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Role of TRPC channels in Parkinson's disease

Pramod Sukumaran*, Yuyang Sun*, Anne Schaar, Senthil Selvaraj, and Brij B Singh

Department of Biomedical Sciences, School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND 58201 USA

Abstract

Parkinson 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 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 calcium channels and it could be anticipated that these channels could play a major role in neurodegenerative diseases, especially in PD. Thus, in this chapter we have entirely focused our attention on TRPC channels and elucidating its role in PD.

Introduction

Calcium (Ca^{2+}) is an important element that functions as a prominent regulator for processes such as transcription and gene regulation, neuronal cell growth and differentiation, motility and axonal development and even neuronal cell death (Berridge et al., 2003; Bollimuntha et al., 2011; Sun et al., 2015). 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 (Albers and Beal, 2000; Bollimuntha et al., 2005; Cali et al., 2011; O'Bryant et al., 2009; Racette et al., 2006; Reboreda et al., 2011; Ruat and Traiffort, 2013; Zuccato and Cattaneo, 2007, 2009). 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. Cumulative studies suggest that both excessive elevation and attenuation of intracellular Ca^{2+} will lead to neuronal degeneration albeit through different mechanisms as suggested in this chapter (Figure 1). Increased intracellular calcium $[\text{Ca}^{2+}]_i$ 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 (Arundine and Tymianski, 2003; Choi, 1988; Herman et al., 1990). In contrast decreased $[\text{Ca}^{2+}]_i$, upon store depletion and the focus of this chapter, could induce ER stress or inhibit activation of proteins that are essential for cell survival (Paschen,

Address correspondence to: Brij B Singh. Ph: 701-777-0834, Fax: 701-777-2382, brij.singh@med.und.edu.

*Both authors contributed equally

2000). 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 (Naziroglu, 2011; Paschen, 2000; Yuruker et al., 2015). 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 (Bollimuntha et al., 2011; Selvaraj et al., 2010). Further, TRPC channel function and expression are altered in various neuronal diseases such as Parkinson's disease (PD) (Badger et al., 2014; Selvaraj et al., 2009; Selvaraj et al., 2010). PD is a neurodegenerative disorder, which includes progressive degeneration of dopaminergic neurons and affects the aging population. Thus, in this chapter we have focused on the functional implication of TRPC channels in neuronal cell function and their role in PD.

TRPC channels and Ca^{2+} signaling

The transient receptor potential (TRP) channel superfamily is one of the largest families of non-selective cation channels (Nilius and Owsianik, 2011) that are activated through diverse mechanism(s). The TRP superfamily is divided into various subfamilies which are TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPP (polycystin), TRPML (mucolipin), TRPA (ankyrin) and TRPN (NOMPC-like, which is found only in invertebrates) (Nilius, 2007)(Abramowitz and Birnbaumer, 2009; Pan et al., 2011; Sukumaran et al., 2012). TRP channels have been identified as candidates involved in regulating cellular functions ranging from pure sensory function to molecular regulation and survival, suggesting that these channels could serve as gatekeepers for transcellular transport of monovalent and divalent cations such as Na^+ and Ca^{2+} ions (Flockerzi, 2007; Löf et al., 2011; Nilius and Owsianik, 2011). In addition, most of the TRPs, especially TRPCs, have been shown to multimerize to form either homo- or heteromeric functional channels that have unique channel properties (Nilius and Owsianik, 2011).

