REVIEW

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LRRK2 mutations: at the crossroads of dopamine, iron, and calcium imbalance in Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons. The G2019S mutation in the leucine-rich repeat kinase 2 (*LRRK2*) gene is the most common genetic cause of familial and sporadic PD. In dopaminergic neurons, increased kinase activity caused by *LRRK2*-G2019S mutation impairs synaptic vesicle recycling and dopamine storage, increasing cytosolic dopamine, which is prone to oxidation and generates reactive oxygen species. Simultaneously, the mutation alters iron metabolism through Rab misregulation, increasing iron uptake and lysosomal dysfunction, further amplifying oxidative stress and creating a pro-ferroptotic environment. At the same time, dysregulated calcium signaling, driven by the enhanced activity of L-type calcium channels and impaired mitochondrial calcium buffering *via* the mitochondrial calcium uniporter, enhances mitochondrial dysfunction. This minireview integrates current evidence linking *LRRK2*-G2019S to these pathological pathways, highlighting this mutation's role in dopamine, iron, and calcium imbalance. Understanding this molecular interplay may provide novel insights into PD pathogenesis and guide the development of targeted neuroprotective therapies.

Key words: LRRK2, dopamine, calcium, iron, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder clinically characterized by both motor and non-motor symptoms. The main hallmark of the disease is loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) (Blauwendraat et al., 2020). Among many mutations in genes associated with PD like *SNCA* (alfa-synuclein), *Parkin*, and *PINK1* encoding protein kinase, leucine-rich-repeat kinase 2 (*LRRK2*) mutations are the most common cause of both sporadic and familial PD, constituting 1–2% of all cases of PD (Lees et al., 2009). LRRK2 is a serine–threonine kinase capable of regulating its own activity through autophosphorylation (Greggio et al., 2008; Guaitoli et al., 2016) and of phosphorylating other proteins. Its main substrates are proteins from Rab GTPases family, which links the kinase with processes such as vesicular protein trafficking, endocytosis, or autophagy (Stenmark, 2009; Steger et al., 2016; Pfeffer, 2018). Simultaneously, mutations of the *LRRK2* gene have been shown to disrupt calcium homeostasis, impair mitochondrial function, and exacerbate iron dysregulation (Verma et al., 2017; Jia et al., 2023).

Labile iron (Fe^{2+}) is a fundamental element in the central nervous system, playing an indispensable role in cellular energy metabolism and neurotransmission (Kulaszyńska et al., 2024). As a cofactor for numerous enzymes, iron is essential for mitochondrial electron transport and oxidative phosphorylation, thereby supporting the high energy demands of neuronal activity (Read et al., 2021). Among central nervous system regions, SNpc is a structure that is enriched in dopaminergic neurons and is uniquely characterized by high physiological iron content (Snyder & Connor, 2009).

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Iron must be tightly controlled because its dysregulation can lead to the generation of reactive oxygen species (ROS), lipid peroxidation, and ultimately neuronal death (Crichton, 2016). This type of cell death, described as ferroptosis has been identified as a central mechanism in PD-related neurodegeneration (Tong et al., 2022; Li et al., 2025). Dopaminergic neurons are particularly vulnerable to Fe^{2+}-mediated oxidative stress because of their high metabolic activity and the inherent reactivity of dopamine, which can auto-oxidize into toxic quinones (Zhou et al., 2010). Additionally, aberrant iron accumulation in the SNpc is a hallmark of PD and has been consistently linked to dopaminergic neuron loss (Foley et al., 2022; López-Aguirre et al., 2025).

Another important pathway that, if dysregulated, may contribute to neurodegeneration is calcium metabolism. The mitochondrial calcium uniporter (MCU) mediates calcium ions (Ca^{2+}) influx into mitochondria, linking cytosolic Ca^{2+} signals to energy metabolism and ROS production. Chronic mitochondrial Ca^{2+} overload, particularly under conditions of sustained L-type calcium channel activation and LRRK2 dysfunction, amplifies oxidative damage and promotes cell death (Verma et al., 2017; Feno et al., 2019). Although calcium, iron, and dopamine dysregulation are central to PD pathology, how they interact particularly in the context of the *LRRK2* G2019S mutation remains poorly understood. The present review sheds light on this complex interplay and identifies key areas for future research.

LRRK2 mutations and calcium homeostasis

LRRK2 is cytosolic multidomain protein which is widely expressed in the human brain (Miklossy et al., 2006). It is composed of two enzymatic domains: Ras of complex protein (ROC) GTPase domain, followed by a C-terminal of ROC (COR) and a serine/threonine kinase domain (KIN) as well as several solenoid domains (involved in protein-protein interactions) that are localized to its C-terminus (WD40 domain) and N-terminus (ankyrin, armadillo, and leucine-rich repeat [LRR] domains). As a serine-threonine kinase with GTPase activity, LRRK2 phosphorylates a subset of 10 Rab GTPases (Rab3A/B/C/D, Rab8A/B, Rab10, Rab12, Rab35, and Rab43), inhibiting their activity and thereby modulating intracellular membrane and protein trafficking, as well as organelle identity and function (Stenmark, 2009; Steger et al., 2016; Pfeffer, 2018). In addition, LRRK2 is involved in multiple signalling pathways that regulate diverse cellular processes, including immune responses and cellular senescence (Ravinther et al., 2022).

Point mutations in *LRRK2* are the most common genetic cause of both familial and sporadic forms of PD, leading to its autosomal-dominant inheritance pattern (Klein & Westenberger, 2012; Verma et al., 2017). N1437H, N1437S, R1441C, R1441G, R1441H, R1441S mutations are localized to ROC domain, V1699C to the COR domain, I1122V to the LRR domain, whereas G2019S and I2020T are localized to the kinase domain (Ito & Utsunomiya-Tate, 2023). All of the aforementioned mutations result in higher kinase activity, which has serious implications for the cellular function of LRRK2 and PD development (West et al., 2005; Gloeckner et al., 2006; Turski et al., 2022) (Table 1).

