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REVIEW ARTICLE

The Role of Voltage-Gated Calcium Channels in Basal Ganglia Neurodegenerative Disorders

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Abstract: Calcium (Ca^{2+}) plays a central role in regulating many cellular processes and influences cell survival. Several mechanisms can disrupt Ca^{2+} homeostasis to trigger cell death, including oxidative stress, mitochondrial damage, excitotoxicity, neuroinflammation, autophagy, and apoptosis. Voltage-gated Ca^{2+} channels (VGCCs) act as the main source of Ca^{2+} entry into electrically excitable cells, such as neurons, and they are also expressed in glial cells such as astrocytes and oligodendrocytes. The dysregulation of VGCC activity has been reported in both Parkinson's disease (PD) and Huntington's (HD). PD and HD are progressive neurodegenerative disorders (NDs) of the basal ganglia characterized by motor impairment as well as cognitive and psychiatric dysfunctions. This review will examine the putative role of neuronal VGCCs in the pathogenesis and treatment of central movement disorders, focusing on PD and HD. The link between basal ganglia disorders and VGCC physiology will provide a framework for understanding the neurodegenerative processes that occur in PD and HD, as well as a possible path towards identifying new therapeutic targets for the treatment of these debilitating disorders.

Keywords: Calcium channels, neurodegenerative disorders, parkinson's disease, huntington's disease, basal ganglia and cell death.

1. INTRODUCTION

Calcium (Ca^{2+}) is an important intracellular second messenger responsible for the regulation of many processes in the central nervous system (CNS), including membrane excitability [1], exocytosis [2], synaptic transmission [3], synaptic plasticity [4], and apoptosis [5]. Baseline intracellular Ca^{2+} concentration $[Ca^{2+}]_i$ ranges between 50 and 100 nM in neurons, but as action potentials arrive at presynaptic terminals and also backpropagate into the dendritic arbour, there is a rapid increase in $[Ca^{2+}]$i ranging from 10-100 μM within neuronal microdomains [6]. Plasma membrane receptors such as N-Methyl-D-Aspartate receptors (NMDARs), transient receptor potential (TRP) channels, and voltage-gated Ca^{2+} channels (VGCCs) are responsible for mediating Ca^{2+} influx into the cell [7]. Furthermore, $[Ca^{2+}]_i$ can be increased *via* inositol-1, 4, 5-trisphosphate receptor (IP3R)- and ryanodine receptor (RyR)-mediated release from endoplasmic reticulum intracellular Ca^{2+} stores, or by efflux from mitochondria through sodium-dependent Ca^{2+} exchangers (Na^+/Ca^{2+}) [8].

Indeed, neuronal Ca^{2+} homeostasis is altered in neurodegenerative conditions, and uncontrolled Ca^{2+} signaling may drive pathological neurodegenerative processes [9, 10]. As VGCCs are the main source of Ca^{2+} entry into neurons, the dysregulation of these channels has been associated with NDs, including Parkinson's disease (PD) and Huntington's (HD) [11-16]. Consequently, VGCCs are considered interesting therapeutic targets for the potential treatment of these progressive NDs of the basal ganglia. This review will examine the putative roles of specific neuronal VGCCs in the pathogenesis and possible treatment of central movement disorders, focusing on PD and HD.

1.1. Subtypes, Structure, and Function of VGCCs

VGCCs are a group of voltage-gated ion channels that mediate Ca^{2+} entry into cells in response to membrane depolarization [17]. Structurally, VGCCs are heteromultimeric complexes composed of a central pore-forming α1 subunit and several auxiliary subunits ($\alpha_2\delta$1-4, β1-4, and γ1-8) [17]. The α1 subunit consists of four major transmembrane domains (I-IV), containing six membrane-spanning helices (S1-S6), a positively charged S4 segment that controls voltage-dependent activation, and a re-entrant P loop motif between the S5 and S6 segments that forms the Ca^{2+} permeation pathway (Fig. **1**). Ten distinct genetically-encoded isoforms (Ca_vx.x) of the α1 subunit have been identified and classified according to their electrophysiological and pharmacological properties into high-voltage activated (HVA) and low-voltage activated (LVA) Ca^{2+} channels (Table **1**)

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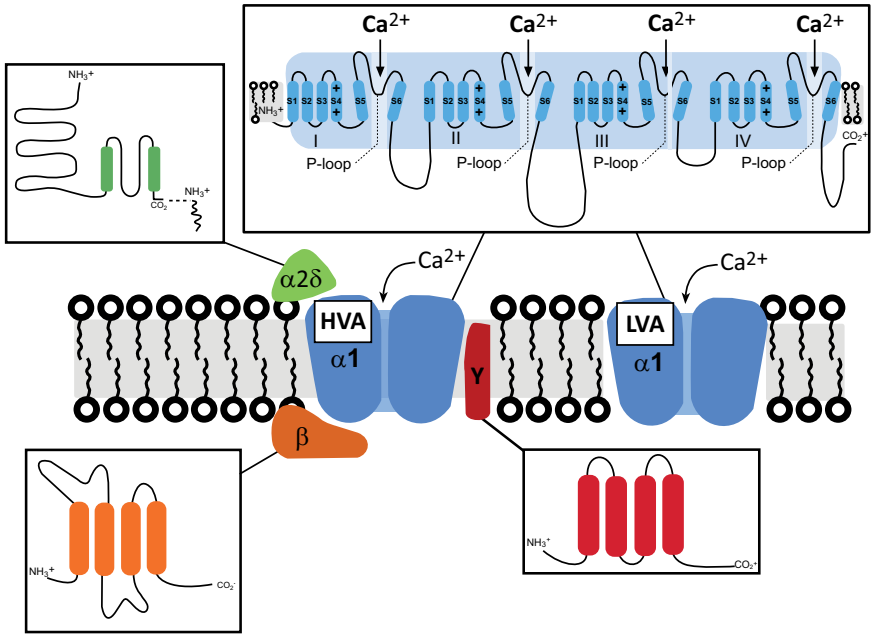

Fig. (1). Schematic representation of VGCCs. HVA channels consist of a pore-forming α1 subunit that coassembles with ancillary β, α2δ, and γ subunits, plus calmodulin (CaM). The α1 subunit is a transmembrane protein composed of four repeated amino acid sequence domains (I-IV), with each containing six transmembrane segments (S1-S6). The intracellular β subunit has no transmembrane segments, while the γ subunit is a glycoprotein with four transmembrane segments. The α2 subunit is an extracellular glycoprotein attached to the membrane by the δ subunit. LVA channels function as α1 subunit monomers. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

[18]. HVA Ca^{2+} channels open in response to large membrane depolarizations and include dihydropyridine (DHP) - sensitive L (long-lasting inward currents)-type Ca_v1 channels and less DHP-sensitive non-L-type Ca_v2 channels. In contrast, LVA channels encoded by the Ca_v3 isoforms open in response to lower membrane depolarization and have rapid inactivation rates to produce transient Ca^{2+} currents and are therefore termed transient or T-type channels [19]. HVA channels consist of a pore-forming α1 subunit that coassembles with ancillary β, α2δ, and γ subunits, plus calmodulin [CaM] [20]. On the other hand, LVA channels consist of an α1 subunit monomer (Fig. **1**). The Ca_v1 channel family encodes three different subtypes of neuronal L-type channels: $Ca_v1.2$, $Ca_v1.3$, and $Ca_v1.4$, plus a skeletal muscle-specific isoform, the $Ca_v1.1$ channel, which is responsible for excitation-contraction coupling (Table **1**) [21, 22]. $Ca_v1.4$ channels which are exclusively expressed in the retina and trigger neurotransmitter release from photoreceptors [23]. $Ca_v1.2$ and $Ca_v1.3$ channels show a highly overlapping expression pattern in many tissues (Table **1**) [24, 25] and are localized postsynaptically rather than presynaptically [26]. Neuronal L-type Ca^{2+} currents do not play a role in synaptic transmission but rather couple neuronal activity to changes in gene transcription (Table **1**, [27]).

