TRPC Channels and Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disorder, which involves degeneration of dopaminergic neurons that are present in the substantia nigra pars compacta (SNpc) region. Many factors have been identified that could lead to Parkinson's disease; however, almost all of them are directly or indirectly dependent on Ca^{2+} signaling. Importantly, though disturbances in Ca^{2+} homeostasis have been implicated in Parkinson's disease and other neuronal diseases, the identity of the calcium channel remains elusive. Members of the transient receptor potential canonical (TRPC) channel family have been identified as a new class of Ca^{2+} channels, and it could be anticipated that these channels could play important roles in neurodegenerative diseases, especially in PD. Thus, in this chapter we have entirely focused on TRPC channels and elucidated its role in PD.

Keywords

Calcium signaling • Dopaminergic neurons • ER stress • Oxidative stress • Parkinson's disease

8.1 Introduction

Calcium (Ca^{2+}) is an important element that functions as a prominent regulator for processes such as gene regulation, neuronal cell growth and differentiation, motility and axonal development, and even neuronal cell death [6, 9, 65]. Thus, it is not surprising that disruption of Ca^{2+} homeostasis in neuronal cells results in decreased neuronal functions leading to neurodegenerative diseases such as Parkinson's, Huntington's, and Alzheimer's [1, 10, 11, 46, 77, 78]. Due to these outcomes, Ca^{2+} homeostasis is strictly maintained in neuronal cells. Cells have evolved a multitude of mechanisms to regulate cellular Ca^{2+} levels and Ca^{2+} channels, and pumps play a key role in this regulation. Cumulative studies

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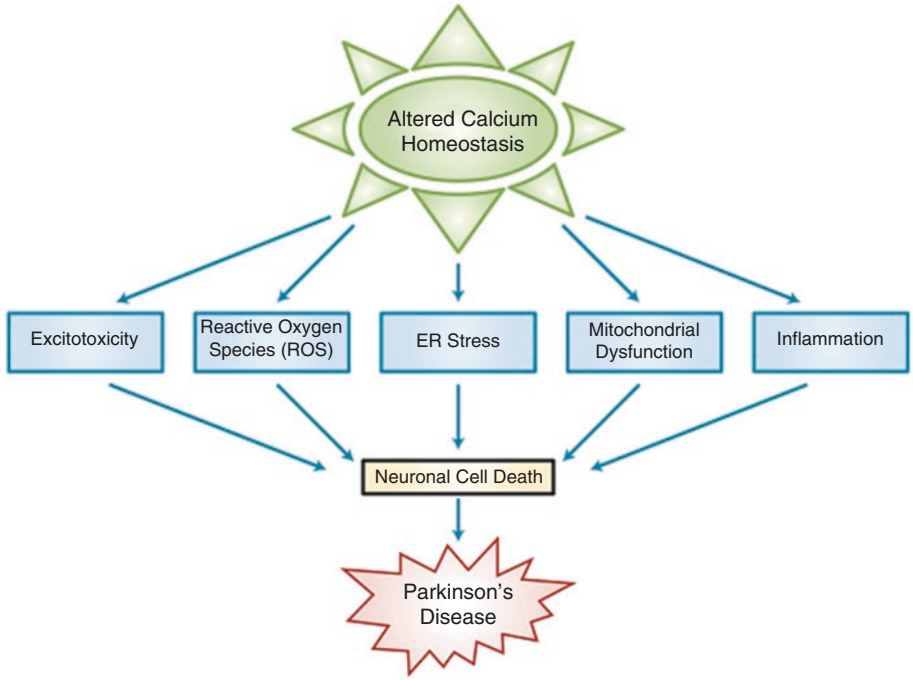