TRPCs are Ca^{2+} -permeable nonselective cation channels in the subfamily of TRP channels. In addition, TRPCs have the highest degree of homology to the first discovered *Drosophila* photoreceptors' TRP channels (Kiselyov et al., 2010) and have been suggested as candidates for the store-operated Ca^{2+} entry channels. Seven members of the TRPC subfamily (TRPC1-7) have been identified and all of them are highly expressed in neuronal cells, with some of the TRPC channels expressing predominantly in neuronal cells (Bollimuntha et al., 2011; Sun et al., 2014). All TRPCs (with the exception of TRPC2 which is a pseudogene in humans) are functional and play an important role in modulating calcium homeostasis. Based on sequence analysis (protein homology) TRPC channels could be again sub divided into four sub groups as they share similar protein sequences: TRPC1, TRPC2, TRPC3/6/7, and TRPC4/5 (Venkatachalam and Montell, 2007). Although the crystal structure of any of the TRPC proteins have yet to be determined, domain predictions suggest that these channels have six transmembrane domains with both N- and C-termini facing intracellularly (Flockerzi, 2007; Ong et al., 2014; Venkatachalam and Montell, 2007). Importantly, both the N and C-terminus have also been shown to interact with many signaling proteins that could contribute to their regulation as well as could modulate neuronal function (Gaudet, 2008).

Functions attributed to TRPC in Neurons

Neuronal cells are heavily dependent on Ca^{2+} signaling for their function and for their survival (Komuro and Kumada, 2005). Initiation of the action potential activates the voltage gated calcium channels that modulate neurosecretion. In addition, channels such as NMDA, AMPA and others are also present on the post-synaptic membranes that induce Ca^{2+} entry to modulate neuronal functions. Finally, another mechanism that could have a role in neuronal function has recently been identified to initiate Ca^{2+} entry, but the mechanism involves the depletion of internal ER. Growing evidence suggest 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 differentiation. This is also evident as TRPCs are highly expressed in all regions of the central nervous system (CNS) (Huang et al., 2011), 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 (Strübing et al., 2003). 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 role in neuronal growth and survival (Fiorio Pla et al., 2005). Importantly, hindering the function of TRPC channels or silencing of TRPC1 alone decreased bFGF-induced intracellular Ca^{2+} increase and proliferation of neuronal stem cells (Li et al., 1999; Montecinos-Oliva et al., 2014; Su et al., 2014). TRPC3 has also been shown to be associated with BDNF receptors regulating the stimulation of neuronal growth (Hirschler-Laszkiewicz et al., 2009; Tong et al., 2008) and Epo-persuade cell differentiation and proliferation (Mattson et al., 1989). Consistent with these results, expression of TRPC1, TRPC2, and TRPC4 was observed to be higher, whereas expression of TRPC6 was decreased in neuronal stem cells. This differential expression of various TRPC channels could suggest that different TRPC channels could play contrasting role during neuronal cell proliferation and differentiation (Su et al., 2014). In addition, using hippocampal neuronal cells (H19-7), Wu and their colleagues showed that Ca^{2+} influx through TRPC1 and TRPC3 were essential in regulating the shift between proliferation and differentiation (Wu et al., 2004b).

Importantly, Ca^{2+} entry is not always beneficial. Activation by glutamate massively increases $[\text{Ca}^{2+}]_i$ mainly through TRPC1 channels that leads to cell death as observed in hippocampal organotypic slice cultures. TRPC1 expression was enhanced after glutamate treatment and both inhibition of TRPC channel by 2APB or knockdown of TRPC1 significantly reduced cell death, indicating that TRPC1 could activate glutamate-induced cell death in the hippocampus (REF). In contrast, studies have also shown that physiological activation of TRPC1 through other G-protein receptors could protect the neurons from several extracellular stimuli (Dhar et al., 2014; Li et al., 2012; Wu et al., 2004). Similarly, loss of Ca^{2+} entry has also shown to decrease endoplasmic reticulum (ER) Ca^{2+} levels inducing ER stress and promoting cell death (Selvaraj et al., 2012). Together these studies suggest that TRPC channels could have a dual role where normal activation of TRPC channels regulates neuronal development and excessive Ca^{2+} influx, as observed upon