The *LRRK2 G2019S* mutation, described in more detail here, has been increasingly implicated in Ca^{2+} dysregulation and mitochondrial dysfunction (Verma et al., 2017). It was shown that the *LRRK2* G2019S mutation disrupts calcium signalling by enhancing voltage-gated calcium channel activity, increasing Ca^{2+} influx, and shifting channel activation to more hyperpolarized voltages, contributing to neuronal vulnerability (Bedford et al., 2016) (Fig. 1). In SNpc dopaminergic neurons (i.e., cells that are particularly susceptible in PD), calcium homeostasis is crucial because of their intrinsic pacemaking activity, which drives continuous Ca^{2+} influx through L-type channels even at resting membrane potential (Guzman et al., 2009). Mitochondria play a central role in buffering cytosolic Ca^{2+} and translating these signals into metabolic output. The MCU mediates Ca^{2+} uptake into the matrix, stimulating tricarboxylic acid cycle dehydrogenases and enhancing nicotinamide adenine dinucleotide (NAD) production to drive adenosine triphosphate (ATP) synthesis. This tightly couples cytosolic Ca^{2+} dynamics to cellular energy metabolism, imposing a substantial metabolic burden (McCormack et al., 1990; Jouaville et al., 1999). Mitochondria are strategically positioned near endoplasmic reticulum (ER) calcium release sites to facilitate efficient, localized Ca^{2+} transfer (Vance, 1990; Rowland & Voeltz, 2012). Regulatory proteins such as mitochondrial calcium uptake 1 (MICU1), which inhibits MCU (Matesanz-Isabel et al., 2016) and the mitochondria sodium/calcium exchanger (NCLX) responsible for Ca^{2+} efflux (Palty et al., 2010; Wasilewska et al., 2025), fine tune these fluxes. Although essential for physiological responses, prolonged or excessive mitochondrial Ca^{2+} entry can promote oxidative stress and trigger cell death pathways (Rosenstock et al., 2004; Maggi et al., 2023). Chronic mitochondrial Ca^{2+} uptake, enhanced by *LRRK2* mutations (G2019S, R1441C), leads to calcium overload. These mutations increase L-type voltage-gated calcium channels (VGCCs) activity by binding to their subunits, causing sustained Ca^{2+} influx into mitochondria. Combined with reduced basal mito-

Table 1. Pathogenic gain-of-function LRRK2 point mutations.

Mutation	Affected domain	Effect on LRRK2 function	Sporadic and/or? Familial	References
N1437H	ROC	Stabilizes ROC dimer conformation, lowers GTP-ase activity and GTP binding affinity	Sporadic & Familial	Aasly et al., 2010; Puschmann et al., 2012; Huang et al., 2019
N1437S	ROC	By similarity to N1437H: stabilizes ROC dimer conformation, lowers GTP-ase activity and GTP binding affinity	Familial	Brockmann et al., 2011
N1437D	ROC	By similarity to N1437H; stabilizes ROC dimer conformation, lowers GTP-ase activity and GTP binding affinity	Only 1 case reported with family history of PD	Li et al., 2020
R1441C	ROC	Stabilizes ROC monomer conformation, enhances GTP binding and kinase activity	Familial	Latourelle et al., 2008; Huang et al., 2019
R1441G	ROC	Stabilizes ROC monomer conformation, enhances GTP binding and kinase activity	Sporadic & Familial	Simón-Sánchez et al., 2006; Gorostidi et al., 2009; Huang et al., 2019
R1441H	ROC	Stabilizes ROC monomer conformation, enhances GTP binding and kinase activity	Familial	Spanaki et al., 2006; L. Zhang et al., 2013; Huang et al., 2019
R1441S	ROC	By similarity to R1441C/G/H; stabilizes ROC monomer conformation, enhances GTP binding and kinase activity	Familial	Mata et al., 2016
I1122V	LRR	Influences protein stability, increases kinase activity without changes in GTP-binding	Familial	Zimprich et al., 2004; West et al., 2005
Y1699C	COR	Strengthens ROC-COR intramolecular binding, decreases GTP-ase activity and increases kinase activity	Familial	Funayama et al., 2005; Daniëls et al., 2011
I2020T	KIN	Localizes to the kinase activation loop, stabilizing Mg^{2+}/ATP binding and increases kinase activity	Familial	Zimprich et al., 2004; Funayama et al., 2005; Kalogeropulou et al., 2022
G2019S	KIN	Localizes to the kinase activation loop, enhances ATP binding and increases kinase activity	Sporadic and/or Familial	Kalogeropulou et al., 2022; Ito & Utsunomiya-Tate, 2023

phagy, this overload triggers excessive ROS production, mitochondrial membrane depolarization, and impaired ATP synthesis, collectively contributing to neuronal degeneration (Feno et al., 2019) (Fig. 1). Additionally, high intracellular Ca^{2+} activates neuronal calcium sensor-1 (NCS1), a key regulator of dopamine D_2 receptor signaling. Active NCS1 blocks D_2 autoreceptor internalization, preventing receptor desensitization. As a result, cytosolic dopamine accumulates, increasing oxidative stress and leading to neuronal damage (Catoni et al., 2019).

LRRK2 mutations and iron homeostasis

Emerging evidence indicates that *LRRK2* G2019S mutations, through greater kinase activity, impairs Ras-related protein 8a (Rab8a) function, potentially disrupting iron uptake and storage pathways in microglia, particularly under inflammatory conditions (Mamais et al., 2021). Rab guanosine triphosphatases are essential coordinators of membrane trafficking in eukaryotic cells, guiding vesicle formation, transport, and fusion, and are critically involved in such processes as protein sorting and autophagy (Stenmark, 2009; Steger et al., 2016, 2017; Bonet-Ponce & Cookson, 2019; Liu et al., 2022; Pfeffer, 2023). However, in the context of the *LRRK2* G2019S mutation, Rab8a and Rab10 are the most affected among Ras-related proteins. Rab8 is closely related to transferrin receptor (TfR) recycling and its endocytic trafficking. It interacts directly with this receptor, and Rab8a-deficient cells are no longer capable of TfR recycling (Hattula et al., 2006). Rab8a is a substrate for LRRK2; thus, kinase mutations directly affect its function. Under conditions of LRRK2 overactivation, Rab8a becomes sequestrated to lysosomes, resulting in the dysregulation of transferrin recycling and an increase in Fe^{2+} accumulation (Mamais et al., 2021). Another LRRK2 substrate is Rab10, which together with Rab8a is recruited to phagosomes during maturation. LRRK2 knockout was shown to disrupt this process, emphasizing Rab10 role in both endosome recycling and the maturation process (Lee et al., 2020).