Fig. 8.1 Mechanisms that potentially leads to PD. Schematic model shows altered Ca^{2+} homeostasis in neuronal cells which causes Parkinson's disease via various mechanism(s) such as ER stress, ROS, mitochondrial dysfunction, excitotoxicity, and inflammation

suggest that both excessive elevation and attenuation of intracellular Ca^{2+} will lead to neuronal degeneration through different mechanisms as suggested in this chapter (Fig. 8.1). Increased intracellular calcium $[Ca^{2+}]_i$ concentrations mainly via the AMPA or NMDA channels lead to enhanced activation of Ca^{2+}-dependent processes that are normally inert or functional at low Ca^{2+} levels, thereby causing metabolic imbalances which result in neuronal death [3, 13, 20]. In contrast, decreased $[Ca^{2+}]_i$, upon store depletion, could induce ER stress or inhibit activation of proteins that are essential for cell survival [48]. Thus, different actions of Ca^{2+} in neuronal cells could be dependent not only on its cellular concentration but also on the ion channels that modulate Ca^{2+} entry [44, 48, 74]. Ca^{2+} channels, mainly the transient receptor potential canonical (TRPC) channels, have recently emerged as a key regulator of Ca^{2+} homeostasis in neuronal cell function [9, 57]. Further, TRPC channel function and expression are altered in various neuronal diseases such as Parkinson's disease (PD) [4, 57, 59]. PD is a neurodegenerative disorder, which is characterized with progressive degeneration of dopaminergic neurons and affects the aging population. Thus, in this chapter we will focus on the functional implication of TRPC channels in neuronal cell function and their roles in PD.

8.2 TRPC Functions in Neurons

Neuronal cells are heavily dependent on Ca^{2+} signaling for their function and survival [32]. Initiation of the action potential activates the voltage-gated calcium channels that modulate neurosecretion. Growing evidence suggests that this mode of Ca^{2+} entry is also essential in maintaining the cytosolic, ER, and mitochondrial Ca^{2+} levels. Importantly, as TRPC proteins have been identified as putative calcium channels that are activated by second messenger-mediated store depletion, they could play a critical role in neuronal survival, proliferation, and differentia-

tion. There is evidence that TRPCs are highly expressed in all regions of the central nervous system (CNS) [24], but in some cases the expression of individual TRPC channels is altered during development, especially as observed with TRPC1 and TRPC3, which are more expressed in embryonic CNS than in adult neurons [62]. Furthermore, neuronal growth in the presence of growth factors, such as basic fibroblast growth factor (bFGF), was dependent on Ca^{2+} entry through TRPC channels, especially TRPC1, 4, but not TRPC5, suggesting their important roles in neuronal growth and survival [17]. Importantly, inhibiting the function of TRPC channels or even silencing of TRPC1 alone decreases bFGF-induced intracellular Ca^{2+} increase and proliferation of neuronal stem cells [36, 40, 63]. TRPC3 has also been shown to be associated with BDNF receptors stimulation of neuronal growth [21, 66] and Epo-persuade cell differentiation and proliferation [39]. Consistent with these results, expression of TRPC1, TRPC2, and TRPC4 is observed to be higher, whereas expression of TRPC6 is decreased in neuronal stem cells. This differential expression of various TRPC channels suggests that different TRPC channels play contrasting roles in neuronal cell proliferation and differentiation [63]. In addition, using hippocampal neuronal cells (H19-7), Wu and their colleagues showed that Ca^{2+} influx through TRPC1 and TRPC3 was essential in regulating the shift between proliferation and differentiation [71].

Importantly, Ca^{2+} entry is not always beneficial. Activation by massive glutamate increases $[Ca^{2+}]_i$ mainly through TRPC1 channels, which leads to cell death as observed in hippocampal organotypic slice cultures. TRPC1 expression is enhanced after glutamate treatment, and both inhibition of TRPC channel by 2APB and knockdown of TRPC1 significantly reduce cell death, indicating that TRPC1 is involved in glutamate-induced cell death in the hippocampus. In contrast, studies have also shown that physiological activation of TRPC1 through other G-protein-coupled receptors could protect the neurons from several extracellular stimuli [15, 35, 37, 71]. Similarly, loss of Ca^{2+} entry has also been shown