glutamate treatment, can induce neuronal degeneration (Figure 2). In addition, there appears to be a set-point for Ca^{2+} entry, where physiologic concentration of calcium is beneficial and both excessive and decreased calcium entry is harmful. Consistent with this notion, it has been shown that equally high Ca^{2+} loads are toxic when entering through the NMDA channels, but not when entering through the voltage-dependent Ca^{2+} channels (Ovey and Naziroglu, 2015; Strübing et al., 2001) suggesting that the Ca^{2+} channel(s) are critical in deciding the fate of the neuron. The other possibility could be that as TRPC forms multimers where different subunits of known TRPC channels could associate and could have a completely different role. 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 stained only at the molecular layer of the dentate gyrus (Chung et al., 2006; Strübing et al., 2001). Furthermore, both TRPC1 and TRPC3 were observed to protect hippocampal cell lines and silencing of either of these channels inhibited cell development and proliferation (Wu et al., 2004). In contrast, both TRPC1 and TRPC6 are found in the substantia nigra region where it co-localizes with tyrosine hydroxylase (TH)-positive neurons, as well as with mGluR1, suggesting their role in modulating dopaminergic neurons (Bollimuntha et al., 2011; Fendt et al., 2008). Selective degeneration of hippocampal and other neurons is a common feature in several neurodegenerative conditions including Alzheimer's disease, epilepsy, Huntington, stroke and Parkinson. Accumulating evidence suggests that glutamate, an excitatory neurotransmitter is intimately involved in neurodegeneration (Phelan et al., 2013); however the identification of a particular TRPC channels is not yet established. In addition, TRPC channels could also function as a scaffold protein where it could regulate other proteins. This function would be independent of their ability to regulate Ca^{2+} influx, since most TRPC have been shown to form large protein-protein complexes. Thus, more research is needed to fully establish the role of TRPC channels in neuronal function and identify if alterations in their expression vs their ability to bring calcium entry modulates neurodegeneration.

Role of TRPC channels in Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, which is caused by the progressive loss of dopaminergic (DA) neurons present in the substantia nigra pars compacta (SNpc) region. Degeneration of DA neurons in the SNpc region is the reason for the observed loss of motor symptoms with this disease (Javitch et al., 1985). Although the mechanism as to why these neurons are specifically degenerated is not well known, a host of pathogenic factors have been suggested to be responsible for the degeneration of dopaminergic neurons in the SNpc. These factors include: mitochondrial dysfunction, ER and oxidative stress, protein aggregation, excitotoxicity, and inflammation where each factors could individually or collectively play a role in the pathogenesis of PD (Figure 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 calcium 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 $[\text{Ca}^{2+}]_i$ could either stimulate intracellular events that could trigger or inhibit cell

death process (Berridge et al., 2000; Putney, 2003). 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 (Chen and Rice, 2001; Patel et al., 2009). Interestingly, Cav1.3 channels were 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 Parkinson's disease (Albers and Beal, 2000; Bollimuntha et al., 2005; Cali et al., 2011; O'Bryant et al., 2009; Zuccato and Cattaneo, 2007; Zuccato and Cattaneo, 2009). As many factors involved in neuronal function are dependent on Ca^{2+} signaling, it could be anticipated that loss of these critical functions could contribute to PD (Berridge et al., 2000; Putney, 2003). In addition, $[Ca^{2+}]_i$ is maintained by the removal of Ca^{2+} through the activity of 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. However, most of these require ATP for functionality and as ATP levels are decreased in PD, it is possible that activity of these proteins could also lead to PD, though more research is needed to fully establish the role of calcium signaling machinery in PD. In addition, 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 function as discussed in this chapter.

TRPC1

TRPC1, the founding member of canonical TRPCs, is ubiquitously expressed including high expression in all neuronal tissues (Ambudkar et al., 2006; Strübing et al., 2003; Tozzi et al., 2003). 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 closely linked with PD (Kazuno et al., 2006). Although several Ca^{2+} channels have been identified that bring Ca^{2+} inside the cells, Ca^{2+} entry through the store-operated channels (SOC) could be the most important. Moreover, as Ca^{2+} entry through SOC channels 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 (Bollimuntha et al., 2006; Selvaraj et al., 2012; Sun et al., 2014) TRPC1 has been shown to be essential for the formation of the functional SOC channel as it is activated by store depletion *per se* in DA neurons (Bollimuntha et al., 2006; Selvaraj et al., 2012; Selvaraj et al., 2009; Sun et al., 2014; Wang and Poo, 2005).