Additionally, recent studies suggest a bidirectional relationship between LRRK2 activity and iron metabolism in PD. Fe^{2+} exposure enhances LRRK2 phosphorylation at key regulatory sites (S935 and S1292), whereas overactive LRRK2, particularly the G2019S mutant, promotes higher total iron (sum of Fe^{2+} and Fe^{3+} ions) content *via* an increase in Fe^{2+} uptake. Such an accumula-

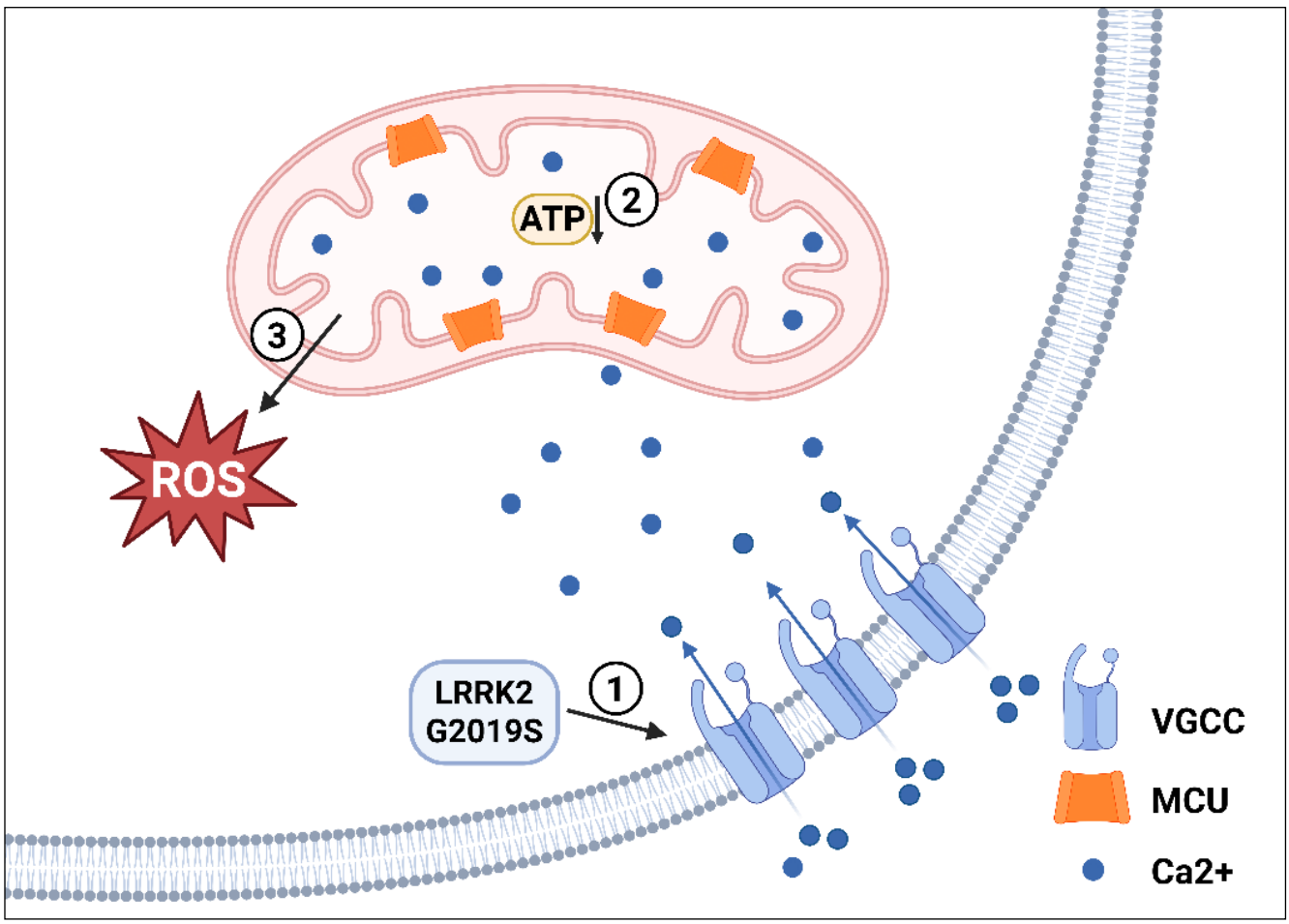

Fig. 1. LRRK2-mediated disruption of calcium homeostasis and mitochondrial function. (1) LRRK2 mutations increase the activity of voltage-gated calcium channels (VGCCs) by binding to their subunits, leading to sustained calcium influx into neurons. (2) The chronic elevation of cytosolic Ca^{2+} leads to excessive mitochondrial calcium uptake, which impairs mitochondrial membrane potential and oxidative phosphorylation, thereby reducing ATP production and contributing to neuronal energy deficits. (3) Calcium overload within mitochondria enhances reactive oxygen species (ROS) generation, promoting oxidative stress and mitochondrial damage.

tion of Fe^{2+} amplifies oxidative stress and ROS production and promotes dopaminergic neuron degeneration (Fig. 2). This interplay emphasizes the role of LRRK2 in maintaining Fe^{2+} homeostasis, positioning Fe^{2+} as both a modulator and downstream effector of LRRK2 signaling (Jia et al., 2023).

Neuroimaging studies provide further support to the role of iron in LRRK2-associated PD. Such techniques as R2* (R2 plus additional signal loss caused by magnetic field inhomogeneities) relaxometry and transcranial sonography have consistently revealed higher total iron levels in the substantia nigra in individuals who carry *LRRK2* mutations (G2019S, R1441H,), often surpassing iron levels that are observed in idiopathic PD cases (Schweitzer et al., 2007; Pyatigorskaya et al., 2015). Moreover, high iron levels were also found in asymptomatic patients, placing its deposition among early, preclinical disease symptoms (Pyatigorskaya et al., 2015). Patients with genetically caused PD showed a small but meaningful increase in SN echogenicity compared with healthy patients. These results were further linked to high iron levels, highlighting its role in PD pathology (Schweitzer et al., 2007). The aforementioned findings underscore the possibility that iron-mediated oxidative stress may be a more prominent feature of LRRK2-linked neurodegeneration, warranting further studies of iron-targeted therapeutic strategies in these genetic PD subtype cases (Schweitzer et al., 2007; Pyatigorskaya et al., 2015; Jia et al., 2023).

Calcium dysregulation and role of MCU in PD

Recent studies highlight how mitochondrial Ca^{2+} dysregulation *via* MCU mediates neurotoxicity, positioning MCU inhibition as a possible neuroprotective