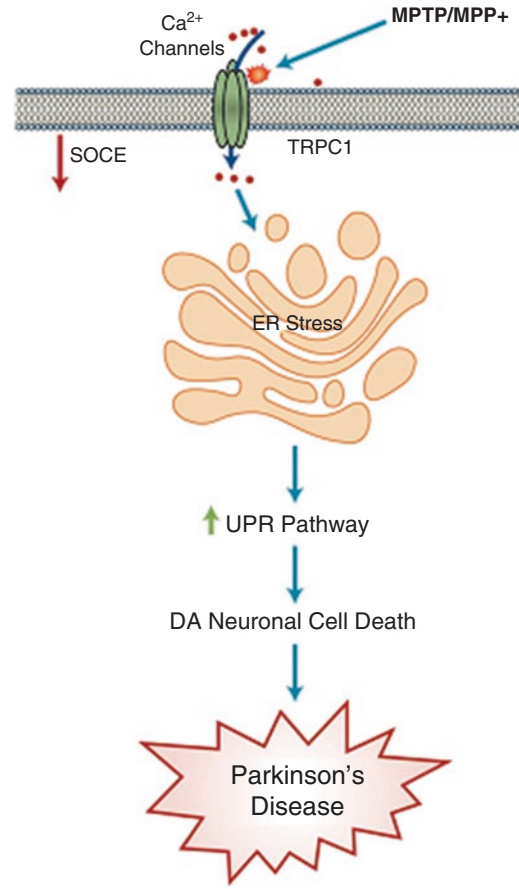

Fig. 8.2 Role of TRPC proteins in PD. Proposed model for MPP^+/MPTP-induced DA loss which could lead to the onset/progression of PD. MPP^+/MPTP attenuates the expression of TRPC1 and SOC-mediated Ca^{2+} influx, which leads to prolonged ER Ca^{2+} depletion and activation of the UPR pathways and subsequent ER stress-mediated neurodegeneration

to decrease endoplasmic reticulum (ER) Ca^{2+} levels, induce ER stress, and promote cell death [58]. Together, these studies suggest that TRPC channels have a dual role where normal activation of TRPC channels regulates neuronal development, while excessive Ca^{2+} influx, as observed upon glutamate treatment, can induce neuronal damage (Fig. 8.2). In addition, there appears to be a set point for Ca^{2+} entry, where physiologic concentration of calcium is beneficial, but either excessive or decreased calcium entry is harmful. Consistent with this notion, studies show that equally high Ca^{2+} loads are toxic through the

NMDA channels, compared to through the voltage-dependent Ca^{2+} channels [47, 61] suggesting that diverse Ca^{2+} channels have different roles in deciding the fate of the neuron. Another explanation could be that TRPC multimers that consist of different subunits could have completely different functions. Consistent with this notion, TRPC1, TRPC4, and TRPC5 are observed to be highly expressed in the pyramidal cell layer of the hippocampus, frontal cortex, and dentate gyrus, while TRPC6 is dispersedly expressed only at the molecular layer of the dentate gyrus [14, 61]. Furthermore, both TRPC1 and TRPC3 are observed to protect hippocampal cell lines, and silencing either of these channels inhibits cell development and proliferation [71]. In contrast, the expression of TRPC1 and TRPC6 is found in the substantia nigra region and colocalizes with tyrosine hydroxylase (TH), as well as with mGluR1, suggesting their role in modulating dopaminergic neuron function [9, 16]. Selective degeneration neuron is a common feature in several neurodegenerative diseases including Alzheimer's disease, epilepsy, Huntington's disease, stroke, and Parkinson's disease. Accumulating evidence suggests that glutamate, an excitatory neurotransmitter, is involved in the neurodegeneration [50]. In addition, TRPC channels could also function as a scaffold protein to regulate other proteins. This function is independent of their traditional role of regulating Ca^{2+} influx, and most TRPC have been shown to form large multimers. Thus, exploring the mechanisms underlying expression regulation and Ca^{2+} entry modulation of TRPC channels would be helpful to clarify their roles in neurodegeneration.

