# TRPM7 and its role in neurodegenerative diseases

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Calcium ($Ca^{2+}$) and magnesium ($Mg^{2+}$) ions have been shown to play an important role in regulating various neuronal functions. In the present review we focus on the emerging role of transient potential melastatin-7 (TRPM7) channel in not only regulating $Ca^{2+}$ and $Mg^{2+}$ homeostasis necessary for biological functions, but also how alterations in TRPM7 function/expression could induce neurodegeneration. Although eight TRPM channels have been identified, the channel properties, mode of activation, and physiological responses of various TRPM channels are quite distinct. Among the known 8 TRPM channels only TRPM6 and TRPM7 channels are highly permeable to both $Ca^{2+}$ and $Mg^{2+}$; however here we will only focus on TRPM7 as unlike TRPM6, TRPM7 channels are abundantly expressed in neuronal cells. Importantly, the discrepancy in TRPM7 channel function and expression leads to various neuronal diseases such as Alzheimer disease (AD) and Parkinson disease (PD). Further, it is emerging as a key factor in anoxic neuronal death and in other neurodegenerative disorders. Thus, by understanding the precise involvement of the TRPM7 channels in different neurodegenerative diseases and by understanding the factors that regulate TRPM7 channels, we could uncover new strategies in the future that could evolve as new drug therapeutic targets for effective treatment of these neurodegenerative diseases.

## Introduction

Calcium ($Ca^{2+}$) acts as a ubiquitous second messenger that has achieved a well-establish role in controlling cellular functions.[1] All cells express various $Ca^{2+}$ channels, pumps, and $Ca^{2+}$ binding proteins that tightly control the intracellular free $Ca^{2+}$ concentration $[Ca^{2+}]_i$. The $[Ca^{2+}]_i$ is maintained at low nanomolar levels, because a small increase in $[Ca^{2+}]_i$ will result in the activation of various cellular processes, that ranging from short-term responses such as muscle contraction, secretion, and neuronal transmission to long term modulation of cell growth and gene transcription.[2-6]

Magnesium ($Mg^{2+}$) is the second most abundant intracellular cation and is also a versatile ion, which is involved in practically every major metabolic and biochemical process within the cell.[7] $Mg^{2+}$ is required for the production of cellular energy, cell growth and development.[8] $Mg^{2+}$ is also an essential cofactor for ATP polyphosphates such as DNA and RNA and metabolic enzymes essential in nerve impulse transmission, and muscle contraction.[9] The compartmentalization of $Mg^{2+}$ within the cell is a key element necessary to coordinate the regulation of pathways in which transphosphorylation reactions serves as the rate-limiting step.[10] Additionally, $Mg^{2+}$ also has a role in the regulation of protein synthesis, which is very sensitive to small changes of intracellular $Mg^{2+}$ within physiological ranges and the onset of DNA synthesis is dependent on the rate of protein synthesis.[11,12] Recent studies reported that $Mg^{2+}$ also plays a part in intracellular signaling (as does $Ca^{2+}$), regulation of neuronal development and modulation of electric synapses.[8,13,14]

In neurons, $Ca^{2+}$ and $Mg^{2+}$ together plays a vital role in a variety of physiological processes, from regulating gene transcription to neuronal growth, survival and even differentiation.[2,15] Interestingly, $Mg^{2+}$ was initially identified as a powerful $Ca^{2+}$ antagonist, despite both having similar charge and chemical properties. Moreover, $Mg^{2+}$ also protects the neuronal cells from $Ca^{2+}$ overload.[16] Previous studies have also indicated a tight balance between $Ca^{2+}$ and $Mg^{2+}$ ions that is needed for maintaining proper physiological functions such as control of muscle movement (motor neurons).[17] Thus, influx of both extracellular $Ca^{2+}$ and $Mg^{2+}$ must be tightly maintained for proper intracellular ion homeostasis as alterations in $Ca^{2+}$ and $Mg^{2+}$ homeostasis will alter cellular functions and possibly lead to cell death.