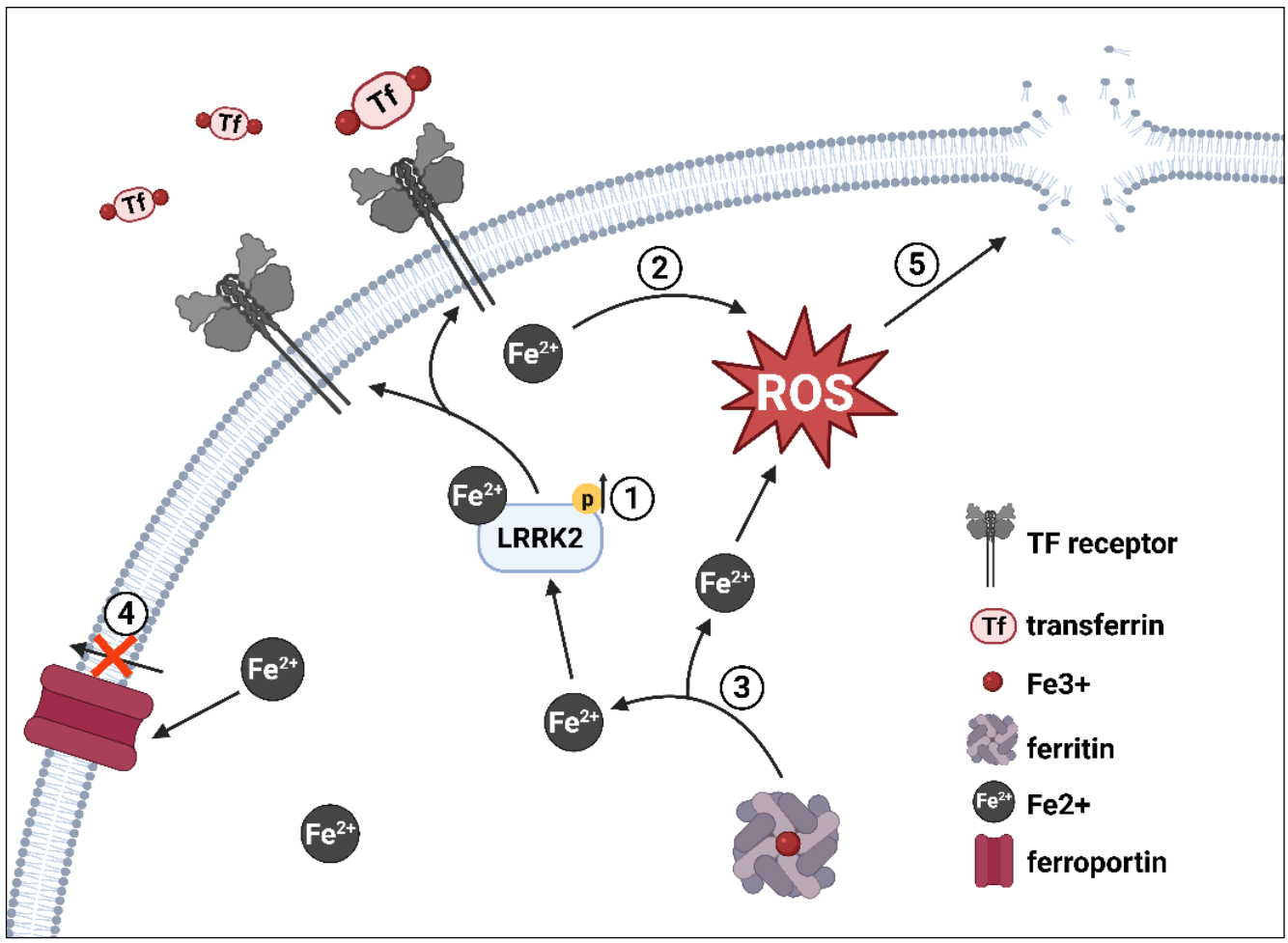

Fig. 2. Disruption of iron homeostasis and LRRK2 signaling: pathway to ferroptosis. (1) Elevated Fe^{2+} levels increase LRRK2 phosphorylation at key regulatory residues, which in turn promotes excessive Fe^{2+} influx into neurons via transferrin (Tf)-mediated transport of ferric iron (Fe^{3+}) that is subsequently reduced intracellularly. (2) The resulting accumulation of Fe^{2+} promotes excessive reactive oxygen species (ROS) production and oxidative stress. (3) The G2019S LRRK2 causes imbalanced ferritin expression, with elevated ferritin light chain (FTL) and reduced ferritin heavy chain (FTH), impairing iron sequestration and ferroxidase activity, thereby increasing the labile iron pool and exacerbating oxidative damage. (Goldman et al., 2025). (4) Lower expression or activity of the iron exporter ferroportin leads to intracellular iron accumulation. (5) Excess iron triggers ferroptosis and contributes to lipid peroxidation, further damaging neuronal integrity.

strategy (Dey et al., 2020; Johnson et al., 2023). In cortical neurons and patient-derived fibroblasts with *LRRK2* (G2019S, R1441C) mutations, mitochondrial Ca^{2+} uptake is elevated, attributable to the mitogen-activated protein kinase 1/2 (MAPK1/2)-driven transcriptional upregulation of MCU and mitochondrial calcium uptake (MICU1) proteins, whereas NCLX levels remain unchanged. This Ca^{2+} imbalance promotes dendritic atrophy and neuritic degeneration, key features of PD pathology. Neuroprotection is achieved by MAPK1/2 inhibition or MCU blockade, which attenuates mitochondrial Ca^{2+} overload and preserves dendritic structure (Verma et al., 2017). Moreover, morpholino (synthetic, nuclease-resistant nucleic acid analogues that suppress gene expression by sterically blocking mRNA translation or pre-mRNA splicing in a sequence-specific manner) mediated inhibition of the Mcu rescues dopaminergic neurons in the *pink1*$^{-/-}$ zebrafish model (Corey & Abrams, 2001; Soman et al., 2017). Extending these findings, studies of CRISPR/Cas9-generated *mcu*$^{-/-}$ zebrafish revealed that the genetic ablation of Mcu restored mitochondrial area and rescued dopaminergic neurons in *pink1*$^{-/-}$ zebrafish and in fish treated with MPTP (Soman et al., 2019), a neurotoxin that models Parkinson's disease (Sian et al., 1999). Functional assays, *in vivo* calcium imaging, and mitochondrial morphology analyses indicate that *mcu* deletion attenuates mitochondrial Ca^{2+} overload and depolarization, conferring neuroprotection (Soman et al., 2019). Another study shows that *MCU* knockdown decreases neu-

roinflammatory responses in hippocampal neurons, in addition to improving PINK1-Parkin signaling (Cai et al., 2022). One of the proteins of the Rho GTPase family, Miro1, was shown to be a modulator of MCU activity, suggesting a potential therapeutic approach (Schwarz et al., 2022). Collectively, recent findings highlight MCU as a key modulator of calcium-dependent neurodegeneration and support its inhibition as a potential therapeutic strategy in both genetic and toxin-induced models of PD (Dey et al., 2020; Johnson et al., 2023). Moreover, in Pink1 Drosophila model of Parkinson's disease, genetic loss of the *mcu*, (in both homozygote and heterozygote), robustly rescues locomotor deficits, dopaminergic neuron loss, and shortened lifespan (Twyning et al., 2024). Importantly, *mcu* knockdown normalized mitochondrial Ca^{2+} levels without altering mitochondria endoplasmic reticulum contact sites (MERCs), indicating that pathological phenotypes arise primarily from excessive mitochondrial Ca^{2+} uptake rather than altered inter organelle coupling. In this model, reducing mitochondrial Ca^{2+} influx *via mcu* loss or enhancing Ca^{2+} efflux through *NCLX* overexpression suppresses key pathological phenotypes (Twyning et al., 2024).