8.3 Role of TRPC Channels in Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, which is caused by progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc). Degeneration of DA neurons in the SNpc region is the reason for the observed motor symptoms with this disease [26]. Although the mechanism underlying the selective degeneration of these neurons is largely unknown, a host of pathogenic factors have been suggested to be responsible for the degeneration of DA neurons in the SNpc. These factors include mitochondrial dysfunction, ER and oxidative stress, protein aggregation, excitotoxicity, and inflammation, and each factor could individually or collectively play a role in the pathogenesis of PD (Fig. 8.1). In addition, lysosomal-mediated degradation has recently been suggested to inhibit the protein degradation pathway that could eventually lead to protein aggregation as observed in PD. The role of Ca^{2+} regulation in PD has been of interest as it overlaps with several of the established pathways that lead to neurodegeneration. Importantly, as discussed above, changes in $[Ca^{2+}]_i$ could mediate intracellular events that trigger or inhibit cell death process [7, 53]. Increases in $[Ca^{2+}]_i$ via the Cav1.3 channels has been shown to be necessary to stimulate the release of dopamine (DA) from dopaminergic neurons of the SNpc [12, 49]. Interestingly, Cav1.3 channels are highly expressed in samples obtained from PD patients, indicating the importance of Ca^{2+} in PD. Furthermore, disturbances in Ca^{2+} homeostasis have been implicated in PD [1, 10, 11, 46, 77, 78]. As many factors involved in neuronal functions are dependent on Ca^{2+} signaling, it could be anticipated that loss of these critical functions could contribute to PD [7, 53]. In addition, $[Ca^{2+}]$i is maintained by the removal of Ca^{2+} through plasma membrane Ca^{2+}-ATPase pump and the Na^{+}/Ca^{2+} exchanger or sequestration into intracellular organelle stores by the sarco-endoplasmic reticulum ATPase pump (SERCA), and most of these processes require ATP. However, ATP level is decreased in PD; thus, it can be speculated that the dysfunction of these Ca^{2+}pump could be involved in PD pathogenesis. Moreover, decreases in ATP levels could decrease ER calcium levels that could stimulate store-operated Ca^{2+} entry which is dependent on TRPC and Orai channels. Thus, it is critical to establish their physiological functions as discussed in this chapter.

8.3.1 TRPC1

TRPC1, the founding member of TRPCs, is ubiquitously expressed in high levels in all neuronal tissues [2, 62]. Alterations in intracellular Ca^{2+}, especially in the storage organelles such as the ER and mitochondria, have also been shown to affect neuronal survival and are associated with PD [28]. Although several Ca^{2+} channels have been identified that bring Ca^{2+} into cells, Ca^{2+} entry through the store-operated calcium channels (SOC) could be the most important. Moreover, as Ca^{2+} entry through SOC has been shown to be essential for maintaining intracellular ER Ca^{2+} stores, along with regulating many cellular functions, they could play an important role in neuronal survival [8, 58, 64]. TRPC1 has been shown to be essential for the formation of the functional SOC as it is activated by store depletion per se in DA neurons [8, 58, 59, 64, 68].

One of the possible mechanisms that lead to neurodegeneration in PD could be the initiation of ER stress or the unfolded protein response (UPR) [22, 23]. Ca^{2+} in the ER is known to be important for protein synthesis and folding; thus, loss of this vital function could induce abnormal protein aggregation as well as ER stress that could activate cell death cascades [52, 73]. Ca^{2+} influx through the SOCE mechanism is essential for the refilling of the ER Ca^{2+} stores, which could prevent abnormal protein aggregation and ER stress. Recently published work [8, 58, 59] suggests that in DA neurons TRPC1 functions as the endogenous plasma membrane SOC Ca^{2+} channel. Importantly, the expression of TRPC1, but not that of other TRPCs as well as ORAI1 or SOCE modulator stromal interaction molecule 1 (STIM1), was decreased in cell and animal models as well as in PD patients. Interestingly, Ca^{2+} entry into DA neurons was also inhibited by neurotoxin that induced PD-like symptoms and decreased ER Ca^{2+} levels. Consistent with these results, overexpression of TRPC1 reduced neurotoxicity induced by MPP^+ or salsolinol [8, 58]. In contrast, knockdown of TRPC1 or by addition of TRPC channel blockers inhibited DA neuron survival, indicating that the neuron protection role of TRPC1 might result from its Ca^{2+} influx ability. Similar results are also found in in vivo model and in tissue samples from human patients. Loss of TRPC1 shows a decrease in ER Ca^{2+} level and initiates the unfolded protein response. Moreover, overexpression of functional TRPC1 is protected against neurotoxin-induced loss of SOCE and the resultant ER stress response. In contrast, silencing of TRPC1 or its modulator STIM1 increased the UPR, which suggests that ER stress is induced in PD and TRPC1 attenuates ER stress [58] (Fig. 8.2). Furthermore, Ca^{2+} entry via TRPC1 also activates AKT/mTOR signaling and contributes to neuronal survival [58].

