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Calcium and Ferrous ion crosstalk driving dopaminergic loss in patients with Parkinsons disease - a systematic review .

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Abstract:

Calcium and iron are vital trace elements that orchestrate critical eukaryotic cellular processes, from signaling and enzyme activity to energy metabolism. Disruptions in their homeostasis trigger cell dysfunction, oxidative damage, and eventual death. Parkinson's disease (PD), the second most prevalent neurodegenerative disorder worldwide, lacks curative therapies or interventions to halt its inexorable progression. Its pathological signatures—selective death of dopaminergic neurons in the substantia nigra and Lewy body formation via α-synuclein aggregation—closely intertwine with dysregulated calcium (Ca^{2+}) and iron homeostasis. This review elucidates how aberrant Ca^{2+} signaling exacerbates PD pathogenesis. Excessive cytosolic Ca^{2+} influx through voltage-gated channels (e.g., L-type VGCCs, NMDA receptors) or release from intracellular stores (mitochondrial MCU, ER RyRs/IP3Rs) overloads mitochondria, impairs ATP production, and activates catabolic pathways like calpains and caspases. This fosters α-synuclein misfolding, synaptic dysfunction, and dopaminergic neurotoxicity, amplified by elevated dopamine auto-oxidation in high-Ca^{2+} milieus. Concomitantly, iron dysregulation drives ferroptosis, an iron-dependent lipid peroxidation form of regulated cell death central to PD. Excess labile ferrous iron (Fe^{2+}) in the basal ganglia—evident via MRI hypointensities—catalyzes Fenton reactions, generating hydroxyl radicals that peroxidise polyunsaturated fatty acids in neuronal membranes. Glutathione peroxidase 4 (GPX4) depletion, often via α-synuclein-mediated ferroportin suppression or xCT inhibition, fails to neutralize these lipids, culminating in ferroptotic collapse. The Ca^{2+}-Fe^{2+} nexus worsens this: calcium promotes iron release from ferritin, while both ions synergize in mitochondrial permeability transition pores, accelerating ROS bursts. Deciphering these intertwined imbalances is paramount for devising disease-modifying strategies, such as MCU inhibitors (e.g., Ru360), iron chelators (deferiprone), or ferroptosis blockers (ferrostatin-1), potentially synergizing to preserve dopaminergic integrity and mitigate PD progression. Parkinson's disease (PD) ranks as the second most common neurodegenerative disorder after Alzheimer's, affecting millions worldwide as populations age and lifespans extend. Its progressive nature draws intense research focus due to the growing burden on healthcare systems

Keywords: Parkinson's disease, Calcium homeostasis, Iron dysregulation, Ferroptosis, α-Synuclein aggregation.

Introduction:

Parkinson's disease (PD), the second most common neurodegenerative disorder after Alzheimer's, commands intense research scrutiny amid a global aging crisis that drives its escalating prevalence.[1] As lifespans lengthen, PD's relentless progression—from motor deficits to cognitive decline[2]—strains healthcare systems worldwide.[3] Aging emerges as the dominant risk factor, heightening vulnerability in substantia nigra dopaminergic neurons, while genetic variants (e.g., SNCA, LRRK2) and environmental insults like pesticides or trauma contribute modestly.[4] These explain only a fraction of cases; most PD likely stems from their intricate interplay, spotlighting downstream cascades like metal dyshomeostasis.[5] Though trace elements, iron and calcium prove indispensable for oxygen handling, enzymatic catalysis, and signaling.[6] Their central nervous system overload sparks oxidative stress through reactive oxygen species, mitochondrial collapse, and protein/receptor wreckage.[7] Metal imbalance fuels neurodegeneration, disability, and neuroinflammation across disorders like PD and Alzheimer's.[8] Compelling data pinpoint calcium overload and iron deposition as PD linchpins. Basal ganglia iron buildup—evident on MRI—ignites Fenton chemistry, yielding hydroxyl radicals[9] that peroxidise lipids and trigger ferroptosis.[10] Concurrently, cytosolic Ca^{2+} surges via L-type channels or MCU/IP3R[11] stores overwhelm mitochondria, exacerbate α-synuclein aggregation,[12] and amplify dopaminergic toxicity via dopamine oxidation.[13] This review dissects the Ca^{2+}-Fe^{2+} axis in PD pathogenesis, probing therapeutic horizons.[14] Iron chelators (deferiprone), MCU blockers (Ru360), and ferroptosis inhibitors (ferrostatin-1) show preclinical promise, potentially synergizing with antioxidants to restore homeostasis,[15] forestall neuron loss, and pioneer disease-modifying interventions beyond symptomatic palliation.[16,17]