One of the possible mechanisms that could lead to neurodegeneration in PD could be due to the initiation of ER stress or the unfolded protein response (UPR), but the mechanism is not well known (Hoozemans et al., 2007; Hoozemans et al., 2012). Moreover, abnormal protein aggregation has been identified as one of the causes of PD, but the mechanism is not well defined. 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 (Putney, 2005; Yoshida et al., 2006). 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 data (Bollimuntha et al., 2006; Selvaraj et al., 2012; Selvaraj et al., 2009; Arshad et al., 2014) suggests that in dopaminergic 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 in PD patients. Interestingly, Ca^{2+} entry into dopaminergic cells was also inhibited upon neurotoxin treatment that induced PD-like symptoms and ER Ca^{2+} levels were also decreased. Consistent with these results, overexpression of TRPC1 reduced neurotoxicity induced by MPP+ or salsolinol (Bollimuntha et al., 2006; Selvaraj et al., 2012). In contrast, knockdown of TRPC1 or by the addition of TRPC channel blockers, inhibited dopaminergic cell survival, indicating that some of the protection exhibited by TRPC1 might be contributed by its Ca^{2+} influx ability. Similar results were also found *in vivo* model and in tissue samples from human patients. Loss of TRPC1 also showed a decrease in ER Ca^{2+} levels and initiated the unfolded protein response. Moreover, overexpression of functional TRPC1 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 revealed that ER stress is activated in PD and TRPC1 could decrease ER stress (Selvaraj et al., 2012) (Figure 2). Furthermore, Ca^{2+} entry via TRPC1 also activated AKT/mTOR signaling and contributes to neuronal survival (Selvaraj et al., 2012).

Mitochondrial dysfunction is another mechanism that has been demonstrated to have a role in the PD pathogenesis (Moon and Paek, 2015). Importantly, Calcium entry via SOC channels have 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 suggested, indicating that lack of Ca^{2+} entry initiates apoptosis (Jayadev et al., 1999). 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 restored mitochondrial membrane potential and inhibited Bax translocation to the mitochondria thus preventing cytochrome c release and mitochondrial-mediated apoptosis. These results suggest that TRPC1 could prevent neurotoxin induced cellular death by preserving the loss of mitochondrial membrane potential, which in turn inhibits degenerative apoptotic signaling to provide neuroprotection (Bollimuntha et al., 2006; Bollimuntha et al., 2005; Selvaraj et al., 2009). In contrast, another study showed that downregulation of STIM1 expression, which is known to activate TRPC channels, inhibited apoptotic cell death and reduced intracellular ROS production in PC12 cells that were treated with 6-hydroxydopamine (Li et al., 2014). Although TRPC channels were not evaluated in this study, mitochondrial dysfunction, loss of mitochondrial membrane potential and the decrease of ATP generation was observed in STIM1 knockdown cells that were treated with 6-hydroxydopamine (Li et al., 2014). One possibility could be that PC12 cells are very different than dopaminergic cells and STIM1 has been shown to modulate other calcium channels that could account for these discrepancies.

TRPC2

Among the seven different members of the TRPC, the TRPC2 channel, being a pseudogene in human is the least investigated member of the TRPC channels (L6f et al., 2011; Tornquist et al., 2014). Therefore, relatively little is known in regard to its physiological significance.

In rodents, TRPC2 is highly localized to the dendritic tip of the vomeronasal sensory neurons (Kiselyov et al., 2010; Yildirim and Birnbaumer, 2007) and hence plays a significant role in pheromone sensing in rodents (Flanagan et al., 2011; Kimchi et al., 2007); however its role in PD is not yet identified.