Ferroptosis in PD

Ferroptosis is a unique type of cell death mechanically distinct from apoptosis and necrosis, and is regulated mostly by glutathione peroxidase 4 (GPX4), nuclear erythroid 2 p45 related factor 2 (NRF2), and heat shock proteins (Yang & Stockwell, 2008; Wolpaw et al., 2011; Friedmann Angeli et al., 2014; Sun et al., 2015, 2016). Ferroptotic cells exhibit several morphological and structural changes, such as loss of plasma membrane integrity, swelling of cytoplasmic organelles, mitochondria condensation, and rupture of their outer membrane (Tang et al., 2021). The main factor that triggers ferroptosis is dysregulated Fe^{2+} metabolism. The disruption of iron homeostasis in PD involves complex molecular changes such as high cellular iron uptake mediated by the upregulation of divalent metal transporter 1 (DMT1), and impairments in ferritin function that compromises iron storage. In parallel, decreases in the expression or activity of the iron exporter ferroportin limit the removal of intracellular iron, collectively promoting cytosolic iron accumulation (Zeng et al., 2024). Restoring the proper level of ferroportin and ferritin reduces cellular levels of Fe^{2+}, thus rescuing cells from ferroptosis (Chen et al., 2020).

The labile iron pool is composed of $Fe^{2+,}$ which is a highly active form. It has a cytotoxic potential and catalyses the production of hydroxyl radical (•OH) *via* the Fenton reaction. This reactive oxygen form is capable of initiating lipid peroxidation by forming lipid radicals (L•) - the most critical factor for ferroptosis induction (Costa et al., 2023). Next, lipid radicals react with oxygen to form lipid peroxyl radicals (LOO•), which may propagate production of new LOO• and LOOH in neighboring lipids (Ding et al., 2023).

Membrane phospholipids are particularly prone to undergo lipid peroxidation due to the weakness of their carbon-hydrogen bonds (Stockwell, 2022). Especially, two fatty acyls from phosphatidylethanolamines undergo oxidation: arachidonoyl (AA) and adrenoyl (AdA) (Kagan et al., 2017). In addition to oxidation resulting from Fenton reaction these lipids can be oxidized by an iron-dependent enzyme, lipoxygenase (LOX) (Yang et al., 2016; Shah et al., 2018). The main ferroptosis inhibition mechanism is GPX4-glutathione (GSH) dependent peroxidase, which works through the x_c^-/GSH/GPX4 axis. The upstream component of this pathway is the cystine/glutamate antiporter (xCT). Cystine that is taken by cells is used for GSH synthesis. In the presence of GSH, GPX4 reduces LOOH to LOH and, in the process, oxidizes GSH to glutathione disulfide (GSSG). It was shown that GSH depletion may inactivate GPX4 and drive cells towards ferroptosis (Yang et al., 2014). However, some systems work independently of GPX4 to prevent excessive oxidative stress and ferroptosis. One of them is ferroptosis suppressor protein 1 (FSP1), whose protection is mediated by coenzyme $Q_{10.}$ In its reduced form (Q_{10}-H_2) coenzyme Q_{10} is a potent mitochondrial and lipid peroxyl radical trapping antioxidant, and FSP1 catalyzes the reduction of coenzyme Q_{10} (Doll et al., 2019). Another mechanism is based on the activity of GTP cyclohydrolase-1 (GCH1), which controls the endogenous production of antioxidant, tetrahydrobiopterin and increases coenzyme Q_{10} synthesis (Kraft et al., 2020).

Recently, growing interest has been seen in the role of ferroptosis in PD pathology. Ferroptosis was shown to be the most common type of cell death in PD cases (Zhang et al., 2020; Tong et al., 2022; Li et al., 2025). Pathological iron accumulation within the SNpc is considered a hallmark of PD and one of its most consistently observed neuropathological features. High total iron levels in the SNpc have been confirmed by multiple methodologies, including magnetic resonance imaging, postmortem histochemical staining, and biochemical assays (Foley et al., 2022; López-Aguirre et al., 2025). This regional iron overload correlates with the degree of dopaminergic neuron loss and inversely with striatal dopamine content, suggesting a direct role in PD progression (López-Aguirre et al., 2025). These alterations increase neuronal susceptibility to oxidative stress and metabolic dysfunction. Some genes described as ferroptosis-related can be found among differentially

expressed genes in patients with PD; the expression of secreted proteins, such as high-mobility group box 1 protein and ceruloplasmin, increased, whereas transferrin decreased (Liu et al., 2023).

LRRK2 in dopamine metabolism

One cellular function of LRRK2 is the regulation of lysosomal processes and endo-lysosomal trafficking (Madureira et al., 2020). However, consistent with its function in endo-lysosomal trafficking, it may also be involved in synaptic vesicle trafficking (Belluzzi et al., 2016). This becomes particularly interesting in the context of neurodegenerative diseases that very often are associated with impairments in synaptic function and the disruption of vesicle trafficking (Esposito et al., 2012; Sanna et al., 2012; Nguyen et al., 2019; Song et al., 2023). LRRK2 was previously linked to brain dopaminoceptive areas that undergo severe damage in PD (Galter et al., 2006). Subsequent studies showed that one PD-associated *LRRK2* mutation, G2019S, impacts dopamine receptor trafficking. It impairs dopamine D_1 receptor internalization and decreases the efficiency of D_2 receptor trafficking, which limits receptor turnover and alters dopamine-mediated signal transduction (Rassu et al., 2017).

The G2019S mutation is also associated with altered levels of two main dopamine transporters (DAT, called dopamine transporter and VMAT2, called vesicular monoamine transporter 2). Studies that used striatum from a mouse model of PD found that this mutation results in higher DAT levels and lower VMAT2 levels (Domenicale et al., 2022) (Fig. 3). Although changes in dopamine transporters become more pronounced with age, they do not appear to affect dopamine homeosta-