The Ca_v2 channel family is composed of three members: $Ca_v2.1$ [P/Q-type, ω -AGA-sensitive channels], $Ca_v2.2$ [N-type, ω-CTX-sensitive channels], and $Ca_v2.3$ [R-type, SNX-482-sensitive channels] [28-31]. Neurotransmitter release at central synapses is primarily mediated by $Ca_v2.1$ and $Ca_v2.2$ channels (Table **1**) [3], while $Ca_v2.3$ channels play a critical role in coupling excitability to dendritic Ca^{2+} influx and neurotransmitter release [32, 33].

The Ca_v3 family contains three members of T-type channels: $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$ (Table **1**) [34]. Historically, the lack of specific blockers for this family made it difficult to determine their specific functions, but the development of small organic T-type inhibitors such as Z944 and TTA-P2 has driven the understanding of their physiological roles forward [35]. To date, Ca_v3 channels have been shown to play roles in exocytosis, specifically catecholamine release from chromaffin cells [36], neurotransmitter release in the retina and olfactory bulb [37, 38], spontaneous synaptic release and excitability of dorsal horn neurons [39, 40], synaptic transmission in hippocampal interneurons [41], and postsynaptic dendritic Ca^{2+} responses in cerebellar Purkinje cells [42].

1.2. Mechanisms of Cell Death that May be Triggered by VGCC Activation

An overload of neuronal Ca^{2+} through VGCCs may trigger several mechanisms of cell damage, including excitotoxicity, oxidative stress, mitochondrial disruption, neuroinflammation, proteasomal dysfunction, autophagy, apoptosis, and necrosis (Fig. **2**).

Glutamatergic excitotoxicity is considered a common feature of many NDs, including PD and HD, and has been linked to alterations in the expression of glutamate transporters and receptors [43, 44]. At presynaptic terminals, N- and P/Q-type channels trigger neurotransmission, including the release of glutamate at central synapses [45]. Glutamate binds to postsynaptic NMDARs to facilitate Ca^{2+} entry. It is well known that excessive glutamate levels impair $[Ca^{2+}]_i$ homeostasis and activate nitric oxide synthase (NOS),

Table 1. Nomenclature, physiology, and function of VGCCs.

	Gene	Ca^{2+} Channel Subtypes	Currents	Location	Function
HVA	CACNA1S	$Ca_v1.1$	L	Skeletal muscle	Excitation-contraction coupling
	CACNA1C	$Ca_v1.2$	L	Neuronal cell body, dendrites, Cardiac myocytes; smooth muscle; endocrine cells	Regulation of transcription, synaptic integration; excitation-contraction coupling; hormone release
	CACNA1D	$Ca_v1.3$	L	Neuronal cell body, dendrites; endocrine cells, cardiac atrial myocytes, and pacemaker cells, cochlear hair cells	Regulation of transcription; synaptic regulation; hormone release; cardiac pacemaking; hearing
	CACNA1F	$Ca_v1.4$	L	Retina, spinal cord	Neurotransmitter release from photoreceptors
	CACNA1A	$Ca_v2.1$	P/Q	Neuronal presynaptic terminals; Purkinje cells; Thalamus	Neurotransmitter release; dendritic Ca^{2+} transients; hormone release
	CACNA1B	$Ca_v2.2$	N	Neuronal presynaptic terminals and dendrites; neuroendocrine cells	Neurotransmitter release; dendritic Ca^{2+} transients; hormone release
	CACNA1E	$Ca_v2.3$	R	Neuronal cell bodies, nerve terminals, and dendrites	Repetitive firing, dendritic; Ca^{2+} transients
LVA	CACNA1G	$Ca_v3.1$	T	Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes	Pacemaker activity; Rhythmic burst firing; pre-and postsynaptic signalling and excitability
	CACNA1H	$Ca_v3.2$	T	Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes	Pacemaker activity; Rhythmic burst firing; pre-and postsynaptic signalling and excitability
	CACNA1I	$Ca_v3.3$	T	Neuronal cell bodies and dendrites	Pacemaker activity; Rhythmic burst firing

Note: Data adapted from [171, 172].

resulting in the generation of free radicals and apoptosis [46]. Interestingly, hippocampal immunohistochemistry experiments showed that the excitotoxic effects after kainic acid (KA) administration are absent in $Ca_v2.3^{-/-}$ mice, whereas $Ca_v2.3^{+/+}$ animals exhibited clear and typical signs of excitotoxic cell death [47, 48], demonstrating a putative role for VGCCs in these neurodegenerative processes.

Oxidative stress is characterized by a disturbance in the balance between the production of reactive oxygen species (ROS) and antioxidant defenses [49]. VGCCs have been described to be redox-sensitive due to cysteine residues in the pore-forming α1-subunit [50]. Altered redox status may affect the activity, expression, open-time probability, and trafficking of VGCCs [51]. Free sulfhydryl groups on L-type Ca^{2+} channels are an additional target for ROS-induced alterations of channel gating [52]. ROS have also been found to stimulate Ca^{2+} entry through L-type and T-type channels in vascular smooth muscle cells [53]. L-type channels, which contribute to the pacemaking activity of dopaminergic (DA) neurons, may also play a role in neurodegenerative mechanisms [11, 54]. Indeed, autonomous pacemaking increases basal mitochondrial oxidative stress in the substantia nigra pars compacta (SNpc) DA neurons, presumably as a direct consequence of Ca^{2+} loading [16, 55].