TRPC3

TRPC3 is highly expressed in brain and with regard to PD, increased Ca^{2+} homeostasis has been linked to altered oxidative stress levels that could lead to neuronal loss. Oxidative stress has also been shown to regulate TRPC3 channels, where TRPC3 channels are directly activated in response to oxidative stress. The oxidant tertiary butyl hydroperoxide completely depolarized endothelial cells by the activation TRPC3 (Selvaraj et al., 2010), suggesting that TRPC3 determines endothelial redox sensitivity. In addition, over expression of TRPC3 in HEK293T cells showed an increase in basal membrane conductance upon tertiary butyl hydroperoxide treatment, which was mainly due to the influx of Na^+ (Poteser et al., 2006). In another study in primary rat cortical neurons and astrocytes, TRPC3 levels and TRPC3-mediated Ca^{2+} fluxes was dose-dependently decreased upon treatment with oxidative stressors (Roedding et al., 2013). In addition, in murine striatal astrocytes addition of neurotoxins, that mimic PD, decreased ATP as well as OAG-induced Ca^{2+} transients and wave formations, suggesting that TRPC3 could be essential for these functions (Streifel et al., 2014). Importantly, a slight increase in TRPC3 expression was observed in PD condition as well as neurotoxin models of PD (Selvaraj et al., 2012). Disruption of Ca^{2+} signaling especially in astrocyte could significantly impact neuronal function and survival especially during neurological injury and in disease conditions such as PD. Together these studies indeed suggest that TRPC3 dysfunction is involved in Ca^{2+} and oxidative stress signaling observed in PD.

Parkinsonian movement disorders are also associated with abnormalities in SN pars reticulata (SNr) (Lee et al., 2007; Nevet et al., 2004; Rivlin-Etzion et al., 2006; Wichmann and Soares, 2006). TRPC3 channels are expressed in SNr GABA projection neurons, where TRPC3 are tonically active and mediate a voltage-independent inward current, leading to a substantial depolarization in these neurons (Zhou et al., 2008). Inhibition of TRPC3 channels induce hyperpolarization, decrease firing frequency, and increase firing irregularity demonstrating 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 (Zhou et al., 2008). In addition, dopamine release from the dendrites excited SNr GABA neurons via the dopamine receptors that could activate TRPC3 channels, to mediate an inward, Na^+ -dependent current, leading to a substantial depolarization and ensuring appropriate firing intensity and pattern in SNr GABA projection neurons (Zhou et al., 2010). TRPC3 channels have also been shown to modulate motor coordination (Becker et al., 2009; Hartmann et al., 2008). In an ataxic mouse mutant (moonwalker, Mwk mice) that displays motor and coordination defects, a gain-of-function mutation (T635A) in TRPC3 channels was observed. As a result sustained activation of TRPC3 channels was observed that diminished dendritic arborization and lead to the progressive loss of Purkinje neurons. Similarly, another study also showed the loss of TRPC3 exhibits atrophy and progressive paralysis suggesting an essential role of TRPC3

channels in neuronal signaling, differentiation and development (Rodriguez-Santiago et al., 2007; Hartmann et al., 2008). Although none of these studies looked at dopaminergic neurons, it could be still suggestive that abnormal TRPC3 function may also contribute to Parkinson's disease which is classified as loss of motor function.