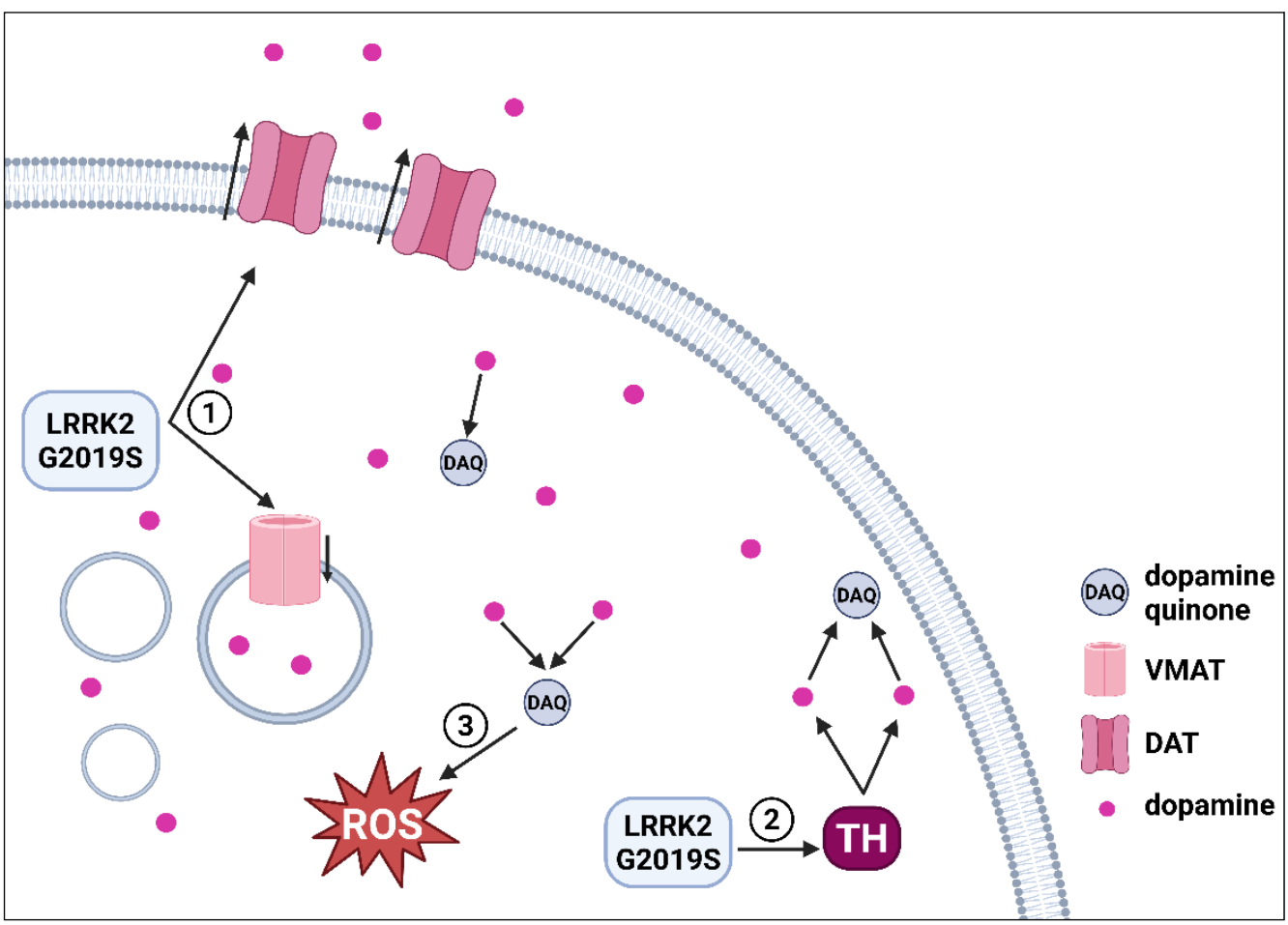

Fig. 3. LRRK2 G2019S mutation impairs dopamine homeostasis and increases oxidative stress. (1) The G2019S LRRK2 is associated with increased expression of the dopamine transporter (DAT) and reduced levels of vesicular monoamine transporter 2 (VMAT2), leading to decreased sequestration of dopamine into synaptic vesicles (2). In parallel, the G2019S mutation has been linked to elevated expression of tyrosine hydroxylase (TH), suggesting a shift toward increased dopamine production. (3) These alterations result in higher levels of cytosolic dopamine, which can undergo auto-oxidation, forming dopamine quinone (DAQ) and contributes to an increase in oxidative stress in dopaminergic neurons.

sis or contribute to neuronal loss (Longo et al., 2017; Domenicale et al., 2022). This may be because both dopamine transporters levels and activity are affected by the *LRRK2* G2019S mutation. These changes in activity may compensate for changes in protein levels and sustain dopamine homeostasis (Longo et al., 2017). However, some evidence appears to be contrary to the aforementioned studies, showing that changes in DAT and VMAT protein levels may lead to impairments in dopamine homeostasis, resulting in improper neuron differentiation and function, as is observed in neurodegeneration processes (Chen et al., 2008; Bayersdorfer et al., 2010; Zhou et al., 2023).

LRRK2 may physically interact with vacuolar protein sorting 35 (VSP35) to mediate the trafficking of synaptic cargo *via* an endo-lysosomal network (Inoshita et al., 2017; Kadgien et al., 2021). In the case of VSP35 haploinsufficiency that is related to PD development (Bu et al., 2023), one can observe an increase in LRRK2 activity, a decrease in DAT expression, and the disruption of dopamine release. Interestingly, mouse studies suggest that inhibiting LRRK2 restores dopamine dynamics by normalizing striatal dopamine transporter (DAT) expression, peak dopamine release, and reuptake kinetics to wild-type levels (Bu et al., 2023). Under normal conditions, LRRK2 phosphorylates Rab35 and Rab10 proteins, which are responsible for the recruitment of the motor adaptor protein JIP4 to lysosomes. This leads to the formation of LAMP1-negative tubules, which allows the release of membranous content and formation of lysosomal vesicles (Bonet-Ponce et al., 2020). One function of these lysosomal vesicles is the degradation of defective synaptic vesicles (Andres-Alonso et al., 2021). However, when LRRK2 is constitutively active through pathogenic mutations, the proper phosphorylation of Rab proteins becomes disrupted. Under these conditions, dysfunctional lysosomes allow the accumulation of defective synaptic vesicles at the presynaptic membrane, leading to impairments in dopamine release (Ma et al., 2024). Another risk that is associated with improper dopamine metabolism is dopamine oxidation. When dopamine remains unpacked in the cytoplasm, it may undergo oxidation and form ROS, dopamine-quinones, and toxic metabolites, such as 3,4-dihydroxyphenylacetaldehyde (Sulzer & Zecca, 1999). To protect cells from this disorderly event, dopamine transporter VMAT2 sequesters resynthesized or re-ingested dopamine into synaptic vesicles to stabilize its homeostasis (Lohr et al., 2016). However, VMAT2 dysfunction that is associated with *LRRK2* mutations (R1441C, G2019S) may severely affect this process by reducing the sequestration of dopamine into vesicles, which leads to increased cytosolic dopamine, elevated oxidative stress, and defective neurotransmission, ultimately promoting neurodegeneration in dopaminergic neurons (Lohr & Miller, 2014; Bucher et al., 2020).

Another study shows that an activating mutation of *LRRK2* (G2019S) decreases glial cell line-derived neurotrophic factor transcription. Glial cell line-derived neurotrophic factor is crucial for dopaminergic neuron development. Its downregulation correlates with the loss of tyrosine hydroxylase (TH), an enzyme that is involved in dopamine production (Khan et al., 2024). The impact of *LRRK2* G2019S mutation in astrocytes on the dopamine synthesis pathway in N27 rat dopaminergic neuronal cells was recently shown. Upon treatment with conditioned medium from mutation-carrying astrocytes, a significant decrease in released dopamine levels was observed. Simultaneously, changes in levels of proteins that are involved in dopamine production occurred, with tyrosine hydroxylase decreasing and DAT and nuclear receptor-related 1 increasing (Nurr1) (Ho et al., 2024).