Calcium Dysregulation in Parkinson's Disease

Calcium ions (Ca^{2+}) function as a universal second messenger across living organisms, enabling cells to sense and respond to environmental shifts.[18] In resting cells, cytoplasmic Ca^{2+} remains tightly clamped at ~100 nmol/L, contrasting sharply with endoplasmic reticulum stores (0.5–1 mmol/L) and extracellular levels (1–2 mmol/L)—a 20,000-fold gradient that powers rapid signaling transients.[19] This steep disparity lets cells harness Ca^{2+} pulses to toggle physiological states via downstream cascades regulating contraction, secretion, and transcription.[20] Neurons exploit this through plasma membrane fluxes: depolarization opens voltage-gated calcium channels (VGCCs), while agonists like the dihydropyridine BAY K8644 amplify L-type VGCC influx.[21] Since Ca^{2+} sculpts every facet of neuronal biology—from excitability to survival—homeostasis demands exquisite precision, encompassing cytosolic levels, microdomain dynamics, buffering capacity, and entry kinetics.[22]

Substantia nigra dopaminergic (SN DA) neurons, prime targets in Parkinson's disease (PD), rely heavily on Ca^{2+} for excitability,[23] dopamine release, mitochondrial ATP synthesis, enzymatic control, gene expression, and apoptosis thresholds.[24,25] Calcium mishandling accelerates aging-related neurodegeneration, disrupting neurogenesis, synaptic plasticity, and neurotransmission.[26,27] PD patients display elevated brain Ca^{2+} versus controls, fuelling excessive dopamine synthesis and autotoxicity that precipitates dopaminergic demise.[28,29,30] Alpha-synuclein aggregates, PD's pathological signature, further derail calcium clearance and signaling.[31]

Regulation spans plasma membrane routes—VGCCs, NMDA/AMPA receptors[32]—and intracellular depots: mitochondrial calcium uniporter (MCU), endoplasmic reticulum RyRs/IP3Rs, plus store-operated systems like STIM/Orai and TRP channels.[33,34] In PD, these falter, unleashing cytosolic overloads that trigger mitochondrial collapse, ROS bursts, and proteinopathy[35,36]—cascades ripe for therapeutic interception via channel modulators or buffers.[37]

Calcium Signaling and Homeostasis in Parkinson's Disease Neurons

Calcium ions (Ca^{2+}) serve as the universal second messenger across all living organisms, enabling cells to detect and respond to environmental changes with remarkable precision.[38] In resting cells, cytoplasmic Ca^{2+} concentration remains clamped at approximately 100 nmol/L, while endoplasmic reticulum (ER) stores maintain 0.5–1 mmol/L and extracellular fluid holds 1–2 mmol/L.[39,40] This creates a staggering 20,000-fold gradient across the plasma membrane, allowing cells to generate rapid, localized Ca^{2+} transients that function as potent signaling cues.[41] These transients activate or inhibit Ca^{2+}-dependent pathways, orchestrating diverse physiological responses from contraction and secretion to gene transcription.[42]

In neurons, Ca^{2+} entry occurs primarily through plasma membrane channels triggered by electrical depolarization or chemical agonists.[43] The dihydropyridine derivative BAY K8644 exemplifies this by enhancing influx through L-type voltage-gated calcium channels (VGCCs).[44] Given Ca^{2+}'s pervasive influence on neuronal biology—spanning excitability, synaptic transmission, survival,[45] and death—maintaining precise homeostasis proves essential.[46] This involves tight regulation of cytosolic levels, microdomain formation, buffering capacity, and spatiotemporal entry patterns.[47]

Substantia nigra dopaminergic (SN DA) neurons, selectively vulnerable in Parkinson's disease (PD), depend critically on Ca^{2+} for multiple functions: membrane excitability, dopamine release, mitochondrial ATP production, enzymatic regulation, gene expression, and apoptosis execution.[48,49] Calcium dysregulation accelerates aging-related neurodegeneration by disrupting neurogenesis,[50] synaptic plasticity, and neurotransmission.[51] PD patients consistently show elevated brain Ca^{2+} levels compared to healthy controls, linking this overload to excessive dopamine biosynthesis and subsequent dopaminergic neurotoxicity.[52,53,54]

Alpha-synuclein aggregation, a pathological hallmark of PD, further compromises calcium homeostasis by impairing clearance mechanisms.[55,56] Multiple pathways govern Ca^{2+} fluxes in SN DA neurons.[57] Plasma membrane entry occurs via VGCCs and glutamate receptors (NMDA-R, AMPA-R). Intracellularly, ER releases Ca^{2+} through ryanodine receptors (RyR) and IP_3 receptors,[58,59,60] while mitochondria contribute via the mitochondrial calcium uniporter (MCU).[61] Store-operated calcium entry (SOCE) systems—STIM/Orai complexes and transient receptor potential (TRP) channels—replenish cytosolic stores after depletion.[62]