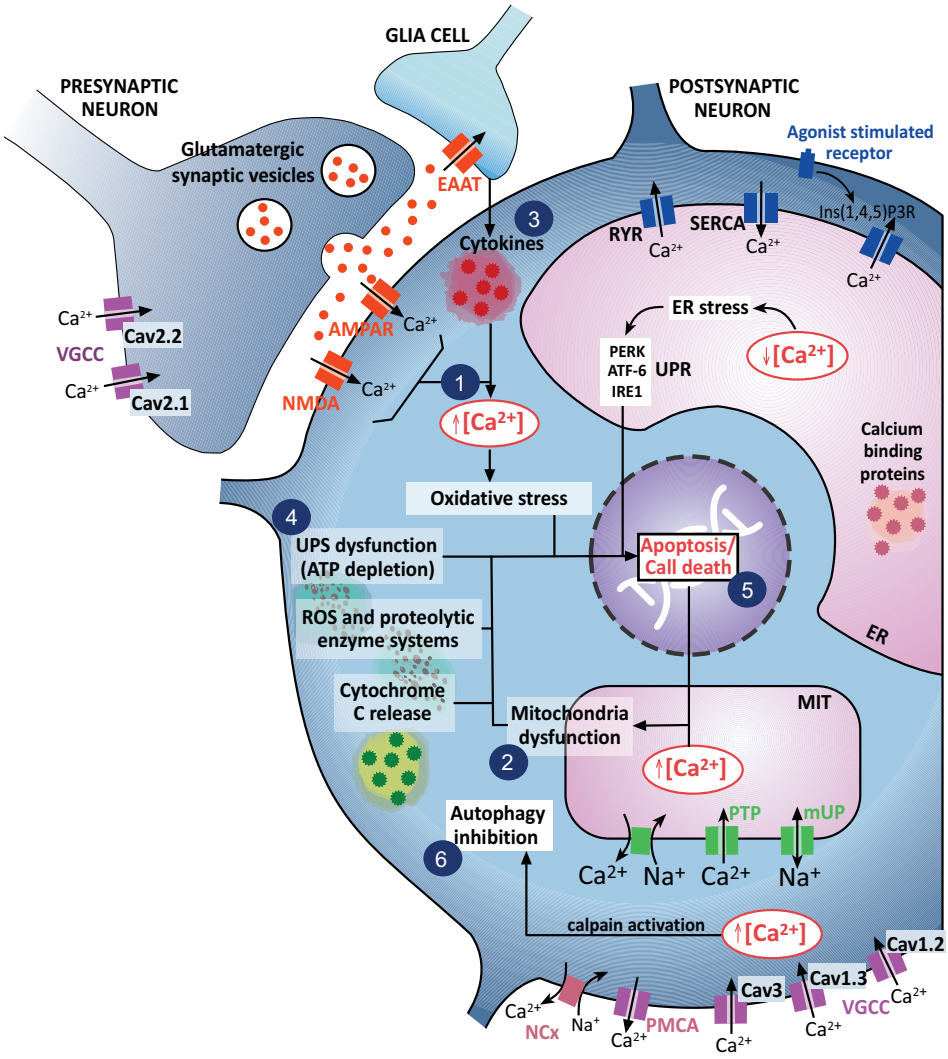

Fig. (2). Mechanisms of cell death triggered by Ca^{2+} in a dopaminergic neuron: Ca^{2+} is finely regulated by intercellular and intracellular signaling mechanisms, which are fundamental for survival and death in biological organisms. Ca^{2+} mainly enters the cytoplasm through ligand-gated channels, such as glutamate receptors, VGCCs, and store-operated channels. Ca^{2+} efflux is regulated primarily by the plasma-membrane Ca^{2+}-ATPase (PMCA) and the Na^{+}/ Ca^{2+}-exchanger (NCX). The largest Ca^{2+} store in the cell is found in the ER, and its concentration is modulated by sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA) pumps, inositol-1, 4, 5- trisphosphate (Ins(1, 4, 5)P3) receptors (Ins(1, 4, 5)P3 Rs), and ryanodine receptors (RYRs) as well as by Ca^{2+} -binding proteins. Mitochondria take up Ca^{2+} *via* the mitochondrial uniporter (mUP), and can release it through the reversal of the uniporter, Na^{+}/Ca^{2+} exchanger, or by the permeability transition pore (PTP) opening. As discussed in the text, excessive Ca^{2+} influx through VGCCs may trigger several mechanisms of cell damage, which results in a cascade of interconnected cellular dysfunction, including (1) excitotoxicity; (2) mitochondrial dysfunction and fragmentation, leading to the generation of ROS, cytochrome C release, and subsequent apoptotic cell death; (3) neuroinflammation, facilitated by the microglia-mediated release of neurotoxic factors and ROS, leading to autonomous neurotoxicity mechanisms; (4) a depletion in ATP and reduction in ATP-dependent processes, such as autophagic clearance of damaged proteins and organelles regulated by the ubiquitin-proteasome system (UPS); and (5) DNA damage, which activates apoptosis cascades. In addition, activating the L-type Ca^{2+} channel may increase its intracellular concentration and activate calpains, leading to the inhibition of autophagy (6), a fundamental process for excluding damaged proteins and organelles. As illustrated, these processes are interconnected and can occur simultaneously. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

Mitochondria also regulate $[Ca^{2+}]_i$ in neurons, and mitochondrial dysfunction may lead to mitochondrial permeability transition pore (PTP) opening *via* high mitochondrial Ca^{2+} levels and mitochondrial depolarization [56]. The opening of mitochondrial pores releases apoptotic factors and leads to apoptosis [57]. The activation of T-type channels may also cause the dysregulation of $[Ca^{2+}]_i$ homeostasis, leading to increased mitochondrial stress in PD patient-derived dopaminergic neurons [58]. Similarly, abnormal Ca^{2+} entry through L-type Ca^{2+} channels can drive mitochondrial disruption and apoptosis through a mechanism that requires activation of the mitochondrial transition pore and superoxide dismutase [59].

Neuroinflammation is a core feature of NDs [60]. In most cases, activated microglia secrete cytokines including NGF, TNF, and free radicals, which leads to oxidative stress and subsequent damage to neurons [61]. Ryanodine receptors [RyRs] and L-type channels may mediate Ca^{2+}-associated microglia activation [62]. Beyond microglia, astrocytes may also play a role in the neuroinflammatory process observed in NDs [63, 64]. L-type channels have been shown to be up-related in astrocytes after certain types of injuries, such as epilepsy and ischemia [65], but the pathophysiological relevance of upregulated L-type channels in astrocytes remains unclear [66].

NDs are also associated with aggregate proteins that may disturb cellular homeostasis and neuronal function [67]. Accumulating evidence indicates that dysfunction of proteasome activity, responsible for removing misfolded proteins, is a critical component of pathogenesis in NDs [68-71]. Changes in $[Ca^{2+}]_i$ concentrations have been reported to alter proteasome activity [72, 73]. This regulation of the proteasome is dependent on Ca^{2+} influx through NMDARs and L-type channels in neurons and also requires the activity of calcium/calmodulin-dependent protein kinase II (CaMKII) [74].

Studies have shown that L-type Ca^{2+} channel activation increases cytosolic Ca^{2+}, which can activate calpains. In turn, calpains activate the α-subunit of heterotrimeric G proteins Gαs, leading to increased cAMP levels, IP3 production, and the inhibition of autophagy [75]. Autophagy is an intracellular catabolic process that targets damaged proteins and organelles into lysosomes for degradation [76]. Interestingly, in the mouse model of Pompe disease, defective autophagy is due to an upregulation of L-type Ca^{2+} channels [77]. Moreover, verapamil, an L-type Ca^{2+} channel antagonist, reversed mitochondrial abnormalities in Pompe model muscle cells and decreased levels of Ca^{2+} in subcellular areas free from autophagic buildup [77]. In contrast, Poewe and colleagues showed that mibefradil, a T-type Ca^{2+} channel blocker, inhibited constitutive autophagy by decreasing the autophagic flux into cardiomyocytes, whereas nifedipine, another L-type Ca^{2+} channel blocker, triggered a macro autophagic process and ultimately promoted apoptosis [78]. These reactions raise an important point that the roles of VGCCs in mechanisms that regulate cell death may be different according to their expression profile and potential for dysregulation in specific cell types.

2. PARKINSON'S DISEASE

PD is the second-most common ND and preferentially affects the aging population over 65 years old [79]. Multifactorial interactions between the environment and genetic and epigenetic factors combined with cellular aging processes are reported to trigger underlying neurodegenerative mechanisms [79]. Sporadic PD corresponds to 90% of cases [80], while less than 10% of PD cases are familial and caused by monogenic mutations [81, 82]. Neurobiologically, PD is characterized by loss of DA neurons in specific areas of the SNpc, leading to motor symptoms such as resting tremors, bradykinesia, and postural rigidity [83]. The substantia nigra participates in the extrapyramidal system, composed of the basal ganglia, thalamus, and the frontal premotor cortex. This system is responsible for automating and modulating movements [84]. Despite these clear neuroanatomical and cellular loci for PD pathology, the specific molecular mechanisms behind neurodegeneration within the SNpc are not fully elucidated. The hallmark neuropathology for PD is an abnormal intracellular protein accumulation of α-synuclein into intraneuronal inclusions called Lewy bodies (LBs) [85, 86].

The exact function of α-synuclein is unknown, but it is postulated to be involved in neurotransmitter release and mitochondrial function [87]. However, the accumulation of these proteins in neurons results in an abnormal and toxic function typical of protein misfolding disorders [87]. Interestingly, it has been proposed that α-synuclein can be released from neurons, enabling cell-to-cell transmission of α-synuclein misfolding in a prion-like manner [88, 89]. Ultimately, misfolding α-synuclein alters cellular energy processes [90]. Aggregated α-synuclein interacts with the mitochondrial membrane to increase oxidative stress, change mitochondrial morphology, decrease the membrane potential, and open mitochondrial permeability pores [91]. Beyond this specific mitochondrial impairment, disruptions in dopamine homeostasis and protein degradation systems, as well as neuroinflammatory processes, are all interconnected to drive the death of DA neurons in the SNpc [92].