TRPC4

TRPC4 α/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 (Chung et al., 2006; Strübing et al., 2001). TRPC4 is specifically detected throughout the layers (2–6) of the prefrontal cortex or the motor cortex (Huang et al., 2007; Morelli et al., 2013). 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 (Wu et al., 2008). The expression of TRPC4 was enhanced whereas TRPC1, TRPC3, TRPC6 and TRPC7 expression remained unchanged after nerve injury persuaded by either sciatic nerve transection or intra-ganglionic microinjection of dibutyryl cAMP (Selvaraj et al., 2010; Wu et al., 2008). In addition, TRPC4 expression in various neuronal cells has been shown to be increased upon addition of NGF and dibutyryl cAMP that induced differentiation (Selvaraj et al., 2010; Wu et al., 2008). Suppression of TRPC4 by specific small interfering RNA significantly reduced the length of neuritis in cultured DRG neurons (Wu et al., 2008). 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 induces cell death in dopamine neurons through a defined, calcium-related downstream pathway (Nagarajan, et al., 2014). 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 shows that TRPC4 is expressed in cells from the ventral tegmental area, a region with extensive inputs from dopamine neurons which are important in regulating the animal behavior (Huang et al., 2011). Importantly, a recent report has shown that self-administration of cocaine was significantly less in the TRPC4 KO group than WT controls (Klipec et al., 2016). Also, spontaneous dopamine 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 significance of TRPC4 channels in various functions of the CNS making them an important molecular target, especially for neurological diseases associated with excitotoxicity like PD or drug addiction that are also dependent on dopaminergic neurons.

TRPC5

Studies by March et al. showed that TRPC5 along with TRPC1 is highly expressed in substantia nigra and TRPC5 is localized in the neuronal cells, thereby suggesting a significant role of TRPC5 channels in neurons (De March et al., 2006). In neurite outgrowth, TRPC5 showed a vital role since the dominant negative pore mutant of TRPC5 inhibits and overexpression of TRPC5 enhances the neurite outgrowth of the transfected neurons (Kumar

et al., 2012). Studies showed that a balance of TRPC5, TRPC1 and TRPC6 expression regulates the neurite extension rate in neuronal cells (Kumar et al., 2012). In another study, they showed that calpain, a calcium activated protease, cleaves and activates TRPC5 channels to participate in semaphoring 3A-induced neuronal growth cone collapse (Kaczmarek et al., 2012). Recent studies by Jemal et al. 2014 detailed how increased expression of TRPC5 at the PM enhances the proportion of neuronal cells that respond to hyposmotic stimulation. They suggested that hypoosmotic cell-swelling activates Gq-coupled receptors, which in turn stimulates the activation of TRPC5 (Jemal et al., 2014). TRPC5 also play a vital role as a switch between proliferation and neuronal differentiation in neural progenitor cells (NPCs) (Shin et al., 2010). TRPC5 channels have been shown to have an inhibitory role on neurite extension (Bezzarides et al., 2004; Tian et al., 2010). Puram et al showed that TRPC5 couples Ca^{2+} signaling to an ubiquitin ligase pathway at the centrosome and thereby orchestrates dendrite patterning and connectivity in the brain (Puram et al., 2011) Thereby, TRPC5 could play a vital role in normal motor coordination and gait in mice. TRPC5 has been found to form a specific complex with CaMKII β , but not CaMKII α . This complex then initiates activation of CaMKII β which leads to the phosphorylation and inhibition of the ubiquitin ligase Cdc20-APC at the centrosome (Puram et al., 2011). Recent studies by Hong et al showed that TRPC5 S-glutathionylation by oxidative stress and attenuated TRPC1 expression contributed to neuronal damage in the striatum. Loss of striatum is very common feature in many neurodegenerative diseases, like Huntington's disease (Hong et al., 2015). To support their finding they also showed that a TRPC5 blocker enriched rearing behavior in Huntington's disease transgenic mice. These finding suggest that TRPC5 channels may have important developmental functions in addition to their sensory receptive roles in mature neurons and could play a significant role in many neuronal disease including PD.

