fährmann, K., Jüngst, C., Schauss, A., Baris, O. R., Aradjanski, M., Trifunovic, A., Eriksson Faelker, T. M., et al. Mitochondrial Dysfunction Combined with High Calcium Load Leads to Impaired Antioxidant Defense Underlying the Selective Loss of Nigral Dopaminergic Neurons. Journal of Neuroscience. 2020, 40(9), pp. 1975-1986. https://doi.org/10.1523/jneurosci.1345-19.2019.

[16] Verkhratsky, A. Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neurons. Physiological Reviews. 2005, 85(1), pp. 201-79. https://doi.org/10.1152/physrev.00004.2004.

[17] Matuz-Mares, D., González-Andrade, M., Araiza-Villanueva, M. G., Vilchis-Landeros, M. M. and Vázquez-Meza, H. Mitochondrial calcium: Effects of its imbalance in disease. Antioxidants (Basel). 2022, 11(5), p. 801. https://doi.org/10.3390/antiox11050801.

[18] Gandhi, S., Wood-Kaczmar, A., Yao, Z., Plun-Favreau, H., Deas, E., Klupsch, K., Downward, J., Latchman, D. S., Tabrizi, S. J., Wood, N. W., et al. PINK1-associated Parkinson's disease is caused by neuronal vulnerability to calcium-induced cell death. Molecular Cell. 2009, 33(5), pp. 627-38. https://doi.org/10.1016/j.molcel.2009.02.013.

[19] Dong-Chen, X., Yong, C., Yang, X., Chen-Yu, S. and Li-Hua, P. Signaling pathways in Parkinson's disease: molecular mechanisms and therapeutic interventions. Signal Transduction and Targeted Therapy. 2023, 8(1), p. 73. https://doi.org/10.1038/s41392-023-01353-3.

[20] Chiasserini, D., Paciotti, S., Eusebi, P., Persichetti, E., Tasegian, A., Kurzawa-Akanbi, M., Chinnery, P. F., Morris, C. M., Calabresi, P., Parnetti, L., et al. Selective loss of glucocerebrosidase activity in sporadic Parkinson's disease and dementia with Lewy bodies. Molecular Neurodegeneration. 2015, 10, p. 15. https://doi.org/10.1186/s13024-015-0010-2.

[21] Barazzuol, L., Giamogante, F., Brini, M. and Calì, T. PINK1/Parkin mediated mitophagy, Ca^{2+} signalling, and ER-mitochondria contacts in Parkinson's disease. International Journal of Molecular Sciences. 2020, 21(5), p. 1772. https://doi.org/10.3390/ijms21051772.

[22] Gregori, M., Pereira, G. J. S., Allen, R., West, N., Chau, K. Y., Cai, X., Bostock, M. P., Bolsover, S. R., Keller, M., Lee, C. Y., et al. Lysosomal TPC2 channels disrupt Ca^{2+} entry and dopaminergic function in models of LRRK2-Parkinson's disease. Journal of Cell Biology. 2025, 224(6), p. e202412055. https://doi.org/10.1083/jcb.202412055.

[23] Xiong, Y. and Yu, J. LRRK2 in Parkinson's disease: upstream regulation and therapeutic targeting. Trends in Molecular Medicine. 2024, 30(10), pp. 982-996. https://doi.org/10.1016/j.molmed.2024.07.003.

[24] Alharbi, A. F. and Parrington, J. TPC2 in drug development: Emerging target for cancer, viral infections, cardiovascular diseases, and neurological disorders. Pharmacological Research. 2025, 213, p. 107655. https://doi.org/10.1016/j.phrs.2025.107655.

[25] Medina, D. L., Di Paola, S., Peluso, I., Armani, A., De Stefani, D., Venditti, R., Montefusco, S., Scotto-Rosato, A., Prezioso, C., Forrester, A., et al. Lysosomal calcium signalling regulates autophagy through calcineurin and TFEB. Nature Cell Biology. 2015, 17(3), pp. 288-99. https://doi.org/10.1038/ncb3114.

[26] Burbulla, L. F. and Krainc, D. The role of dopamine in the pathogenesis of GBA1-linked Parkinson's disease. Neurobiology of Disease. 2019, 132, p. 104545. https://doi.org/10.1016/j.nbd.2019.104545.

[27] Giamogante, F., Barazzuol, L., Maiorca, F., Poggio, E., Esposito, A., Masato, A., Napolitano, G., Vagnoni, A., Calì, T. and Brini, M. A SPLICS reporter reveals [Formula: see text]-synuclein regulation of lysosome-mitochondria contacts which affects TFEB nuclear translocation. Nature Communications. 2024, 15(1), p. 1516. https://doi.org/10.1038/s41467-024-46007-2.