In PD, these regulatory systems fail, unleashing pathological Ca^{2+} surges that trigger mitochondrial dysfunction,[63] oxidative stress cascades, and protein misfolding[64]—driving inexorable dopaminergic degeneration characteristic of the disease.[65,66]

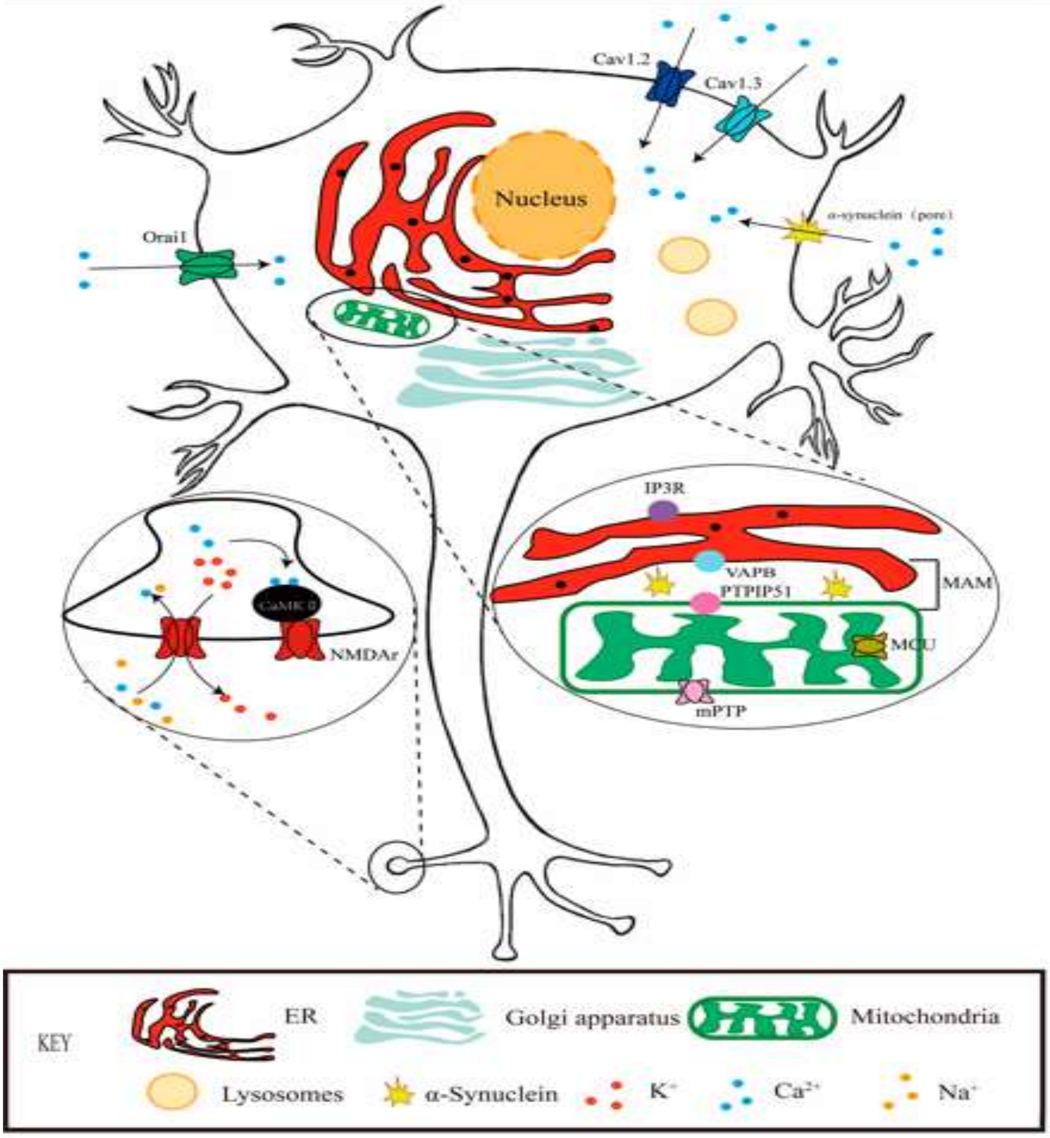

Fig 1: Neuronal Ca^{2+} Chaos: Entry Routes, ER-Mito Crosstalk and Overload Triggering Apoptosis"