2.1. Evidence of Neurodegeneration through VGCCs in PD

Neurons transiently increase $[Ca^{2+}]_i$ through VGCCs or receptor-operated channels during physiological processes [7]. To maintain proper $[Ca^{2+}]i$ homeostasis, intracellular Ca^{2+}-buffering is accomplished through high-affinity Ca^{2+}-binding proteins. It is hypothesized that the degeneration of SNpc neurons is driven by low calbindin-D28k, a calcium-binding protein, which underlies the susceptibility of these neurons to Ca^{2+}-mediated excitotoxicity [93, 94]. Neuronal spikes within SNpc neurons are broad, enhancing Ca^{2+} entry and promoting slow rhythmic activity [95].

The main motor symptoms of PD are due to the death of DA neurons in the SNpc [96]. Within these neurons, Ca^{2+} entry through Ca_v1 channels in the plasma membrane leads to an induction of mitochondrial oxidative phosphorylation [97]. This mitochondrial activity helps prevent bioenergetic failure in case of sustained activity, but it also leads to basal oxidative stress [97]. Along with pore-formation in the mitochondrial membrane, $Ca_v1.2$ and $Ca_v1.3$ channels are major contributors to the elevation of $[Ca^{2+}]_i$ in SNpc DA neurons [98, 99]. Relatively low threshold $Ca_v1.3$ channels remain activated near resting membrane potentials, which is why these channels do not fully close during the pacemaking cycle of SNpc DA neurons [98]. Moreover, the expression of splice variants in the C-terminal of $Ca_v1.3$ channels maintains the dependence on Ca^{2+} for channel activation, which contributes to ongoing Ca^{2+} influx [100, 101]. Additionally, L-type Ca^{2+} currents through $Ca_v1.3$ channels have been described as key factors for the retrograde-propagation of spikes into dendrites, leading to increased Ca^{2+} entry that modulates synaptic responses and initiates and promotes burst firing [102].

As indirect evidence for the relationship between Ca^{2+} oscillations and PD, an inverse correlation exists between calbindin expression levels and the risk of degeneration in

PD-like pathology, which has also been described using a transgenic mouse model [103]. Thus, the imbalance of $[Ca^{2+}]_i$ may contribute to the increasing vulnerability of DA neurons to other stressors [99]. As a primary mediator of increasing $[Ca^{2+}]$, Ca_v1 blockade could, therefore, potentially lead to neuroprotection by preventing excessive Ca^{2+} elevations in spontaneously active cells [99]. It remains to be tested if additional mechanisms, such as a reduction in mitochondrial oxidative stress or reduced inflammatory features, are involved in this neuroprotection [99].

In similar correlative studies, DHPs used to block Ca_v1 channels in the clinic are associated with a possible decrease in risk and progression of PD [104, 105]. Retrospective analysis of Ca_v1 channel blockers in patients with arrhythmia and hypertension indicated a decreased risk for PD, suggesting a neuroprotective role of the Ca_v1 channel in the disease [106, 107]. In preclinical rodent models, the effects of nanomolar or micromolar concentrations of DHPs on dendritic Ca^{2+} oscillations have also been tested [54]. Moreover, VGCC blockade by DHPs reduced elevated cytosolic Ca^{2+} in SNpc DA neurons and restored the activity of enzymes involved in the synthesis of DA, enabling a match in supply and demand for this neurotransmitter [55, 108].

Additionally, Ca^{2+} entry through Ca_v1 channels and subsequent Ca^{2+}-dependent control of mitochondrial metabolism have been hypothesized to be key mediators of degeneration in SNpc DA neurons [99]. Neuronal Ca^{2+} oscillations are proposed to promote Ca^{2+} entry into mitochondria through junctions within the endoplasmic reticulum, stimulating oxidative phosphorylation and the generation of ATP [54, 99]. However, there is insufficient evidence to support this hypothesis, as genetic models of PD with manipulations in these molecular and cellular features are lacking. However, in dyskinesia pre-clinical models, the inhibition of Ca_v1 channels by isradipine or nimodipine has proven to reduce the damage by 6-hydroxy dopamine (6-OHDA), rotenone, and 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) in SNpc DA neurons [11, 99, 109]. Moreover, preclinical studies in rodent PD models demonstrated that pretreatment with isradipine or nimodipine could protect DA neurons from MPTP- and 6-OHDA-induced toxicity [11, 109]. This mechanism seems to occur by inhibiting $Ca_v1.3$ channels expressed in the SNpc, which leads to reduced Ca^{2+} influx, decreased energy use, and reduced oxidative stress [99].

Preclinical studies also demonstrate that $Ca_v1.3$ channels are required to maintain pacemaking between DA neurons from SNpc and the dorsal motor nucleus of the vagus nerve [99, 110, 111]. The continuous activation of $Ca_v1.3$ channels is essential for maintaining this pacemaking activity, as rhythmic Ca^{2+} oscillations are disrupted by the blockade of dendritic Ca^{2+} channels with DHPs [112]. However, there is still a lack of evidence investigating how the role of $Ca_v1.3$ channels within these dopaminergic neurons may change with advanced age [113].

Pacemaker activity is also maintained by voltage-dependent sodium and potassium channels expressed in the active autonomous regions of the midbrain and brainstem [112]. Administration of $Ca_v1.3$ blockers has been found to reduce mitochondrial oxidative stress in DA neurons within the brainstem and midbrain firing rhythmically [55, 96]. Consequently, blocking $Ca_v1.3$ channels should reduce oxidative stress within these surviving neurons, providing neuroprotection without affecting their autonomous and physiological activity [54, 55, 94, 96]. In this regard, isradipine, a DHP drug with an almost equimolar affinity for $Ca_v1.2$ and $Ca_v1.3$, protected DA cells against neurotoxicity in *in vitro* PD models [11, 114] and reduced the risk for PD in the clinic [115]. This process putatively occurs through a shift of pacemaking activity in these neurons from a Ca^{2+}-dependent state to a sodium-dependent one (Fig. **3A**) [99].

3. HUNTINGTON'S DISEASE

Huntington's disease (HD) is a fatal autosomal dominant disease leading to progressive degeneration of the basal ganglia and cerebral cortex, in which symptoms include motor alterations, cognitive dysfunction, and psychiatric disorders [116]. Morphologically, HD is defined by progressive dysfunction and, ultimately, the death of the medium-sized spiny GABAergic neurons (MSNs) of the striatum [117]. Cortical glutamatergic pyramidal neurons that project to striatal dopaminergic neurons degenerate, and striatal neurons projecting to the SNpc also degenerate in presymptomatic patients [84]. It is well established that HD is caused by polyglutamine expansion (CAG repeats) in exon-1 of the huntingtin (HTT) gene [68, 118, 119]. This expansion results in mutant huntingtin (mHtt) protein with an elongated polyglutamine tract. Within neurons and other cells, Htt has been detected in the nucleus, mitochondria, Golgi, and endoplasmic reticulum and can be found in the soma, dendrites, and synapses [120]. It has been postulated that Htt may be involved in the trafficking of vesicles and organelles, gene transcription, and protection from apoptosis [121, 122]. The mHtt may promote dysfunctional protein-protein interactions, resulting in neuronal loss and dysfunction in the striatum, cortex, and other parts of the brain [123, 124]. mHtt has several interacting partners that affect the physiology of cells in different manners, thus leading to dysfunctional axonal transport, dysregulation of gene expression, and altered mitophagy and autophagy [125]. However, the molecular mechanisms linking the Htt mutation to neuronal cell death have not yet been fully elucidated.