[28] Kaur, S., Sehrawat, A., Mastana, S. S., Kandimalla, R., Sharma, P. K., Bhatti, G. K. and Bhatti, J. S. Targeting calcium homeostasis and impaired inter-organelle crosstalk as a potential therapeutic approach in Parkinson's disease. Life Sciences. 2023, 330, p. 121995. https://doi.org/10.1016/j.lfs.2023.121995.

[29] Filadi, R., Theurey, P. and Pizzo, P. The endoplasmic reticulum-mitochondria coupling in health and disease: Molecules, functions and significance. Cell Calcium. 2017, 62, pp. 1-15. https://doi.org/10.1016/j.ceca.2017.01.003.

[30] Ramezani, M., Wagenknecht-Wiesner, A., Wang, T., Holowka, D. A., Eliezer, D. and Baird, B. A. Alpha synuclein modulates mitochondrial Ca^{2+} uptake from ER during cell stimulation and under stress conditions. NPJ Parkinsons Dis. 2023, 9(1), p. 137. https://doi.org/10.1038/s41531-023-00578-x.

[31] Bellomo, G., Paciotti, S., Gatticchi, L. and Parnetti, L. The vicious cycle between α-synuclein aggregation and autophagic-lysosomal dysfunction. Movement Disorders. 2020, 35(1), pp. 34-44. https://doi.org/10.1002/mds.27895.

[32] Lang, M., Pramstaller, P. P. and Pichler, I. Crosstalk of organelles in Parkinson's disease - MiT family transcription factors as central players in signaling pathways connecting mitochondria and lysosomes. Molecular Neurodegeneration. 2022, 17(1), p. 50. https://doi.org/10.1186/s13024-022-00555-7.

[33] Bastioli, G., Piccirillo, S., Graciotti, L., Carone, M., Sprega, G., Taoussi, O., Preziuso, A. and Castaldo, P. Calcium deregulation in neurodegeneration and neuroinflammation in Parkinson's disease: Role of calcium-storing organelles and sodium-calcium exchanger. Cells. 2024, 13(15), p. 1301. https://doi.org/10.3390/cells13151301.

[34] Chung, Y. C., Shin, W. H., Baek, J. Y., Cho, E. J., Baik, H. H., Kim, S. R., Won, S. Y. and Jin, B. K. 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. Experimental and Molecular Medicine. 2016, 48(1), p. e205. https://doi.org/10.1038/emm.2015.100.

[35] Ruan, Z., Zhang, D., Huang, R., Sun, W., Hou, L., Zhao, J. and Wang, Q. Microglial activation damages dopaminergic neurons through mmp-2/-9-mediated increase of blood-brain barrier permeability in a Parkinson's disease mouse model. International Journal of Molecular Sciences. 2022, 23(5), p. 2793. https://doi.org/10.3390/ijms23052793.

[36] Rommelfanger, K. S. and Wichmann, T. Extrastriatal dopaminergic circuits of the Basal Ganglia. Frontiers in Neuroanatomy. 2010, 4, p. 139. https://doi.org/10.3389/fnana.2010.00139.

[37] McGregor, M. M. and Nelson, A. B. Circuit mechanisms of Parkinson's disease. Neuron. 2019, 101(6), pp. 1042-1056. https://doi.org/10.1016/j.neuron.2019.03.004.

[38] Cazorla, M., Kang, U. J. and Kellendonk, C. Balancing the basal ganglia circuitry: a possible new role for dopamine D2 receptors in health and disease. Movement Disorders. 2015, 30(7), pp. 895-903. https://doi.org/10.1002/mds.26282.

[39] Ellens, D. J. and Leventhal, D. K. Review: electrophysiology of basal ganglia and cortex in models of Parkinson disease. Journal of Parkinson's Disease. 2013, 3(3), pp. 241-54. https://doi.org/10.3233/jpd-130204.

[40] Galvan, A., Devergnas, A. and Wichmann, T. Alterations in neuronal activity in basal ganglia-thalamocortical circuits in the parkinsonian state. Frontiers in Neuroanatomy. 2015, 9, p. 5. https://doi.org/10.3389/fnana.2015.00005.

[41] Stoessl, A. J., Lehericy, S. and Strafella, A. P. Imaging insights into basal ganglia function, Parkinson's disease, and dystonia. Lancet. 2014, 384(9942), pp. 532-44. https://doi.org/10.1016/s0140-6736(14)60041-6.

[42] Surmeier, D. J., Halliday, G. M. and Simuni, T. Calcium, mitochondrial dysfunction and slowing the progression of Parkinson's disease. Experimental Neurology. 2017, 298(Pt B), pp. 202-209. https://doi.org/10.1016/j.expneurol.2017.08.001.