Voltage-gated calcium channels (VGCCs) comprise ten distinct subtypes,[67] classified by their unique pharmacological profiles and pore-forming α1 subunits, with function fine-tuned through alternative splicing and accessory subunits (β1–β4, α2δ1–α2δ4).[68] These channels cluster into three families based on sequence homology and properties: Cav1 (L-type), Cav2 (P/Q-, N-, R-type), and Cav3 (T-type).[69,70] The Cav1 family includes four L-type channels (Cav1.1–Cav1.4), highly sensitive to dihydropyridine (DHP) blockers at nanomolar concentrations.[71] In Parkinson's disease (PD), Cav1.2 and Cav1.3 emerge as key players, particularly in substantia nigra pars compacta (SNc) dopaminergic neurons.[72,]

Juvenile SNc neurons predominantly express Cav1.2, but aging shifts reliance to Cav1.3, which supports oscillatory Ca^{2+} influx critical for autonomous pacing—the intrinsic,[73,74] slow depolarization sustaining basal dopamine release to the striatum.[75] Unlike Cav1.2, Cav1.3 channels resist full closure during pacing cycles, maintaining elevated cytosolic Ca^{2+} essential for physiologic dopamine secretion.[77,78] However, chronic Ca^{2+} excess synergizes with aging, mitochondrial toxins, or genetic mutations, precipitating metabolic stress and organelle damage.[79] Notably, upregulated Cav1.3 expressions in early PD cerebral cortex precedes pathology, positioning calcium dysregulation as an initiator rather than mere consequence. DHP antihypertensives offer neuroprotection; epidemiological data show 20–30% reduced PD risk with chronic use.[80]

Cav2 family channels (Cav2.1–2.3) localize presynaptically, driving rapid neurotransmitter release via P/Q-, N-, and R-type currents.[81] T-type Cav3 channels (Cav3.1–3.3) activate at hyperpolarized potentials, shaping neuronal firing patterns through subthreshold oscillations.[82,83]

Dopaminergic neuron activity hinges on Ca^{2+} carriers and homeostasis, with ~80% of cellular Ca^{2+} sequestered in organelles.[84,85,86] While endoplasmic reticulum (ER) dominates as the primary reservoir, mitochondria, lysosomes, and Golgi also contribute significantly.[87,88] ER-mediated signaling proves pivotal, particularly store-operated Ca^{2+} entry (SOCE).[89] ER Ca^{2+} depletion activates STIM1 on the ER membrane, which couples to plasma membrane Orai1 channels, driving extracellular Ca^{2+} influx that SERCA pumps refill into ER.[90,91] STIM1 governs classical SOCE, while lower-affinity STIM2 fine-tunes subtle fluctuations. Orai1/STIM1 mutations disrupt SOCE, linking to diverse pathologies.[92,93]

In PD, STIM1-TRPC1 complexes inhibit Cav1.3, deranging homeostasis, while reduced STIM1 occurs in Alzheimer's disease (AD).[94] Hippocampal STIM2 supports dendritogenesis via Ca^{2+}/calmodulin-dependent kinase pathways.[95] Synaptotagmin-7 (Syt7), a presynaptic Ca^{2+} sensor, amplifies spontaneous release through STIM2-mediated SOCE.[96,97] Chronic hyperactivity risks synaptic exhaustion and apoptosis, implicating presynaptic SOCE in neurodegeneration across PD, AD, and beyond.[99,100]

Mitochondrial Ca^{2+} handling centers on ER-mitochondria associated membranes (MAMs), where ~20% of mitochondria tether ~10–25 nm from ER.[101] IP3R on ER releases Ca^{2+} into cytosol, funnelled through VDAC1 on mitochondrial outer membrane into the matrix via MCU.[102,103] Pathologic VDAC1 upregulation triggers oligomerization, MCU hyperactivation, and MAM coupling to IP3R, culminating in Ca^{2+} overload.[104] This opens mitochondrial permeability transition pore (mPTP) or promotes Bax/Bak pore formation, releasing cytochrome c to trigger caspase-9/3-mediated apoptosis.[105,106]

Paradoxically, α-synuclein at MAMs disrupts VAPB-PTPIP51 tethers—whether wild-type or mutant—impairing ER-mito Ca^{2+} transfer and ATP synthesis via tricarboxylic acid cycle dysregulation.[107,108] Both Ca^{2+} excess (mPTP opening) and deficiency (energy failure) threaten neuronal survival.[109]

Ca^{2+} signalling's ubiquity positions dyshomeostasis as a convergent aging mechanism across neurodegeneration.[110] Plasma membrane influx, intracellular buffering, and inter-organelle trafficking orchestrate metabolism, signaling, and survival.[111] Targeting VGCCs (DHPs), SOCE (STIM/Orai modulators), or MAM integrity holds transformative therapeutic promise for PD.[112]