3.1. Evidence of Neurodegeneration through VGCCs in HD

Several studies have demonstrated that Ca^{2+} signaling pathways are elevated across different models of HD [126]. According to the Ca^{2+} hypothesis, changes in Ca^{2+} homeostasis in HD patients drive the degeneration and atrophy of neurons [127]. This Ca^{2+} imbalance is observed at an early stage and may be an important process involved in the pathogenesis of the disease [9]. mHtt protein has been reported to bind directly to VGCCs, corroborating the idea that mHtt can impact VGCCs [128, 129]. More specifically, mHtt modulates N-type channels to regulate presynaptic neurotransmitter release [2] through direct binding to the II-III linker region of the N-type calcium channel, displacing syntaxin and resulting in an increase in Ca^{2+} influx [129]. Moreover, in young BACHD mice that expressed full-length Htt, an increase in striatal glutamate release was described, which was reduced to control levels by selective inhibition of $Ca_v2.2$ channels [13]. Silva and colleagues also observed a direct

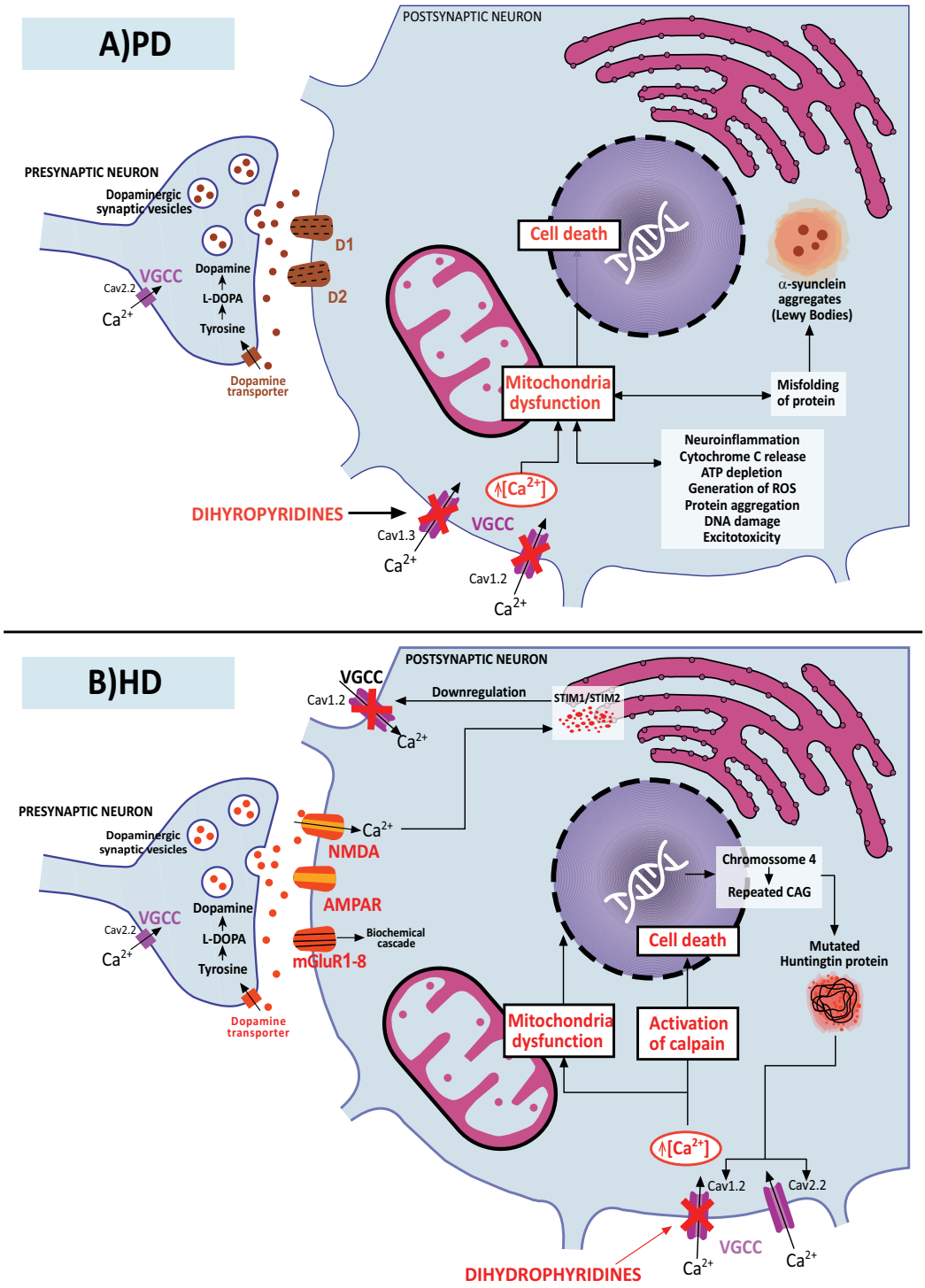

Fig. (3). Pathogenic cellular mechanisms in PD and HD. **A**. PD is characterized by a degeneration of dopaminergic neurons in the SNpc of the midbrain and the development of neuronal Lewy Body accumulation in neurons. The schematic representation shows the main mechanisms that lead to cell death in PD - aggregation of Lewy Bodies is associated with a process related to mitochondrial dysfunction, which is a key element in the pathogenesis of PD. Such a process can be precipitated by excessive Ca^{2+} input by VGCCs, whose inhibition by dihydropyridines (DHPs) has been shown to play an important role in managing the evolution of neuronal degeneration. **B**. HD is a neurodegenerative disorder whose mechanism involves the accumulation of mutated huntingtin protein (mHtt), followed by the death of GABAergic neurons. The neuronal cell loss in HD is associated with glutamatergic excitotoxicity, mediated by an excessive influx of intracellular Ca^{2+}, N-type Ca^{2+} channels ($Ca_v2.2$), and L-type Ca^{2+} channels ($Ca_v1.2$), which are affected by mHtt. Furthermore, L-type channels can be inhibited by the ER STIM1 and DHPs. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

increase in plasma membrane expression and function of N-type Ca^{2+} channels, which likely mediated the elevation of glutamate release [13]. An additional study using BACHD mice showed that mHtt protein might disrupt Ca^{2+} homeostasis *via* upregulation of cortical $Ca_v1.2$ channels and resultant L-type currents [14]. Interestingly, it has been reported that stromal interaction molecule 1 (STIM1), which is present in the endoplasmic reticulum (ER), can detect elevated Ca^{2+} concentrations and promote L-type channel inhibition [130]. In hippocampal neurons, glutamatergic depolarization of neurons activates Ca^{2+} influx through NMDARs and L-type channels, causing activation of STIM1, which leads to a negative feedback mechanism that downregulates L-type channels to control plasticity and nuclear signaling [131]. Notably, the expression of the N-terminal fragment of mHtt in human or mouse neuroblastoma cells and primary cultures of mouse MSN results in increased store-operated Ca2+ entry through STIM1 and activation of both transient receptors potential channel 1 (TRPC1) and calcium release-activated calcium channel protein 1 (Orai1) [132, 133]. Recently, elegant work showed that Ca^{2+} entry through L-type channels is potentiated in neurons from HD rodent models [134]. The authors found that this upregulation of L-type currents depended on suppressing stromal interaction molecule 2 (STIM2) [134]. Thus, it is quite tempting to postulate that mHtt interaction with STIM1 and/or STIM2 may interfere with the homeostatic regulation of L-type channels (Fig. **3B**).

Also, electrophysiology and $[Ca^{2+}]_i$ imaging experiments have demonstrated that Huntingtin-associated protein 1 (Hap1) depletion decreases Ca^{2+} influx through L-type channels [135]. Given that HAP1 is preferentially expressed in neurons and controls axonal transport, its association with mHtt could contribute to HD neuropathology by altering the intracellular trafficking and plasma membrane localization of $Ca_v1.2$ channels [135].

Post-mortem studies of HD brains show a decrease in tyrosine hydroxylase (TH) as well as DA receptor (D1 and D2R) density in specific states of the disease [136-138]. Moreover, dopaminergic stimulation, *via* D2R, in enkephalin-expressing medium spiny neurons suppresses transmembrane Ca^{2+} currents through L-type channels, resulting in diminished excitability [139]. Thus, a decrease in D2Rs may lead to a dysregulation of L-type currents, resulting in an abnormal increase in Ca^{2+}, increased DA synthesis through the activation of TH [140], and intracellular damage *via* neurotransmitter auto-oxidation [141].