Disturbances in $Ca^{2+}$ homeostasis have been involved in neurodegenerative diseases such as Parkinson, Alzheimer, and Huntington's,[18-20] which is mainly due to the high dependence of $Ca^{2+}$ signaling in modulating neuronal functions.[21] In contrast, brain $Mg^{2+}$ levels have been shown to decline in a number of acute and chronic pathologies including neurodegeneration, traumatic brain injury, and depression.[15] Prominently, cation mobilization in neuronal cells is tightly regulated by different ion channels and pumps in the plasma membrane and the organelle membrane. In this regard, one potentially important ion influx pathway may be the activation of TRPM channels. TRPM7 channels are selective to $Ca^{2+}$ and $Mg^{2+}$ and activation of TRPM7 channels are tightly regulated by intracellular $Mg^{2+}$ levels, which emerges as a key factor in various neurodegenerative disorders. The current review therefore highlights recent progress in research on neurodegenerative diseases focusing on advances of TRPM7 channel to various pathologies.

## TRPM Subfamily

TRP channels constitute a family of ion channels that are divided into TRPC (Canonical/Classical), TRPV (Vanilloid), and TRPM (Melastatin) sub-families. Importantly, all members of TRP family are moderately conserved and share significant homology among them.[22,23] The TRPM subfamily consist of 8 members, which are sub-divided into 3 subgroups on the basis of sequence homology; TRPM1/TRPM3, TRPM4/TRPM5 and TRPM6/7, with TRPM2/TRPM8 being distinct proteins from the other groups (**Table 1**). TRPM channels lack the multiple N-terminal ankyrin repeats present in TRPC and TRPV channels; instead they contain a conserved N-terminal intracellular domain of unknown function and a conserved coiled-coil region in the C-terminus that is thought to facilitate subunit assembly. The modes of activation and regulation of TRPM channels are diverse which separates them from other members. In general TRPM channels are cation channels that contribute to changes in $[Ca^{2+}]_i$ concentrations by acting as $Ca^{2+}$ entry channels in the plasma membrane directly or by changing membrane potential, modulating the driving force for other $Ca^{2+}$ entry channels with the exceptions of TRPM4 and TRPM5, which are only permeable to monovalent cations.[24,25] TRPM6 channels are highly selective to $Mg^{2+}$.[26] Among all the TRPM channels only TRPM7 is the cation selective ion channel that is highly permeable to both $Ca^{2+}$ and $Mg^{2+}$ signifying its importance and thus could have unique function in neuronal cells. In addition, TRPM7 can also conduct toxic metals,[27] that could also lead to neurodegeneration.

The physiological functions and biophysical properties of TRPM1 are not as yet characterized. This is mainly due to the fact that TRPM1 is primarily localized to intracellular vesicles rather than at the plasma membrane.[28] However, recent effort revealed that TRPM1 is critical for a non-selective cation conductance in melanocytes and retinal bipolar cells.[28,29] Similarly, TRPM2 is also a divalent cation-permeable channel, which transports $Ca^{2+}$ and is activated by adenosine diphosphoribose (ADPR), $H_2O_2$ and heat.[30] TRPM2 also contains a functional ADPR hydrolase enzyme on its C-terminus and has been suggested to play an indirect role in anoxic-mediated neurodegeneration.[31] However, physiological function for TRPM2 in neuronal cells has yet to be identified.

TRPM3 has multiple splice variants that differ in their ion selectivity. TRPM3 channels are, much like TRPM6 and TRPM7, but are known to be constitutively active, outwardly rectifying, and are inhibited by intracellular $Mg^{2+}$ ions; however their *in vivo* role in neuronal cells remains unknown. TRPM4 and TRPM5 are heat-sensitive, $Ca^{2+}$ activated channels that are monovalent selective. TRPM4 is thought to play an important role in regulating smooth muscle contraction,[32] suggesting that it may play a role in regulating cerebral blood flow. In contrast, TRPM5 is limited to cells of the gastrointestinal tract, and taste buds [24] and thus may not be relevant to neuronal function.