Role of Iron in Parkinson's disease

Iron serves as an essential trace element fuelling cellular metabolism, with outsized importance in the central nervous system where it supports synapse formation, myelination, and neurotransmitter synthesis and release.[113,114] These roles extend to childhood brain development, influencing IQ, cognition, motor skills, and social behavior.[115,116] However, brain ferritin levels rise with age, driving iron overload that contributes to neurodegeneration in older adults.[117,120]

Excess iron sparks oxidative stress, inflammation, and cell death, with elevated levels consistently detected in Parkinson's disease (PD)[119,] and Alzheimer's disease (AD) brains,[120] particularly in basal ganglia and substantia nigra. As a redox-active metal, iron powers ATP production in neurons, but overload renders neural tissue vulnerable to oxidative damage and proteolysis.[121] Beyond aging, hereditary hemochromatosis (HH)—an autosomal recessive disorder from HFE gene mutations (C282Y, H63D) disrupting hepcidin regulation—accelerates brain iron deposition.[122,123] Though the blood-brain barrier normally shields the CNS during systemic imbalance, overload compromises this defence, potentially elevating PD risk in HH patients through dysregulated storage and export.[124] Iron dysregulation culminates in ferroptosis, a caspase-independent regulated cell death (RCD) form distinct from apoptosis, necrosis, or autophagy.[129,126] First described by Brent Stockwell, ferroptosis features shrunken mitochondria with reduced cristae density, outer membrane rupture, and no plasma membrane lysis or bioenergetic catastrophe. In neurodegeneration, it unleashes inflammation, neurotransmitter oxidation, synaptic failure, myelin breakdown, astrocyte dysfunction, and neuronal demise.[125]

Ferroptosis triggers via glutamate/iron/polyunsaturated fatty acid (PUFA) buildup or glutathione (GSH)/NAD(P)H/glutathione peroxidase 4 (GPX4) depletion. Iron uptake begins with transferrin receptor 1 (TFR1) binding, endosomal endocytosis, ferric (Fe^{3+}) reduction by STEAP3, and ferrous (Fe^{2+}) export via DMT1 into the labile iron pool (LIP) or ferritin storage.[127] Excess LIP Fe^{2+} catalyzes Fenton reactions, generating hydroxyl radicals that initiate PUFA peroxidation in plasma membranes.[128] Lipid hydroperoxides (PL-OOH) decompose into toxic aldehydes, epoxides, and oxo products, forming nanomembrane pores that rupture cells.[130] This peroxidation propagates cell-to-cell in waves, perpetuating iron-lipid vicious cycles.[131] Three anti-ferroptotic pathways counter this: the canonical GSH/GPX4 axis neutralizing peroxides; the FSP1/coenzyme Q10/NAD(P)H system; and the GCH1/bh4/DHFR route.[132] In PD, basal ganglia iron excess—visible as MRI hypointensities—amplifies dopaminergic ferroptosis, positioning iron chelators like deferiprone and ferroptosis inhibitors (ferrostatin-1) as promising disease-modifying strategies.[133]