4. PRECLINICAL AND CLINICAL EVIDENCE FOR USE OF CCBS IN TREATING PD

There are more preclinical studies investigating the effects of CCBs in PD models compared to HD. In these studies, the prophylactic administration of CCBs provides neuroprotective effects against the onset and development of PD (Table **2**). The administration of CCBs later in disease progression also provides symptom rescue [112].

In preclinical *in vitro* models of PD, the human SH-SY5Y neuroblastoma cell line and primary rat cortical neurons exhibit changes in Ca^{2+} homeostasis and increased neuronal death. Moreover, pretreatment with nifedipine and ω-conotoxin GVIA (an N-type channel blocker) protected neuronal cells against secreted α-synuclein-mediated neurotoxicity [12]. Furthermore, pretreatment with nimodipine (an L-type blocker) was able to protect cultured midbrain neurons from L-DOPA-induced neurotoxicity [142]. Another *in vitro* disease model involving PD patient-specific iPSC-derived DA neurons showed that the selective vulnerability of DA neurons to rotenone-induced stress was attributable to the dysregulation of $[Ca^{2+}]_i$ homeostasis *via* T-type calcium channels. Indeed, pretreatment with a selective T-type Ca^{2+}channel antagonist, ML218, was able to suppress the rotenone-mediated increase in $[Ca^{2+}]_i$ and cell death [58]. Elegant data using cultured ventral mesencephalic neurons treated with dopamine to promote the clustering of alpha-synuclein showed that post-treatment with isradipine reversed the increase of alpha-synuclein clusters or dopamine toxicity [143]. Another preclinical study analyzed the effect of extracellular application of α-synuclein on depolarization-evoked Ca^{2+} influx, $Ca_v2.2$ Ca^{2+} current density, and neurotransmitter release from primary cortical neurons. The authors identified that the molecular mechanism of α-synuclein involves an increase in $Ca_v2.2$ activity to induce DA release. Posttreatment with ω-conotoxin GVIA decreases $[Ca^{2+}]_i$ and dopamine release triggered after extracellular α -synuclein application [144]. To investigate potential cell type-specific mechanisms of toxicity, Lieberman and colleagues investigated the sensitivity of SN and ventral tegmental area (VTA) DA neurons to a mitochondrial neurotoxin, 1-methyl-4-phenylpyridinium (MPP^+). The authors demonstrated that the α-synuclein- and L-type Ca^{2+} channel-dependent elevation of Ca^{2+} was the primary mediator of mitochondrial oxidation and toxicity in SN neurons. Notably, L-type Ca^{2+} channel basal activity, but not the MPP^+-mediated increase in Ca^{2+}, appears to underlie the different DA levels in SN and VTA neurons as *in vitro* pretreatment with isradipine decreased MPP^+-mediated toxicity [145].

Preclinical *in vivo* studies of PD have attributed several beneficial effects to systemic isradipine treatment, such as lower mitochondrial oxidative stress and rotenone- and MPTP-induced TH loss, higher survival of SNpc DA cells, and a decrease in motor deficits [55, 99]. In terms of direct actions on L-type Ca^{2+} channel-mediated activity, the systemic administration of isradipine at low nanomolar plasma concentrations, close to those achieved in patients, diminished cytosolic Ca^{2+} oscillations in midbrain slices from transgenic animals, TH-mito-roGFP mice [55]. This model expresses a redox-sensitive variant of green fluorescent protein targeted to the mitochondrial matrix, which engages plasma membrane L-type calcium channels during normal autonomous pacemaking creating oxidant stress specific to vulnerable SNpc DA neurons [54]. Moreover, chronic isradipine treatment also lowered mitochondrial oxidative stress, which reduced the high rate of mitophagy and normalized mitochondrial mass [55]. Interestingly, isradipine-treated adult mice (7 days through slow-release, subcutaneous pellets) subjected to repeated injections of the toxin MPTP over the course of 5 weeks showed a reduction of DA cell loss in SNpc and motor impairment as compared to placebo groups [99]. However, a preclinical study involving the administration of isradipine at plasma concentrations approved for therapy reported that this drug was not neuroprotective in a Parkinsonism mouse model induced by striatal unilateral 6-OHDA lesions. Isradipine pretreatment

Table 2. Pre-clinical studies targeting CCBs in PD.

Disorder	Drug, Dose/Concentration and Administration	Pre-Clinical Model/ *In Vivo*/*In Vitro*	Results	Refs.
PD	Isradipine 3 mg/kg/day	C57BL/6 mice / *in vivo*	↑ the survival of SNpc dopaminergic cells after 6-OHDA-induced degeneration	[11]
PD	Nifedipine 1 μM; ω-conotoxin GVIA 100 nM	SH-SY5Y cells / *in vitro*	↓ the elevation of $[Ca^{2+}]_i$ after application of extracellular α-synuclein	[12]
PD	Isradipine 5 μM	Midbrain slices of Mito-roGFP transgenic mice/ *in vivo*	↓ the mitochondrial oxidant stress in SNpc dopaminergic neurons	[54]
PD	Isradipine 3 μg/g/d ay	Transgenic TH-mito-GFP mice *in vivo*	↓mitochondrial oxidant stress by reducing Ca^{2+} oscillation in SNpc neurons	[55]
PD	ML218 10 μM	iPSCs derived from dopaminergic neurons of PARK-2 patients/ *in vitro*	Ameliorated the effect of rotenone treatment through the rescue of the neuronal apoptotic phenotype	[58]
PD	Isradipine 20 μM	Male C57BL/6 mice/ *in vivo*	Reversed rotenone and MPTP-induced TH-loss and motor deficits	[99]
PD	Nimodipine 10 μM	Primary dopaminergic neurons/ *in vitro*	↓ increase of cytosolic levels of dopamine after L-DOPA-induced neurodegeneration	[142]
PD	Isradipine 5 μM	Ventral mesencephalic primary neurons/ *in vivo*	Reversed the clustering of α-synuclein positive vesicles and α-synuclein aggregation	[143]
PD	ω-conotoxin GVIA 300 nM	Rat primary cortical neurons/ in vitro	↓ $[Ca^{2+}]_i$ and dopamine release triggered after extracellular α-synuclein application	[144]
PD	Isradipine, 5 μM, Nimodipine, 5 μM	Primary dopaminergic neurons/ *in vitro*	Prevented the MPP^+-induced $[Ca^{2+}]_i$ elevation in SNpc but not in VTA	[145]
PD	Isradipine extended-release pellets (6 or 9 mg/kg/day;) or s.c. (3 mg/kg/day)	6-OHDA-treated mice/ *in vivo*	Failed to achieve neuroprotection of SNpc neurons due to low selectivity for $Ca_v1.3$ VGCCs	[146]
PD	Felodipine 1 and 5 μM	SNCA mice/ *in vivo*	Felodipine induces autophagy and clear aggregate-prone, neurodegeneration disease-associated proteins (α-synuclein).	[147]
PD	ML218 (1, 10 or 30 mg/kg)	MPTP-treated parkinsonian monkeys/ *in vivo*	No antiparkinsonian effects in MPTP-treated parkinsonian monkeys	[148]
PD	ω-conotoxin GVIA 10 μM ω-agatoxin IVA 10 μM	Sprague-Dawley rats/ *in vivo*	↓dopamine release from striatal terminals	[173]
PD	SNX-482, 0.1-10 μM	Sprague-Dawley rats/ *in vivo*	↓ the somatodendritic DA release in SN	[174]
PD	Mibefradil 1-3 μM	STN slices and Wistar rats/ *in vivo*	↓ the burst activity in STN neurons and improved locomotor deficits in 6-OHDA lesioned rats	[175]

Note: Isradipine, Felodipine, Nimodipine= L-type blocker; Mibefradil=T-type blocker; ω-conotoxin GVIA= N-type blocker; ML218= T-type blocker; s.c.= subcutaneous; i.p= intraperitoneal; ↓= decrease; ↑= increase; TH= tyrosine hydroxylase; SNpc= substantia nigra pars compacta; ω-agatoxin IVA= P/Q blocker; SNX-482 = R-type blocker; Dantrolene= ryanodine receptor (RyR) antagonist; STN=subthalamic nucleus.