[43] Swart, T. and Hurley, M. J. Calcium channel antagonists as disease-modifying therapy for Parkinson's disease: Therapeutic rationale and current status. CNS Drugs. 2016, 30(12), pp. 1127-1135. https://doi.org/10.1007/s40263-016-0393-9.

[44] Caulfield, M. E., Manfredsson, F. P. and Steece-Collier, K. The role of striatal Cav1.3 calcium channels in therapeutics for Parkinson's disease. Handbook of Experimental Pharmacology. 2023, 279, pp. 107-137. https://doi.org/10.1007/164_2022_629.

[45] Vijiaratnam, N., Simuni, T., Bandmann, O., Morris, H. R. and Foltynie, T. Progress towards therapies for disease modification in Parkinson's disease. Lancet Neurology. 2021, 20(7), pp. 559-572. https://doi.org/10.1016/s1474-4422(21)00061-2.

[46] Liss, B. and Striessnig, J. The potential of L-type calcium channels as a drug target for neuroprotective therapy in Parkinson's disease. Annual Review of Pharmacology and Toxicology. 2019, 59, pp. 263-289. https://doi.org/10.1146/annurev-pharmtox-010818-021214.

[47] Duda, J., Pötschke, C. and Liss, B. Converging roles of ion channels, calcium, metabolic stress, and activity pattern of Substantia nigra dopaminergic neurons in health and Parkinson's disease. Journal of Neurochemistry. 2016, 139 Suppl 1(Suppl Suppl 1), pp. 156-178. https://doi.org/10.1111/jnc.13572.

[48] Habets, J. G. V., Heijmans, M., Kuijf, M. L., Janssen, M. L. F., Temel, Y. and Kubben, P. L. An update on adaptive deep brain stimulation in Parkinson's disease. Movement Disorders. 2018, 33(12), pp. 1834-1843. https://doi.org/10.1002/mds.115.

[49] Chen, D., Zhao, Z., Shi, J., Li, S., Xu, X., Wu, Z., Tang, Y., Liu, N., Zhou, W., Ni, C., et al. Harnessing the sensing and stimulation function of deep brain-machine interfaces: a new dawn for overcoming substance use disorders. Transl Psychiatry. 2024, 14(1), p. 440. https://doi.org/10.1038/s41398-024-03156-8.

[50] Mao, Z., Ling, Z., Pan, L., Xu, X., Cui, Z., Liang, S. and Yu, X. Comparison of efficacy of deep brain stimulation of different targets in Parkinson's disease: A network meta-analysis. Frontiers in Aging Neuroscience. 2019, 11, p. 23. https://doi.org/10.3389/fnagi.2019.00023.

[51]Porta, M., Servello, D., Zekaj, E., Gonzalez-Escamilla, G. and Groppa, S. Pre-dopa deep brain stimulation: Is early deep brain stimulation able to modify the natural course of Parkinson's disease? Frontiers in Neuroscience. 2020, 14, p. 492. https://doi.org/10.3389/fnins.2020.00492.

[52] Limousin, P. and Foltynie, T. Long-term outcomes of deep brain stimulation in Parkinson disease. Nature Reviews: Neurology. 2019, 15(4), pp. 234-242. https://doi.org/10.1038/s41582-019-0145-9.

[53] Wang, S., Zhu, G., Shi, L., Zhang, C., Wu, B., Yang, A., Meng, F., Jiang, Y. and Zhang, J. Closed-loop adaptive deep brain stimulation in Parkinson's disease: Procedures to achieve it and future perspectives. Journal of Parkinson's Disease. 2023, 13(4), pp. 453-471. https://doi.org/10.3233/jpd-225053.

[54] Johnson, L. A., Nebeck, S. D., Muralidharan, A., Johnson, M. D., Baker, K. B. and Vitek, J. L. Closed-Loop Deep Brain Stimulation Effects on Parkinsonian Motor Symptoms in a Non-Human Primate - Is Beta Enough? Brain Stimulation. 2016, 9(6), pp. 892-896. https://doi.org/10.1016/j.brs.2016.06.051.

[55] Parastarfeizabadi, M. and Kouzani, A. Z. Advances in closed-loop deep brain stimulation devices. Journal of Neuroengineering and Rehabilitation. 2017, 14(1), p. 79. https://doi.org/10.1186/s12984-017-0295-1.

[56] Rosa, M., Arlotti, M., Ardolino, G., Cogiamanian, F., Marceglia, S., Di Fonzo, A., Cortese, F., Rampini, P. M. and Priori, A. Adaptive deep brain stimulation in a freely moving Parkinsonian patient. Movement Disorders. 2015, 30(7), pp. 1003-5. https://doi.org/10.1002/mds.26241.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgment

This paper is an output of the science project.