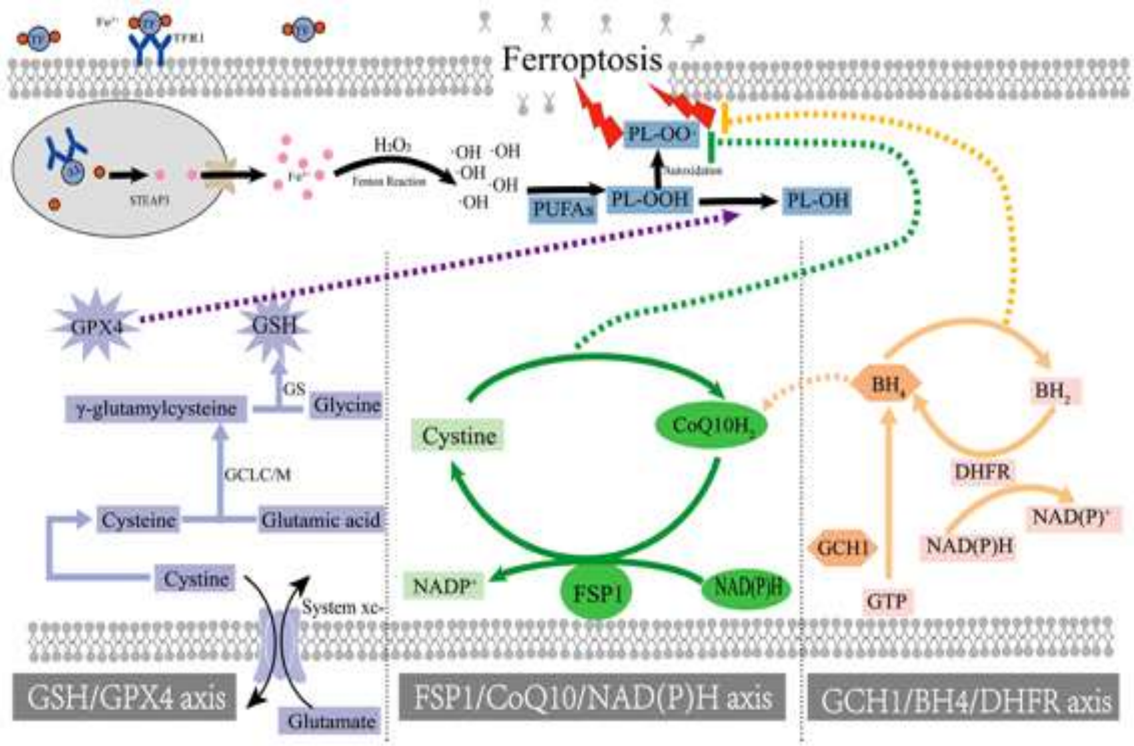

Figure 2. Anti-Ferroptotic Pathways: TFR1-STEAP3 iron uptake → Fenton-driven PUFA peroxidation countered by GSH/GPX4, FSP1/CoQ10, and GCH1/BH4/DHFR radical scavenging.

Ferroptosis Defence Pathways: GPX4, FSP1/CoQ10, and GCH1/BH4 Systems

Glutathione peroxidase 4 (GPX4) stands as the cornerstone selenoenzyme suppressing ferroptosis, the iron-dependent lipid peroxidation cell death. Physiologically, GPX4 harnesses glutathione (GSH) to reduce cytotoxic lipid hydroperoxides (PL-OOH) to harmless alcohols (PL-OH), directly countering the Fenton reaction-driven membrane damage in Parkinson's disease (PD). GSH depletion or GPX4 inactivation unleashes ferroptotic cascades in dopaminergic neurons.[134,135,136]

GSH biosynthesis hinges on the cystine/glutamate antiporter system xc⁻, which imports cystine for reduction to cysteine by GSH itself or thioredoxin reductase 1 (TRR1).[137] ATP-dependent glutamate-cysteine ligase (GCL) then forms γ-glutamylcysteine, followed by glutathione synthetase (GS) addition of glycine to yield GSH.[138] Transcription factors orchestrate this: Nrf2 (nuclear factor erythroid 2-related factor 2) upregulates GCL, GS, GCLC (GCL catalytic subunit), GSTs (glutathione S-transferases), HO-1 (heme oxygenase-1), and NQO1 (NAD(P)H quinone dehydrogenase 1), mounting a broad antioxidant defence.[139] Nrf2 modulation emerges as a promising neuroprotective strategy for PD, potentially amplifying GSH/GPX4 resilience against iron overload.[140]

Parallel to this canonical axis operates the FSP1-CoQ10-NAD(P)H pathway, a GSH-independent ferroptosis suppressor.[140] Ferroptosis suppressor protein 1 (FSP1) features N-myristoylation for membrane targeting and a flavoprotein oxidoreductase domain. FSP1 reduces coenzyme Q10 (CoQ10)—the lipophilic mitochondrial electron carrier—to ubiquinol

(CoQ10-H2) using NAD(P)H.[141] Both oxidized and reduced CoQ10 scavenge lipid peroxides at plasma membranes, safeguarding PUFA-rich phospholipids.[142] NQO1 synergizes with FSP1, further reducing ubiquinone to ubiquinol, with Nrf2 governing NQO1 expression.[143] This system's potency rivals GPX4/GSH, positioning FSP1/CoQ10 activators as viable PD therapeutics.[144]

The GCH1/BH4/DHFR pathway, though underexplored in neurodegeneration, offers a third defence line. Tetrahydrobiopterin (BH4)—essential for dopamine biosynthesis—traps lipid peroxidation radicals while boosting CoQ10 synthesis via phenylalanine hydroxylase.[145] GTP cyclohydrolase 1 (GCH1) rate-limits de novo BH4 production; dihydrofolate reductase (DHFR) recycles oxidized BH4.[146] DHFR inhibition synergizes with GPX4 blockers to induce ferroptosis therapeutically,[147] but BH4 supplementation may conversely protect neurons. GCH1/BH4's role in PD ferroptosis warrants deeper investigation given BH4's dopamine linkage.[148]