Mitochondrial dysfunction is another mechanism that has been demonstrated to have a role in the PD pathogenesis [41]. Importantly, calcium entry via SOC has been shown to modulate mitochondrial Ca^{2+} levels, and alterations in these Ca^{2+} levels could also lead to neurodegeneration. In addition, a strong correlation between SOCE and apoptosis has also been proposed, indicating that lack of Ca^{2+} entry would contribute to apoptosis [27]. Neurotoxins induce neuronal loss by decreasing TRPC1 levels, which could decrease mitochondrial Ca^{2+} levels necessary for ATP synthesis followed by disrupting mitochondrial membrane potential and initiation of apoptosis. Consistent with these results, activation of TRPC1 maintains mitochondrial membrane potential and inhibits Bax translocation to the mitochondria to prevent cytochrome c release and mitochondrial-mediated apoptosis. These results suggest that TRPC1 could prevent neurotoxin-induced cellular death by maintaining mitochondrial membrane potential, which prevents neurons from apoptosis [8, 10, 59]. Moreover, another study shows that downregulation of STIM1 expression, which is known to activate TRPC channels, inhibits cell apoptosis and reduces intracellular ROS production in PC12 cells by 6-hydroxydopamine [38].

8.3.2 TRPC2

Among the seven members of the TRPC, the TRPC2 channel, being a pseudogene in human, is the least investigated [33, 67]. Therefore, little is known about its physiological function. However, in rodents TRPC2 is highly expressed to the dendritic tip of the vomeronasal sensory neurons [30, 72] and plays an important role in pheromone sensing [18, 29], while its role in PD is not yet identified.

8.3.3 TRPC3

TRPC3 is highly expressed in the brain and oxidative stress has been shown to activate TRPC3 channels. The oxidant tertiary butyl hydroperoxide completely depolarized endothelial cells by activating TRPC3 [57], suggesting that TRPC3 determines endothelial redox sensitivity. In addition, overexpression of TRPC3 in HEK293T cells shows an increase in basal membrane conductance upon tertiary butyl hydroperoxide treatment, which is mainly due to the influx of Na^+ [51]. In another study in primary rat cortical neurons and astrocytes, TRPC3 levels and TRPC3-mediated Ca^{2+} flux are dose-dependently decreased upon treatment with oxidative stressors [56]. In addition, in murine striatal astrocytes, additions of neurotoxins which mimic PD decrease ATP level and OAG-induced Ca^{2+} transients, [60]. Importantly, a slight increase in TRPC3 expression is observed in PD condition as well as neurotoxin models of PD [58]. Disruption of Ca^{2+} signaling especially in astrocytes significantly impairs neuronal function and survival in neurological injury and in disease conditions such as PD. Together, these studies suggest that TRPC3 dysfunction is involved in Ca^{2+} dyshomeostasis and oxidative stress signaling observed in PD.