Dopamine toxicity in PD

Improper dopamine metabolism is closely related to PD, and dopamine-dependent toxicity was linked to α-synuclein accumulation and neurodegeneration processes (Bayersdorfer et al., 2010; Zhou et al., 2023). High DAT expression causes chronic exposure to unpacked cytosolic dopamine, resulting in dopaminergic neuron neurodegeneration (Chen et al., 2008). The *LRRK2* G2019S mutation resulted in higher TH expression levels and dopamine production as observed in human cell line (SH-SY5Y) (Fig. 3). This can contribute to an increase in dopamine-mediated oxidative stress and a reduction of neuron viability (Zhou et al., 2022). Another study established a link between an *LRRK2* mutation (R1441C, G2019S) and synaptic dysfunction that was caused by dopamine toxicity. High kinase activity may contribute to the phosphorylation of auxilin, an important mediator of synaptic vesicles. Consequently, oxidized dopamine starts to accumulate in cells, and multiple downstream effects begin to appear (Nguyen & Krainc, 2018).

However, oxidative stress that is caused by dopamine metabolites may also contribute to ferroptotic cell death that is initiated by iron-dependent phospholipid peroxidation (Yao et al., 2024). Experiments on rat neurons show that oxidized dopamine is capable of directly targeting GPX4, leading to the disruption of anti-ferroptotic pathways. The mechanism is based on the irreversible, covalent modification of GPX4, followed by degradation *via* the ubiquitin-proteasome pathway (Sun et al., 2023). One agent that is involved in the dopamine oxidation process is α-synuclein, which

exhibits ferrireductase activity and elevates the Fe^{2+} pool, resulting in higher levels of toxic dopamine metabolites (McDowall et al., 2017).

Interplay between dopamine and iron in PD

Iron's redox activity is a major contributor to oxidative stress in the PD brain (Medeiros et al., 2016). Fe^{2+}, through the Fenton reaction, catalyzes the generation of hydroxyl radicals from hydrogen peroxide. These highly reactive species initiate lipid peroxidation, particularly targeting membrane phospholipids that are enriched with polyunsaturated fatty acids (Galaris et al., 2019). The accumulation of lipid hydroperoxides is a central trigger for ferroptosis (Do et al., 2023). Moreover, studies demonstrate that iron overload leads to classic ferroptotic phenotypes, including mitochondrial shrinkage, an increase in lipid ROS, and compromised membrane integrity (Sui et al., 2018; Chen et al., 2023; Feng et al., 2023). Additionally, iron overload exacerbates dopamine oxidation, which amplifies oxidative stress, forming a vicious cycle of neuronal injury (Zhou et al., 2010). What is more, iron metabolism itself is closely related to dopamine. Fe^{2+} acts as a cofactor for TH, the rate-limiting enzyme in dopamine biosynthesis (Daubner et al., 2011), and regulates dopaminergic transmission by modulating neurotransmitter release, uptake, and receptor sensitivity (Erikson et al., 2001; Unger et al., 2008, 2014; Larsen et al., 2020; Gustavsson et al., 2023). Dopamine was previously shown to form complexes with Fe^{3+}, and it may be one aspect of PD-related pathology (Arreguin et al., 2009). More recent studies suggest that Fe^{3+} may be shuttled across intracellular membranes while in complex with dopamine. Under physiological conditions, this phenomenon promotes mitochondrial dysfunction and ROS production (Paris et al., 2005; Buoso et al., 2024). Dopamine oxidation drives neuromelanin synthesis. This black, neuroprotective pigment appears as a mix of melanin, proteins, lipids, and metal ions and is involved in maintaining iron balance (Zecca et al., 2008). It has two types of iron binding sites; high-affinity sites that allow the formation of highly stable complexes and store iron, and low-affinity sites where iron can be easily released. In case of iron overload, when all high-affinity sites are saturated, neuromelanin may become toxic due to excessive iron release, thus increasing labile iron pool and oxidative stress (Sun et al., 2016). The convergence of disruptions of Fe^{2+} and dopamine homeostasis, impairments in antioxidant defense mechanisms, and an enhancement of lipid peroxidation underscores the relevance of ferroptosis as a mechanistic contributor to neurodegeneration in PD.

CONCLUSIONS

Dopaminergic neurons in the SNpc are uniquely vulnerable to neurodegeneration processes because of their continuous pacemaking activity and high dependence on mitochondria for energy production and calcium regulation. In this fragile setting, mutations of *LRRK2* and the persistent activation of L-type calcium channels cause excessive mitochondrial calcium uptake through an overactive MCU. This Ca^{2+} overload triggers oxidative stress and reduces mitochondrial energy output, creating a harmful cycle of mitochondrial dysfunction that heightens neuronal susceptibility. At the same time, excess Fe^{2+} accumulates as a result of an enhancement of cellular uptake, combined with impairments in export mechanisms, leading to the formation of ROS. Additionally, Fe^{2+} promotes assembly of the MCU complex, increasing Ca^{2+} import into mitochondria and contributing to calcium overload. Iron simultaneously decreases levels of the NCLX and MCUb (one of the MCU complex components) increasing mitochondrial calcium retention (Bharat et al., 2023). Meanwhile, the dysfunction of VMAT2 or dopamine D_2 receptor signaling that is associated with the *LRRK2* G2019S mutation disrupts dopamine homeostasis and causes dopamine to accumulate in the cytosol. Unpacked dopamine is more prone to auto-oxidization into quinones. These toxic dopamine metabolites both directly and indirectly downregulate the anti-ferroptotic pathway. Blocking GPX4 activity, in addition to impairing mitochondrial function and releasing Fe^{2+} from ferritin stores, fuels a damaging iron-dopamine-ROS cycle that promotes lipid peroxidation and triggers ferroptosis. Ferroptosis thus emerges as a key mechanism that links calcium-induced mitochondrial stress, dopamine dysregulation oxidative imbalance, with iron toxicity (Fig. 4).