Therapeutic Horizons

Ferroptosis inhibition offers disease-modifying potential for PD, targeting iron dysregulation at multiple nodes. Iron chelators like deferiprone[149] reduce labile Fe^{2+} pools, blunting Fenton chemistry.[150] Nrf2 agonists (e.g., dimethyl fumarate) amplify GSH/GPX4 and NQO1 defenses. GPX4 stabilizers or GSH precursors (N-acetylcysteine) restore canonical protection.[151] CoQ10 supplementation—already trialled in PD—leverages FSP1 pathway radical trapping.[152] Emerging GCH1/BH4 modulators could enhance dopamine synthesis alongside anti-peroxidant effects.[153]

Recent (2021–2026) PD trials highlight ferrostatin-1 analogs, liproxstatin-1, and α-lipoic acid as ferroptosis inhibitors attenuating nigral lipid peroxidation in MPTP/6-OHDA models.[154] TFR1 antagonists curb iron import; xCT activators replenish GSH.[155] Combined chelation-antioxidant regimens show synergistic dopaminergic preservation.[156]These strategies shift PD therapy from L-DOPA palliation toward upstream homeostasis restoration, potentially halting progression in iron-vulnerable basal ganglia circuits.[157,158]

Medicine	Mechanism and Function
Iron Chelators	
Deferiprone	Iron chelator; inhibits pathological α-synuclein toxicity in sporadic PD mouse models
Desferrioxamine	Iron chelator; directly binds excess iron
Nrf2 Pathway Activators	

Medicine	**Mechanism and Function**
Alpha lipoic acid	Antioxidant/iron chelator; activates SIRT1/Nrf2 signaling to regulate iron metabolism and suppress ferroptosis
Gastrodin	Antioxidant; upregulates Nrf2, GPX4, ferroportin-1 (FPN1), and HO-1 protein expression
Hinokitiol	Antioxidant/iron chelator; activates Nrf2 cytoprotective transcription
Icariside II	Antioxidant; activates Keap1/Nrf2/GPX4 signaling pathway
Morroniside	Antioxidant; activates Nrf2/ARE signaling to protect PD dopaminergic neurons from ferroptosis
Paeoniflorin	Antioxidant; activates Akt/Nrf2/GPx4 pathway
Quercetin	Antioxidant; inhibits ferroptosis via Nrf2 activation
GPX4/GSH Axis Modulators	
Lapatinib	Activates GPX4/GSH/NRF2 axis; inhibits oxidative markers (iron, TfR1, PTGS2, 4-HNE); suppresses p-EGFR/c-SRC/PKCβII/PLC-γ/ACSL-4 pathway
Idebenone	Inhibits NAD(P)H dehydrogenase downregulation, reduces lipid peroxidation, increases GPX4 expression
Ferritinophagy & Iron Regulators	
Buddlejasaponin IVb	Suppresses IRP2-mediated iron overload

Medicine	Mechanism and Function
Dl-3-n-butylphthalide	Regulates ferritin expression, promotes Nrf2 nuclear translocation, inhibits NCOA4-mediated ferritinophagy
Antioxidants & Multi-target	
Doxycycline & Demeclocycline	Prevent intracellular oxidative stress and mitochondrial membrane depolarization
Probiotic Strain L. lactis MG1363-pMG36e-GLP-1	Activates Keap1/Nrf2/GPX4 pathway; downregulates ACSL4, upregulates FSP1 to suppress ferroptosis
Novel Pathway Modulators	
Pazopanib	Targets HSP90/CDC37 and multiple regulated cell death (RCD) mechanisms
Rapamycin	Autophagy inducer; inhibits ferroptosis via autophagy activation
β-hydroxybutyrate	Alleviates oxidative stress/ferroptosis via ZFP36/ACSL4 axis modulation

Table 1: Depicting the different forms of Iron chelating agents and modulators

Iron and Calcium Interplay

Iron generates reactive oxygen species (ROS) that serve vital signaling roles in neurons, sculpting synaptic plasticity through structural and functional remodelling. ROS fine-tunes key effectors like NMDA receptors, voltage-gated Ca^{2+} channels (VGCCs), K^+ channels, and CaMKII[159]—central to activity-dependent plasticity. Notably, ROS triggers redox modifications of ryanodine receptors (RyR) in hippocampal neurons, unleashing ER Ca^{2+} release that phosphorylates plasticity-linked enzymes.[160] Iron-driven ROS similarly activates RyR-mediated Ca^{2+} signaling, boosting ERK1/2 phosphorylation even in Ca^{2+}-free conditions, underscoring physiologic synergy.[161] Yet excess ROS proves neurotoxic. Heightened iron sparks RyR-dependent Ca^{2+} liberation, promoting pathological mitochondrial fission and dysfunction.[162] Iron-catalyzed lipid peroxidation further devastates mitochondria, elevating matrix Ca^{2+} that hyperactivates calcineurin—a Ca^{2+}-dependent phosphatase—culminating in neuronal demise.[163,164]