Parkinsonian movement disorders are also associated with abnormalities in SN pars reticulata (SNr) [34, 45, 54, 69]. TRPC3 channels are expressed in SNr GABA projection neurons, where TRPC3 channels are tonically active and mediate a voltage-independent inward current, leading to a substantial depolarization in these neurons [76]. Inhibition of TRPC3 channels induces hyperpolarization, decreases firing frequency, and increases firing irregularity, suggesting that TRPC3 channels play critical roles in maintaining the depolarized membrane potential, high firing frequency, and firing regularity in these basal ganglia output neurons crucial to Parkinsonian movement disorders [76]. In addition, dopamine released via the dopamine receptors from the dendrites activates TRPC3 channels in SNr GABA neurons and mediates an inward, Na^+-dependent current, leading to a substantial depolarization and ensuring appropriate firing intensity and pattern in SNr GABA projection neurons [75]. TRPC3 channels have also been shown to modulate motor coordination [5, 19]. In an ataxic mouse mutant (moonwalker, Mwk mice) that displays motor and coordination defects, a gain-of-function mutation (T635A) in TRPC3 channels is observed. Sustained activation of TRPC3 channels is observed to be associated with diminished dendritic arborization and progressive loss of Purkinje neurons. Similarly, another study also shows that loss of TRPC3 exhibits atrophy and progressive paralysis [55].

8.3.4 TRPC4

TRPC4α/β isoforms are the most abundantly expressed and functionally characterized in brain. TRPC4 and TRPC5 are the major TRPC subtypes in the adult rat brain because both are expressed highly in the pyramidal cell layer of the hippocampus, frontal cortex, and dentate gyrus [14, 61]. TRPC4 is specifically detected throughout the layers (2–6) of the prefrontal cortex or the motor cortex [25, 42]. Although the role of TRPC4 in PD is not yet defined, its role in axonal regeneration in adult rat dorsal root ganglia (DRG) has been reported [70]. The expression of TRPC4 is enhanced, whereas TRPC1, TRPC3, TRPC6, and TRPC7 expression remains unchanged after nerve injury persuaded by either sciatic nerve transection or intra-ganglionic microinjection of dibutyryl cAMP [57, 70]. In

addition, TRPC4 expression in various neuronal cells has been shown to be increased upon addition of NGF and dibutyryl cAMP that induced differentiation [57, 70]. Suppression of TRPC4 by specific small interfering RNA significantly reduced the length of neuritis in cultured DRG neurons [70]. Taken together, these results suggest that TRPC4 contributes to axonal regeneration especially after nerve injury. If these findings have generality, TRPC4 could be an important molecular target for potential regeneration therapies in patients suffering from neuronal injury. In contrast, by using whole-genome sequencing, a recent report showed that gain-of-function mutations in TRPC4 gene induce cell death in DA neurons through a defined, calcium-related downstream pathway [43]. High expression of TRPC4 is also found in the PM of soma and proximal dendrites of lateral septal neurons, colocalizing with mGlu receptors, which could also contribute to cell death. Studies also show that TRPC4 is expressed in cells in the ventral tegmental area, a region with extensive inputs from dopamine neurons which are important in regulating the animal behavior [24]. Importantly, a recent report has shown that self-administration of cocaine was significantly less in the TRPC4 KO group than WT controls [31]. Also, spontaneous DA neuronal activity in the ventral tegmental area revealed fewer cells with high-frequency firing rate in rats that lack TRPC4. Together these studies show the roles of TRPC4 channels in various functions of the CNS making them a potential target, especially for neurological diseases associated with excitotoxicity like PD or drug addiction that are also dependent on DA neurons.

8.4 Conclusion

Plenty of research in the past decades has explored the role of TRPC channels in neuronal survival, differentiation, and neurodegeneration as observed in Parkinson's disease. It could be suggested that Ca^{2+} influx via the TRPC channels has an important role in the neurodegenerative diseases such as Parkinson's, although further studies are needed. Therefore, targeting Ca^{2+} entry (both inhibition and activation) through TRPC channels could be critical for maintaining normal physiological function in dopaminergic neurons. Moreover, recent findings have also implicated STIM1 as a regulator for SOCE, making STIM1 a potential target, as they may be involved in neurological diseases such as Parkinson's.

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