Emerging evidence further suggests that these pathogenic processes are not restricted to neurons. Dopamine and LRRK2, which are central to neuronal vulnerability, also exert powerful effects on the immune system, creating another layer of complexity in PD (Colombo et al., 2003; Fuzzati-Armentero et al., 2019). Dopamine, acting through its receptors on immune cells, influences T-cell activation and differentiation and cytokine production and can shape antibody responses *via* dopamine release at the immunological synapse (Feng & Lu, 2021; Channer et al., 2023). Likewise, LRRK2 is abundantly expressed in monocytes, microglia, and lymphocytes, where it regulates inflammatory signaling and autophagy (Cook et al., 2017). Mutations of LRRK2 can bias immune cells toward a proinflammatory phenotype, linking peripheral immune activation with central neurodegeneration (Fuzzati-Armentero et al., 2019; Gillardon et al., 2012). In this way, immune

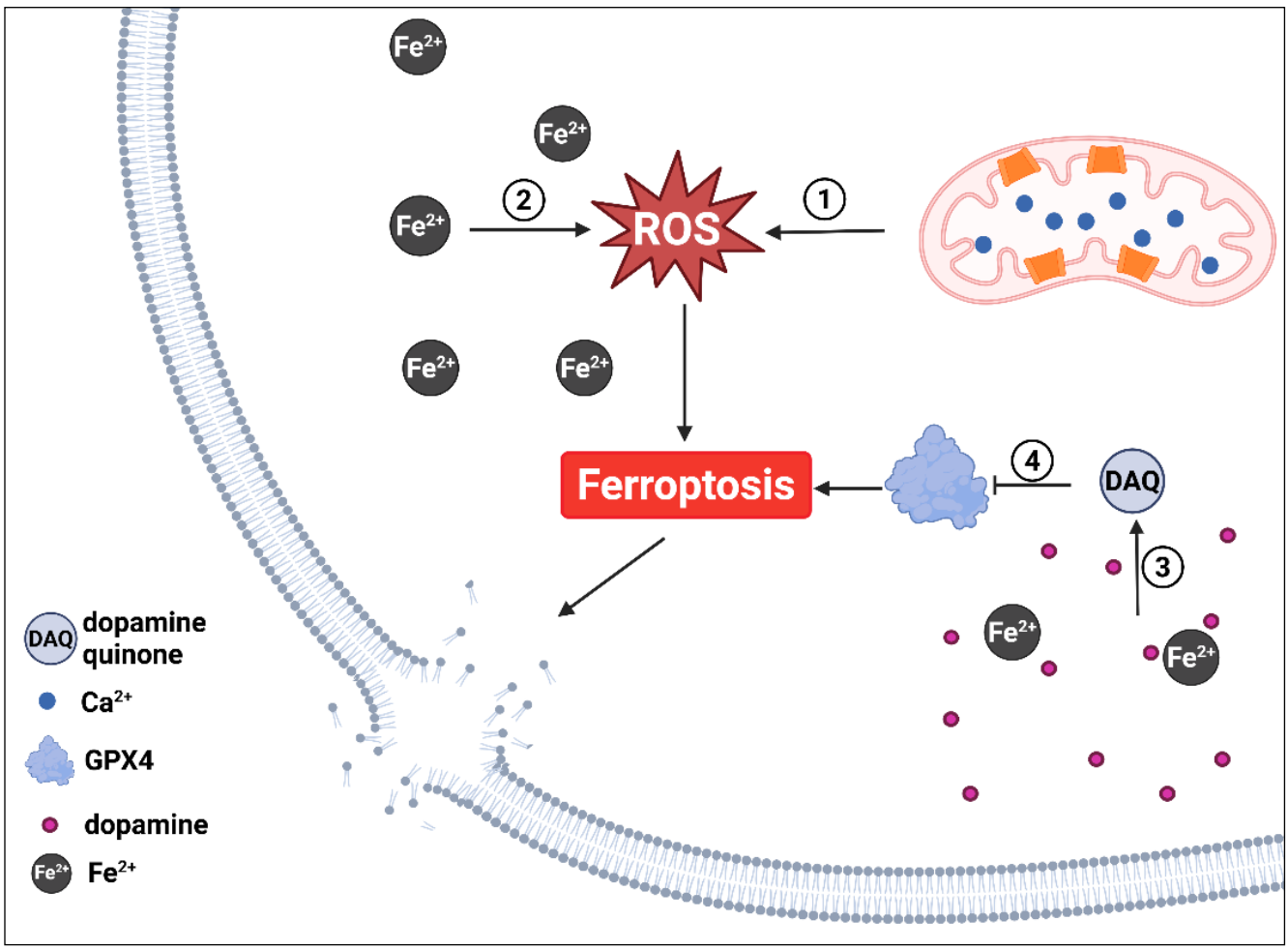

Fig. 4. Calcium and iron dyshomeostasis promote oxidative stress and ferroptotic vulnerability in dopaminergic neurons. (1) Overactivation of the MCU leads to excessive calcium uptake into mitochondria, triggering oxidative stress and promoting mitochondrial dysfunction and neuronal vulnerability. (2) Simultaneously, increases in iron uptake and impairments in export result in intracellular Fe^{2+} accumulation, which enhances the generation of reactive oxygen species (ROS). (3) Iron also catalyzes dopamine oxidation, leading to the formation of dopamine quinone (DAQ) and the generation of neurotoxic metabolites. (4) Oxidized dopamine, in turn, directly inhibits glutathione peroxidase 4 (GPX4), a key anti-ferroptotic enzyme, thereby weakening cellular defenses against ferroptosis and further sensitizing neurons to oxidative damage.

dysregulation, neuronal stress, and iron and calcium dysregulation may converge to accelerate disease progression. Although this immune dimension is beyond the scope of the present minireview, acknowledging it is crucial because it represents an integral yet broad aspect of PD pathogenesis and is a promising frontier for future therapeutic innovation.

Given the intricate interplay between iron, dopamine, and calcium signaling in the SNpc, understanding how their homeostatic disruption contributes to PD pathogenesis is essential. Identifying the molecular intersections among these pathways will provide critical insights into early disease mechanisms and open new avenues for targeted interventions in both sporadic and familial PD. This review highlights key vulnerabilities of dopaminergic neurons in PD that may be therapeutically exploited. Experimental evidence that inhibition of Mcu is neuroprotective in PD models, suggests that pharmacological modulation of mitochondrial calcium uptake could slow or prevent neurodegeneration (Dey et al., 2020; Johnson et al., 2023). But dysregulated dopamine metabolism can also contribute to neuronal toxicity. Excess of cytosolic dopamine undergoes autooxidation, generating reactive oxygen species and toxic metabolites. Mouse model with enhanced dopamine synthesis, exhibit increased oxidative stress and dopaminergic neurotoxicity, supporting the concept that dopamine normalization rather than maximal replacement may represent a safer therapeutic strategy (Vecchio et al., 2021). Importantly neurons in the substantia nigra have high total iron levels, making them more prone to ferroptosis. Preventing ferroptosis

protects neurons in experimental models, suggesting it could be a useful treatment target. In summary, calcium overload, dopamine toxicity, and ferroptosis are interconnected in PD. Targeting these early processes may help develop therapies that slow or prevent neurodegeneration in both inherited and sporadic forms of the disease.

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