This iron-Ca^{2+} interplay runs bidirectional. Ca^{2+} governs numerous antioxidant defenses and ROS-generating enzymes.[164] Lipid peroxidation by-products like 4-hydroxynonenal (4-HNE) directly gate plasma membrane Ca^{2+} channels, including hippocampal VGCCs.[165,166] Elevated 4-HNE disrupts Na^+/Ca^{2+} pumps and alters channel permeability, provoking energy failure and cell death.[167,68] Conversely, Ca^{2+} dysregulation amplifies ROS cascades.[169] Cytosolic Ca^{2+} overload or mitochondrial influx unleashes ROS bursts, destabilizing the labile iron pool.[170] Excess cytoplasmic Ca^{2+} stimulates neuronal nitric oxide synthase (nNOS) and NAD(P)H oxidase[171,172]—both ROS sources and plasticity modulators—forming vicious feed-forward loops.[173] This intimate crosstalk renders neurons exquisitely vulnerable: iron dysregulation provokes Ca^{2+} storms, while Ca^{2+} mishandling exacerbates iron toxicity.[173,174] In Parkinson's disease, substantia nigra iron deposits ignite Fenton chemistry, generating hydroxyl radicals that sensitize RyR/IP3R channels[175] and overwhelm mitochondrial Ca^{2+} uniporters (MCU).[176] Resultant matrix Ca^{2+} spikes open permeability transition pores (mPTP), while cytosolic surges activate calpains and calcineurin, shredding dopaminergic circuits.[177,178]

Therapeutically, dual-targeting holds promise. Iron chelators like deferiprone blunt ROS ignition,[179] while MCU inhibitors (Ru360) or RyR stabilizers (dantrolene) curb Ca^{2+} amplification. [180,181] Nrf2 agonists simultaneously bolster GSH/GPX4 defenses against peroxidation while rebalancing ion homeostasis.[182,183] This convergence positions the Fe^{2+}-Ca^{2+} axis as a high-yield therapeutic nexus for neurodegeneration, where untangling one strand inevitably stabilizes the other.[184]

Conclusion:

Parkinson's disease (PD) remains a prevalent neurodegenerative disorder with elusive etiology, where metal ion dyshomeostasis—particularly calcium (Ca^{2+}) and iron—emerges as a pivotal driver of pathogenesis. This review underscores Ca^{2+} as an indispensable second messenger, orchestrating neuronal excitability, synaptic plasticity, and survival through plasma membrane channels (VGCCs, NMDA-R) and intracellular stores (ER IP3R/RyR, mitochondrial MCU). Disruptions in Ca^{2+} homeostasis precipitate dopaminergic demise in the substantia nigra, yet calcium channel blockers (e.g., dihydropyridines) reveal neuroprotective potential, illuminating microscopic Ca^{2+} signaling as a therapeutic linchpin. Concurrently, nigral iron overload—evident via MRI hypointensities—fuels ferroptosis, an iron-dependent lipid peroxidation cascade distinct from apoptosis. While the canonical GPX4/GSH axis dominates research, with Nrf2 agonists amplifying antioxidant defenses (HO-1, NQO1, GCLC), parallel pathways warrant exploration. The FSP1/CoQ10/NAD(P)H system deploys ubiquinol radical trapping at membranes, though CoQ10 biosynthesis and membrane targeting pose key challenges. Similarly, the GCH1/BH4/DHFR pathway—critical for dopamine synthesis—offers untapped anti-peroxidant potential via BH4 radical scavenging, meriting PD-specific validation.

Critically, Ca^{2+}-iron crosstalk amplifies vulnerability: iron-catalyzed ROS sensitizes RyR channels and VGCCs, unleashing cytosolic/mitochondrial Ca^{2+} storms, while Ca^{2+} overload destabilizes labile iron pools via nNOS/NADPH oxidase activation. This bidirectional synergy culminates in mPTP opening, calcineurin hyperactivation, and ferroptotic collapse.

Future prospect:

Future therapies must transcend unidimensional targeting. Multifunctional agents—combining iron chelators (deferiprone), MCU inhibitors (Ru360), Nrf2 inducers, and CoQ10/FSP1 stabilizers—hold transformative promise. Precision nanotherapeutics or bifunctional small molecules addressing the Ca^{2+}-Fe^{2+} nexus could pioneer disease-modifying interventions, shifting PD management from symptomatic palliation to homeostasis restoration.

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