TRPC6

TRPC6 is shown to play a vital role in ischemic brain damage. Studies by Du et al showed that in rats TRPC6 inhibition suppressed ischemic brain damage. The expression of TRPC6 protein in ischemia was specifically downregulated by the NMDA receptor-dependent calpain proteolysis which blocked its degradation and protected the neurons and brains against cerebral ischemia (Du et al., 2010). A following study by the same group showed that TRPC6 attenuates the NMDA receptor and activities and protects the neuronal cells from ischemic excitotoxicity. They also showed that the infarct volume in TRPC6 transgenic (Tg) mice was reduced as compared to wild-type (WT) littermates (Li et al., 2012a). An interesting connection between TRPC6 and depression has been suggested since TRPC6 is activated by hyperforin, an antidepressant extract (Tu et al., 2010). TRPC6 has also been suggested to have a significant role in AD. Transient expression of presenilin (PS) mutant, a gene linked to early-onset of Alzheimer's disease, with TRPC6 in HEK-239 cells resulted in a strong inhibition of agonist induced Ca^{2+} entry (Lessard et al., 2005). Recent studies by Kim and Kang showed a significant role of TRPC6 in seizure exposure and seizure-related neuronal damage in the rat dentate gyrus. In their study, they showed that TRPC6 expression is attenuated in chronic epileptic rats and a TRPC6 knockdown increased the seizure susceptibility in dentate gyrus of wildtype rats (Kim and Kang, 2015). Another recent study

by Chauvet et al, showed that the Na⁺/K⁺-ATPase and the amyloid-beta peptide a β 1-40 regulates the activity of TRPC6 channels (Chauvet et al., 2015). The study suggested that the abundance, distribution and activity of TRPC6 can be regulated by amyloid peptide, which is known to increase in PD patients, hence this study clearly indicate a significant role of TRPC6 channels in PD.

TRPC7

Recently studies showed a critical role of TRPC7 in initiation of seizures induced by pilocarpine both in vitro and in vivo (Phelan et al., 2014) owing to the importance of TRPC7 in neuronal diseases like PD, but broad understanding of the role TRPC7 in neuronal physiology remains elusive. In the proliferating rat H19-7 hippocampal neurons, the expression of TRPC7 was enhanced and following differentiation attenuated the expression (Goel et al., 2002). Significant studies have been done on heteromeric dimers of TRPC7 with TRPC3 in neuronal cells. Studies show that TRPC3/C7 are molecular targets for metabotropic glutamate receptor signaling in rat striatal cholinergic interneurons (Berg et al., 2007)

Conclusion

Significant research in the past decades has explored the role of TRPC channels with regard to neuronal survival, differentiation, and neurodegeneration as observed in Parkinson disease. Although several questions still remain unanswered, it could be suggested that Ca²⁺ influx *via* the TRPC channels have a significant role in the onset/progression/suppression of neurodegenerative diseases such as Parkinson's. Thus, targeting Ca²⁺ entry (both inhibition as well as activation) through these TRPC channels could be critical for maintaining normal physiological function in dopaminergic neurons. Recent findings have also implicated STIM1 as a regulator for SOCE making research in STIM1 function/expression in neuronal cells as an interesting topic as they may be involved in neurological diseases such as Parkinson's. Although the current data with regard to the function of TRPC in neuronal cells is overwhelming, significant information including that from human and animal tissues is still missing.