TRPM6 and TRPM7 are homologous in their protein structure, each containing an atypical α kinase domain on their C-terminus. TRPM6 expression is limited to renal and intestinal epithelium where it is thought to play a role in physiological $Mg^{2+}$ homeostasis.[26] TRPM8 is primarily known as a thermosensor, activated by cool temperatures (comprised between 15 and 28°C), and is also gated by exogenous compounds that elicit a cooling sensation.[33] TRPM7 channels are also activated by oxidative stress, and/or ADPR and are highly expressed in neuronal tissues.[27] Notably, TRPM7 is crucial to both $Ca^{2+}$ and $Mg^{2+}$ homeostasis and alterations in TRPm7 function has been reported to play pathological roles in the brain especially in neurodegeneration, which will be discussed in depth in this review.

## TRPM7 Channels Properties and Mode of Activation

TRPM7, formerly known as LTRPC7, TRP-PLIK and ChaK1, is a ubiquitously expressed dual-function plasma membrane protein consisting of a TRP ion channel fused to a protein kinase domain.[34-36] TRPM7 protein forms a nonselective cation channels with a strong outwardly rectifying current–voltage signature ($P_{Ca}/P_{Na} \sim 0.34$).[36] Previous studies indicated that phosphotransferase activity is not required for TRPM7 channel activity.[37,38] However, recently, annexin 1, a $Ca^{2+}$-dependent membrane binding protein, was identified as a substrate for TRPM7 kinase.[39] Furthermore, phosphorylation of annexin 1 by TRPM7 kinase at Ser5 within the N-terminal α-helix is stimulated by $Ca^{2+}$ influx through the channel domain and implicate an interaction between channel and kinase functions.[40,41] Thus, it can be suggested that cations entering through TRPM7 channel may play a crucial role in regulation of the kinase function and the subsequent activation of downstream signaling components. TRPM7 is an $Mg^{2+}$ and $Ca^{2+}$ permeable ion channel that maintains the cellular $Mg^{2+}$ and $Ca^{2+}$ homeostasis.[42] Intracellular free $Mg^{2+}$, MgATP, pH, phosphatidylinositol 4,5-bisphosphate ($PIP_2$), cyclic adenosine 3,5-monophosphate (cAMP) and polyvalent cations have all been reported to regulate TRPM7 channel activity.[44-46] Phosphorylation of TRPM6 has recently been shown to regulate TRPM7 channel activity.[43] There is a general consensus that TRPM7 channel is inhibited by free intracellular $Mg^{2+}$,[47] but there is some discrepancy whether TRPM7 is activated or inhibited by phospholipase C (PLC).[44,48] In addition, it has also been proposed that TRPM7 channels are either activated or inhibited by cellular ATP. Early characterization of

**Table 1.** *Ion selectivity of TRPM subfamily*: The TRPM subfamily consists of 8 members. All TRPM channels are cation channels and ion selectivity is diverse as shown in the table.

| TRPM | Ion Selectivity | References |
|---|---|---|
| TRPM1 | $Ca^{2+}$ permeable | 28,110 |
| TRPM3 | $Ca^{2+}$ permeable | 111 |
| TRPM6 | $Zn^{2+} > Ba^{2+} > Mg^{2+} > Ca^{2+} > Mn^{2+}$ | 26,112 |
| TRPM7 | $Zn^{2+} > Ba^{2+} > Mg^{2+} > Mn^{2+} > Ca^{2+}$ | 112,113 |
| TRPM2 | $Na^+ > Ca^{2+} > Mg^{2+} > Cs^+$ | 114-116 |
| TRPM8 | $Ca^{2+} > K^+ = Na^+$ | 117,118 |
| TRPM4 | $Na^+ K^+$ Permeable, $Ca^{2+}$ impermeable | 119,120 |
| TRPM5 | $Na^+ K^+$ Permeable, $Ca^{2+}$ impermeable | 24,121 |