(extended-release pellets one week before 6-OHDA lesioning) failed to protect SNpc DA terminals and cell bodies against 6-OHDA-induced DA cell loss. To explain this failure, the authors postulated that the SN DA neuronal activity depends more on $Ca_v1.3$ channels and those channels are less sensitive to isradipine blockade [146]. When SCNA mice (transgenic mice expressing PD-causing A53T mutant α-synuclein) were implanted with subcutaneous felodipine-loaded osmotic minipumps for 28 days, the researchers found that treatment decreased the level of the insoluble fraction of α-syn in the cerebral cortex and brainstem, followed by improved grip strength and increased cell numbers in the substantia nigra [147]. Interestingly, felodipine is an L-type blocker clinically approved as an antihypertensive drug [147]. Further studies will be required to determine if felodipine has more affinity to $Ca_v1.3$ channels as well as its brain concentrations in humans.

In addition to the above HVA Ca^{2+} channels, T-type LVA channels have been investigated as a novel potential therapeutic target for the treatment of PD [148]. However, in a monkey chronically treated with MPTP, post systemic administration of a T-type Ca^{2+} channel blocker, ML218, induced no antiparkinsonian effects. However, the sedative effect of the drug may have confounded potential interpretation of these behavioral results, as electrocardiograms revealed an increase in sleepiness in Rhesus monkeys after ML218 administration [148]. Nevertheless, the therapeutic relevance of T-type channels in PD pathology (as well as in sleep gating) still requires further investigation.

In terms of clinical studies that directly test the effects of CCBs in PD patients, phase 2 and 3 clinical trials have been limited to the study of isradipine (Table **4**). Primary studies evaluated the safety and tolerability of isradipine's controlled-release (CR) in patients with early PD [149, 150]. The maximum tolerability of isradipine CR was 10 mg [150]. These studies revealed lower disability scores in PD patients, alongside some possible adverse effects depending on the dosage, including peripheral edema and dizziness [149, 150]. A clinical multi-center study involving 336 participants analyzed the effectiveness of isradipine (10mg for 36 months) in slowing the progression of untreated individuals with early PD [151, 152]. However, this long-term treatment with immediate-release isradipine was found to not slow the clinical progression of early-stage PD [153]. Yet, long treatment with isradipine did appear to delay the use of other anti-parkinsonism drugs [154, 155].

Given conflicting evidence regarding efficacy, the differences between the main outcomes of preclinical and clinical studies involving CCBs must be pointed out here. Remarkably, around 95% of drugs that enter clinical trials do not make it to the market, despite all preclinical data supporting their use [156]. Interesting analysis has investigated the outcomes of the isradipine clinical studies in detail [157]. The authors postulate that primary clinical outcome measurements were not ideal, as advances in disease progression were not assessed. For example, investigating changes in the deposition of synuclein pathology in samples from treatment versus control groups could reveal whether treatment was altering underlying neuropathological mechanisms. Another important point is to determine whether the dose of isradipine administered to patients achieved adequate levels in the brain to impact targets and mechanisms to the same degree as reported for preclinical evidence. These target engagement and disease progression measurements will be critical to bridging the translational gap between preclinical models and future new clinical treatments and management approaches for PD.

5. PRECLINICAL AND CLINICAL EVIDENCE FOR USE OF CCBS IN TREATING HD

Compared to the wealth of evidence relating to CCBs and PD, there is a lack of preclinical and clinical research investigating the effects of CCBs on HD pathological mechanisms and associated symptoms (Table **3**). The lack of clinical research is unexpected given the interesting effects of CCBs on neurodegenerative processes associated with HD, including neuronal protection against glutamate toxicity, reductions in Ca^{2+} oscillations, protection against oxidative stress, and rescue from NMDAR-mediated toxicity [13, 14, 147, 158-160]. Preclinical *in vitro* data using striatal synaptosomes from BACHD mice showed an increase in glutamate release, which was reduced to control levels by inhibition with ω-conotoxin GVIA, an N-type channel antagonist [13]. Moreover, $Ca_v1.2$ L-type channels increased, and pretreatment with isradipine protected against glutamate-induced neuronal cell death in cultured corticostriatal neurons from BACHD mice [14]. Additional preclinical evidence showed that in rat primary corticostriatal co-cultures, co-administration of nifedipine and memantine (an NMDAR-blocker) rescued neurons from NMDA-mediated toxicity [158]. *In vivo* preclinical data using an animal model of 3-nitropropionic acid (3-NP)-induced oxidative stress demonstrated that pretreatment with the L-type channel blocker nimodipine could also ameliorate associated behavioral dysfunction [159]. Moreover, in B6HD mice, which express the first 171 amino acids of mhtt, 6 weeks of treatment with felodipine decreased the number of aggregates in the piriform and motor cortex [147]. In contrast, *in vivo* pretreatment with nimodipine did not prevent striatal lesions in an excitotoxicity model induced by quinolinic acid [161]. Recent work in slices from the transgenic mouse model of HD, R6/2 mice showed that pretreatment with nifedipine significantly reduced somatic Ca^{2+} transient amplitude and area in cortical pyramidal neurons [155]. Notably, in the face of this accumulating preclinical evidence, clinical trials involving CCBs in HD patients are still lacking.

6. LIMITATIONS IN CCBS USE IN PD AND HD

Based on preclinical data demonstrating the neuroprotective effects of CCBs, these classes of channel antagonists may be effective treatments for ND. However, some important fundamental questions remain regarding the role of VGCC subtypes in controlling mechanisms of cell death. For example, how does the differential expression and/or upregulation of specific channel variants mediate mechanisms of neurotoxicity across defined subpopulations in the brain? Another major barrier to future translation is the lack of exploring underlying neurodegenerative mechanisms across sex. The vast majority of preclinical evidence discussed here is from male or unsexed animals. As many examples of sex differences in neuronal pathology and neurological disease are emerging, it is critical to directly assess whether the roles of VGCCs in neurodegeneration and the efficacy of CCBs in

Table 3. Pre-clinical studies targeting CCBs in HD.

Disorder	Drug, Dose/Concentration	Pre-Clinical Model/ *In Vivo*/*In Vitro*	Results	Refs.
HD	ω-conotoxin GVIA 50 nM	Striatal synaptosomes from BACHD mice/ *in vitro*	↓ striatal glutamate release observed in BACHD mice	[13]
HD	Isradipine 1 nM	Corticostriatal neurons from BACHD mice/ *in vitro*	Neuronal protection against glutamate toxicity	[14]
HD	Felodipine 1 and 5 μM	HD transgenic mice (B6HD mice) */ in vivo*	Felodipine induces autophagy and clear aggregate-prone, neurodegeneration disease-associated proteins (mhtt).	[147]
HD	Nimodipine, 2, 4, and 10 mg/kg, i.p.	Male Sprague-Dawley rats/ *in vivo*	No beneficial effect against quinolinic acid striatal lesion	[156]
HD	Nifedipine 5 μM	Cocultured striatal and cortical neurons/ *in vitro*	Mixed solution with memantine rescued neurons from NMDA-mediated toxicity	[158]
HD	Nimodipine 12 mg/kg	Male Sprague-Dawley rats/ *in vivo*	Protective against oxidative stress	[159]
HD	Nifedipine 10 μM	Cortical pyramidal neurons from R6/2 mouse mice/ *in vitro*	Nifedipine significantly ↓ both somatic Ca^{2+}transient amplitude and area	[160]

Note: Isradipine, Felodipine, Nimodipine= L-type blocker; Mibefradil=T-type blocker; ω-conotoxin GVIA= N-type blocker; ML218= T-type blocker; s.c.= subcutaneous; i.p= intraperitoneal; ↓= decrease; ↑= increase; TH= tyrosine hydroxylase; SNpc= substantia nigra pars compacta; ω-agatoxin IVA= P/Q blocker; SNX-482 (R-type blocker); Dantrolene= ryanodine receptor (RyR) antagonist; STN=subthalamic nucleus.

reversing or preventing ND symptoms are conserved from males to females [162, 163]. Thus, there are still challenges and limitations in using CCBs that require further investigation as we move towards novel treatment approaches for PD and HD.