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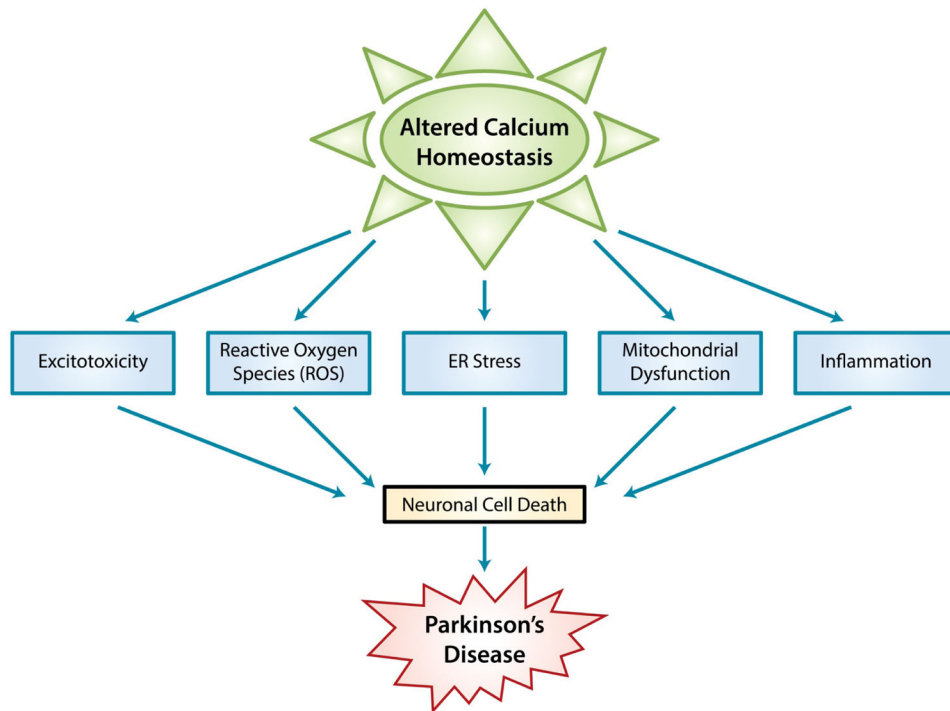


Figure 1. Mechanisms that leads to PD

Schematic model showing altered Ca^{2+} homeostasis in the neuronal cells which causes Parkinson's disease via various mechanism(s) such as ER stress, ROS, mitochondrial dysfunction, excitotoxicity, and inflammation as shown in the model..

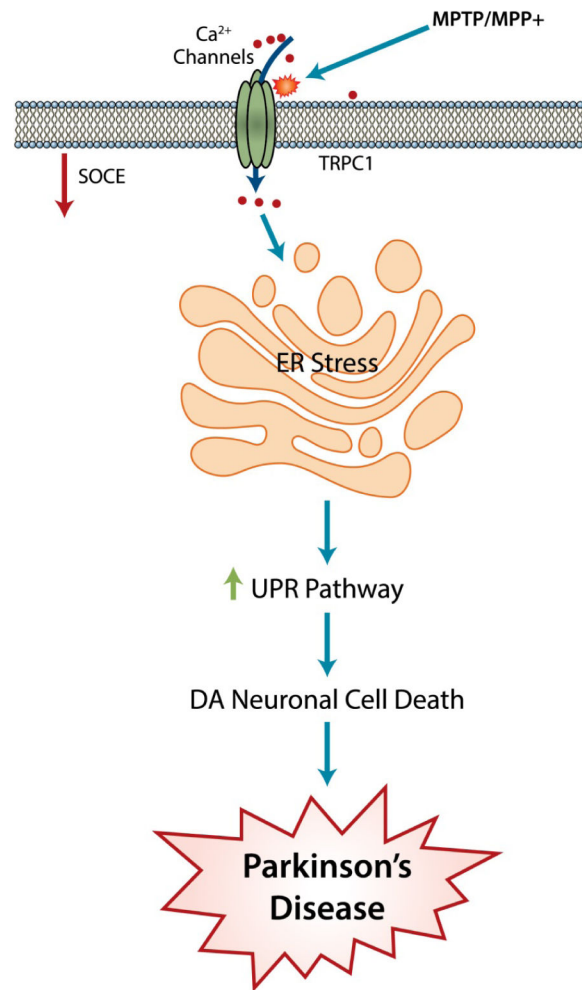


Figure 2. Role of TRPC proteins in PD
 proposed model for MPP⁺/MPTP-induced DA loss which could lead to the onset/ progression of PD. MPP⁺/MPTP attenuates the expression of TRPC1 and SOC-mediated Ca²⁺ influx that leads to prolonged ER Ca²⁺ depletion and activation of the UPR pathways and subsequent ER stress-mediated neurodegeneration which leads to many neuronal disease like PD.