TRPM7 showed currents that were activated by low MgATP levels and were thus termed as magnesium-nucleotide-regulated metal ion current (MagNuM).[36,46] One potential reason for this difference could be that cytoplasmic MgATP effectively inhibits only when a weak $Mg^{2+}$ chelator is present in the pipette solution. Under such conditions, MgATP acts as a source of $Mg^{2+}$ rather than a source of ATP.[46] TRPM7 is also sensitive to changes in pH and significantly potentiated by acidic pH,[49] which implies that TRPM7 may play a role under acidic pathological conditions. TRPM7 has been proposed to maintain normal physiological functions, by regulating $Ca^{2+}$ and $Mg^{2+}$ homeostasis. This is essential for regulating cell growth and proliferation, synaptic vesicle release, detoxification, cell adhesion and cell spreading, and myosin stability. Similarly, TRPM7 has also been shown to play a role in cancer proliferation, stroke, hydrogen peroxide dependent neurodegeneration, and even heavy metal toxicity.[27,50,51] However, it is not clear if much of these functions are due to abnormal $Ca^{2+}$ and $Mg^{2+}$ homeostasis or due to the fact that TRPM7 also has an α kinase with multiple targets and could very well regulate some of these conditions by changing the phosphorylation status of proteins essential for thewe functions. Importantly, initial studies showed that TRPM7 can form fully functional channels in the absence of its C-terminal domain that lacks the kinase domain;[37,38] however others have shown that the kinase activity was required for TRPM7 channel function.[40,41]

TRPM7 is a unique protein that contains an atypical kinase domain at its C-terminus, that is similar to eukaryotic elongation factor-2 kinase (eEF2K).[35] TRPM7 is cleaved by caspases at D1510, disassociating the C-terminal kinase domain from the pore without disrupting the phosphotransferase activity of the released kinase. The cleaved kinase fragments (M7CKs) have been shown to translocate to the nucleus and bind to the multiple components of the chromatin-remodeling complexes.[52] Karpivinsky et al showed that in the nucleus, the kinase domain of TRPM7 phosphorylates specific serines/threonines of histones and M7CK-dependent phosphorylation of H3Ser10 at promoters of TRPM7-dependent genes and correlates with their activity. The authors also showed that TRPM7-mediated modulation of intracellular zinc concentration couples ion-channel signaling to epigenetic chromatin covalent modifications that affect gene expression patterns.[53] Where else the studies by Kaitsuka et al in the same year showed that TRPM7 kinase activity does not impair its channel activity and kinase activity is not essential for regulation of mammalian $Mg^{2+}$ homeostasis.[54] Some of these discrepancies could be explained by the differential expression of various other TRPM channels in various cells as TRPM channels have been shown to form heteromers, which could exhibit different channel properties leading to alteration in the biological function.

## Biological Functions of TRPM7 in Neuronal Cells

TRPM7 is the most abundantly expressed TRPM channel in the majority of mouse organs and widely distributed in the central nervous system including hippocampus, cerebrum,

cerebellum and truncus encephali.[55] TRPM7 also plays a key role in embryonic development. The global deletion of TRPM7 in mice is lethal and death occurs before embryonic day 7.5.[59] The proposed mechanism suggests that TRPM7 deletion leads to growth defects and embryonic lethality which involves a role for both channel activity and $Mg^{2+}$. Deletion of TRPM7 also leads to proliferative arrest and cellular quiescence,[36] which could be ameliorated either by supplementation of high concentrations of $Mg^{2+}$ or by co-expression of a TRPM7 mutant that are $Mg^{2+}$-permeant but lack the phosphotransferase activity. Consistent with these results overexpression of other magnesium transporters particularly, the plasma-membrane $Mg^{2+}$ transporters MagT1 and SLC41A2 can restore $Mg^{2+}$ uptake and stimulate growth in TRPM7-deficient cells,[60] suggesting that these functions are truly dependent on magnesium influx.

TRPM7 has been shown to be required for increased cell proliferation and migration.[50] Overexpression of TRPM7 in a neuroblastoma cell line increased focal adhesion formation and cellular spreading. TRPM7 could phosphorylate myosin II and thus regulate actomyosin relaxation and myosin filament stability to alter the cellular cytoskeleton.[61] Furthermore, knockdown of TRPM7 in retinoblastoma cells decreased proliferation and halted cell cycle progression.[62] In contrast although TRPM7 channels are highly expressed in the tips of the growth cone, both knockdown of TRPM7 and blockage of the channel by a specific blocker waixenicin A enhanced axonal outgrowth in culture.[63] Furthermore, TRPM7 co-immunoprecipitated and colocalized with F-actin and α-actinin-1 at the growth cone, which suggested that $Ca^{2+}$ influx through TRPM7 inhibits axonal outgrowth and maturation by regulating the F-actin and α-actinin-1 protein complex.[63] Thus, these evidences indicated TRPM7 channels function as a mechanosensitive regulator of neuronal cytoskeleton, which may affect axonal growth in a way that is different from other stimulus.