Despite the advances in CCB research in PD that has made it possible to conduct clinical trials, there are still some limitations in using these agents. For example, some researchers have observed that CCB administration does not cause significant neuroprotection of SNpc neurons in PD models [146]. Moreover, it is not clear from a translational perspective if the initiation of CCB treatment after motor symptom onset will be able to slow PD progression. At this time point, there is considerable loss of SNpc DA neurons and other factors such as α-synuclein aggregation or neuroinflammation that may aggravate the pathogenesis. Notably, epidemiologic studies of CCBs demonstrated a reduction in the risk for a new diagnosis of PD [106, 107, 164], and one study showed a reduced rate of disease progression [165]. Thus, it is likely that treatment with CCBs before the development of motor disability would be more effective. Another point is to investigate if CCBs may decrease L-DOPA-induced dyskinesia. Preclinical data showed that in animals with nigrostriatal 6-hydroxydopamine (6-OHDA) lesions that were treated with levodopa, subsequent treatment with isradipine caused a dose-dependent reduction in L-DOPA-induced rotational behavior and abnormal involuntary movements [166]. However, clinical trials using levodopa-treated patients should be conducted to further investigate this phenomenon. Future investigations are also needed to test the potential roles of CCBs in preventing or reversing non-motor symptoms of ND.

The pharmacokinetics, bioavailability, and side-effect profiles of CCBs must also be taken into account when considering their utility as potential treatments for NDs.CCBs can induce cardiovascular side effects linked to VGCC [*i.e.*, $Ca_v1.2$] blockade, such as peripheral edema, when tested in preclinical and clinical PD studies [97, 149, 150]. There is also a lack of consensus on the required time for washout of some CCBs, such as isradipine [167]. A lack of validated biomarkers of disease progression also means that the potential therapeutic effects of CCBs have only been studied in the

Table 4. Clinical studies for PD treatment targeting VGCCs.

Disorder and Ca^{2+} Channel Blocker	Population and Sample Size	Study Design	Results	Refs.
PD, isradipine	Subjects with early idiopathic PD, n = 336	Phase 3, randomized, parallel assignment, double masking, the primary purpose of treatment	↓ disability from PD was observed.	[151]
PD, isradipine	Patients with idiopathic PD, n = 31	Phase 2, single group assignment, open-label, dose-escalation, safety and tolerability	No tolerability differences between isradipine treatment or not treatment with dopaminergic medications. Isradipinehad no effect on PD motor disability. The main adverse effects were: headache, dizziness, and peripheral edema.	[149]
PD, isradipine	Subjects with early idiopathic PD, n = 99	Phase 2, randomized, parallel assignment, double masking, the primary purpose of treatment	Isradipine at the dose of 10 mg daily was the maximal tolerable dosage. Adverse events were: peripheral edema and dizziness.	[150]
PD, isradipine	Patients with early-stage PD (duration <3 years) who were not taking dopaminergic medications, n=336	Phase 3 is a multicenter, randomized, parallel-group, double-blind, placebo-controlled trial.	Long-term treatment with immediate-release isradipine did not slow the clinical progression of early-stage PD.	[153]
PD, isradipine	Subjects with early idiopathic PD, n = 417	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial	Isradipine plasma exposure did not affect clinical assessment measures of PD severity. Yet, isradipine exposure decreased the risk of needing anti-parkinson treatment.	[154]

premotor phases of PD. Finally, one of the biggest challenges for potential translation to the clinic is the adequate dosage of CCBs required to effectively treat PD, given that preclinical model dosages might not be sufficient for human treatment. Isradipine studies identified that drug tolerability depended on the dose, with side effects such as dizziness and peripheral oedema at higher isradipine dosages [149, 150]. Additionally, early-stage patients in a phase 3 clinical trial in North America have been treated with isradipine to potentially slow the progression of PD, but the higher exposure of isradipine in the plasma did not impact clinical measures of PD severity and instead managed to decrease the dose and timing of levodopa PD treatments [154]. Therefore, more studies and potential solutions are required to address these concerns around better and safer usage of these clinically-approved drugs in the treatment of NDs [96].

In terms of novel molecular targets and approaches, *in vivo* analyses from preclinical studies have not yet explained if $Ca_v1.2$, $Ca_v1.3$, or both, are the primary drivers of Ca^{2+} toxicity in neurodegenerative processes. However, clinical trials identified that off-target effects on $Ca_v1.2$ are capable of mediating some side effects, including hypotension and peripheral edema, that are linked to long-term PD treatment with high doses of DHPs. This discovery has strengthened the impetus for discovering novel $Ca_v1.3$ inhibitors for potential PD treatment, even though it remains unknown whether targeting $Ca_v1.3$ is as effective as $Ca_v1.2$ for inducing neuroprotection [168].

In terms of potential CCBs use as a treatment for HD, one of the biggest barriers is the lack of fundamental preclinical studies that complement existing research using PD models. This gap in basic science research explains the lack of clinical studies. Despite this lack of data, analyses of the current literature highlight a few potential limitations in using CCBs for HD, such as a lack of protection against striatal lesion and cardiovascular side-effects such as tachycardia [14, 161], depending on the type of CCBs used. Some studies have not directly analyzed the effects of CCBs alone but rather administered a mixture that includes CCBs as one component [161, 169]. Additionally, some adverse effects have also been observed when CCBs were used in HD preclinical models, such as tremors, swelling in the injection area, diarrhea, eye infection, perpetual abscess, and a swollen anus [147]. Despite the severity of these symptoms, adequate dosage to reach clinical efficacy is still a challenge that needs to be addressed, given the difference in CCB half-lives in preclinical models compared to humans.

Given the totality of literature on the use of CCBs in these two NDs, it is clear that more systematic experiments, analyses, and solutions are urgently needed to address the

remaining challenges centered on these novel treatment approaches for both PD and HD.

CONCLUSION

It has been proposed that a neuronal Ca^{2+} imbalance underlies the central pathogenesis of NDs, including PD and HD. The various sources of Ca^{2+} dysregulation across different neuronal compartments, such as the activation of VGCCs, serve as distinct molecular players that can be specifically targeted to potentially treat these debilitating disorders [170]. New methods of brain analyses in combination with innovative molecular, biological, and electrophysiological methods have uncovered L-type and T-type Ca^{2+} channels as promising potential therapeutic targets for ND, with their associated CCBs preventing or reversing neuronal toxicity and behavioral deficits in PD models. However, many critical gaps in foundational research and unresolved clinical questions need to be addressed to bring these potential therapeutics closer to the clinic. Examples include comprehensive testing of CCBs in preclinical models of HD, sex-inclusive preclinical and clinical studies, better testing and optimization of candidate pharmacokinetics and bioavailability properties, and the selection of clinical endpoints that align with preclinical evidence. As the molecular mechanisms responsible for VGCCs dysfunction in NDs are unlocked, specific VGCC subtypes and their modulators may move from attractive molecular targets to new treatment approaches for these severe disorders.

AUTHORS' CONTRIBUTION

LBV coordinated the organization of the manuscript. LBV and BHMC prepared the draft. CRM designed and prepared figures and the graphical abstract; MEH critically revised the manuscript. LBV and MEH carried out the language and editing revision of the manuscript; all the authors approved the final version of the manuscript.

LIST OF ABBREVIATIONS

PD	=	Parkinson's disease
NDs	=	Neurodegenerative disorders
CNS	=	Central nervous system
TRP	=	Transient receptor potential
VGCCs	=	Voltage-gated Ca^{2+} channels
IP3R	=	Inositol-1, 4, 5-trisphosphate receptor
HVA	=	High-voltage activated
LVA	=	Low-voltage activated

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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