TRPM7 may also play a major role in vesicular trafficking, membrane reorganization, and neurotransmitter release. TRPM7 has been shown to be located in the membranes of acetylcholine (ACh)-secreting synaptic vesicles of sympathetic neurons. TRPM7 forms a molecular complex with proteins of the vesicular fusion machinery and is critical for stimulated neurotransmitter release.[58] Studies also indicated that TRPM7 is located in ACh-secreting small synaptic-like vesicles (SSLV). Knocking down the TRPM7 channel or abolishing TRPM7 channel activity by mutation, attenuated the frequency of spontaneous and voltage-stimulated SSLV fusion events without affecting large dense core vesicle secretion, thereby suggesting that the conductance of TRPM7 across the vesicle membrane is important in SSLV fusion.[57]

## TRPM7 Channels and Neurodegeneration

Neurodegeneration comprises the assembly of pathological events that give rise to a progressive loss of neuronal structure and function including cellular damage, diseases development, or cellular death.[64] In most of these processes, $Ca^{2+}$ and $Mg^{2+}$ play
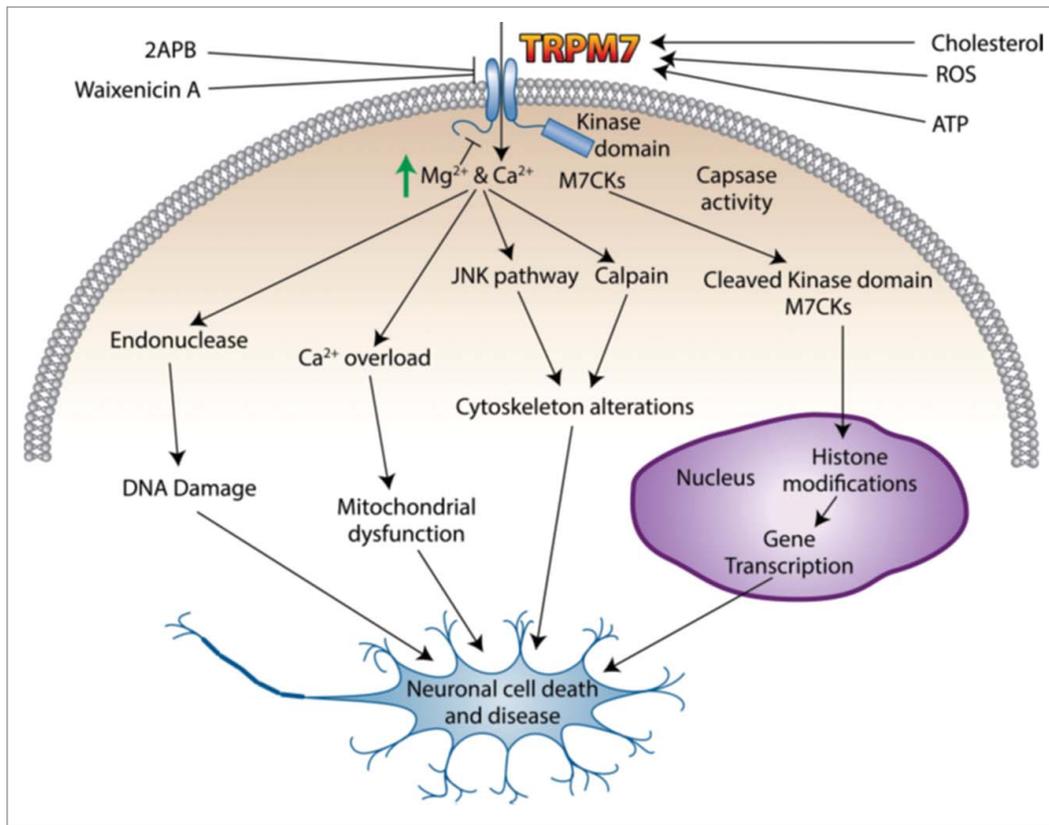
**Figure 1.** Schematic diagram of TRPM7 channel action in neuronal disease and cell death.

neurons and permitted the survival of neurons previously destined to die from prolonged anoxia. Considering all these results, TRPM7 emerges as a key factor in anoxic neuronal death.[72] Interestingly, in primary cortical neurons, knockdown of TRPM7 also resulted in knockdown of TRPM2 suggesting that expression of these 2 proteins in cortical neurons is co-ordinated in some manner.[72] These two channels form heteromers in cortical neurons. The observed anoxia-induced current is carried by TRPM2/TRPM7 heteromers. Although interaction between TRPM2 and TRPM7 at a protein level has not yet been demonstrated, TRPM2/TRPM7 heteromeric channels may represent a critical cation channel species that are modulated by intracellular free radicals and conducts

a pivotal role and as TRPM7 regulates both these ions it can be postulated that TRPM7 will play a major role in these conditions (**Fig. 1**).

Several physiological pathways are responsible for the production of reactive oxygen species (ROS) including respiration and activation of the arachidonic acid cascade.[65] Overproduction of ROS has been proposed to play crucial roles in the pathogenesis of neurodegenerative disorders including Alzheimer disease (AD) and Parkinson disease (PD).[66-68] Oxidative stress could result in cellular defects including a defect in ER $Ca^{2+}$ uptake and $Ca^{2+}$ efflux, thereby increasing $[Ca^{2+}]_i$ and $Ca^{2+}$ influx. This increase in $[Ca^{2+}]_i$ induces an exacerbation of oxidative stress, and activates several $Ca^{2+-}$ dependent enzymes including, calpain and the endonuclease pathways, which ultimately cause cytoskeleton alterations and cell death.[69-71] In oxidative stress, ROS activated TRPM7 channels induced an increase in $[Ca^{2+}]_i$ concentrations and TRPM7 currents are prominently facilitated by $H_2O_2$ exposure.[36] In addition, application of 2-aminoethoxydiphenyl borate (2-APB), an inhibitor of TRPM7, or knockdown of TRPM7 protected the neurons from $H_2O_2$- mediated injury. In contrast, overexpressing TRPM7 channels has also shown to increase $H_2O_2$- mediated injury,[51] suggesting that a set-point of TRPM7 expression is vital for neuronal function and alteration in its activity and/or expression could alter this tight balance. Importantly, suppression of TRPM7 rescued anoxic

toxic levels of $Ca^{2+}$ which contribute to an increased susceptibility to degenerative processes.

AD is a form of dementia in which patients show neurodegeneration, complete loss of cognitive abilities. In AD, central to the neurodegenerative process is the inability of neurons to properly regulate $[Ca^{2+}]_i$ concentration. Increased levels of amyloid β-peptide (Aβ) induce neurotoxic factors including ROS and cytokines, which impair cellular $Ca^{2+}$ homeostasis and render neurons vulnerable to apoptosis and excitotoxicity.[73] Familial Alzheimer disease (FAD)-associated presenilin (PS) mutations cause an imbalance in $PIP_2$ metabolism, which is an important cellular effector whose functions include the regulation of TRPM7 channel. Modulation of cellular $PIP_2$ also closely correlates with 42-residue amyloid β-peptide (Aβ42) levels. Importantly, a recent study indicated that TRPM7 channel underlies $Ca^{2+}$ entry deficits in presenilin FAD mutant cells and the observed channel deficits are restored by the addition of $PIP_2$.[74] These results suggests that TRPM7 is involved in the normal function of PS and in its regulation through a $PIP_2$-dependent mechanism.[75]

TRPM7 is also an important $Mg^{2+}$ transporter. A critical role for $Mg^{2+}$ has been implicated in AD, Huntington's disease, and mitochondrial cytopathies, although most recent studies have focused on PD.[15,76-78] PD is a common neurodegenerative disorder and loss of dopaminergic (DA) neurons in the substantia

nigra (SN) region underlies the main motor symptoms of PD. In vitro animal PD models showed $Mg^{2+}$ deficiency increased the susceptibility to methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity.[79] Furthermore, that $Mg^{2+}$ administration significantly inhibited the toxicity of (methyl-4-phenylpyridium ion (MPP$^+$) and prevented any decrease in the number of DA neurons and the length of DA neurites is also significantly preserved,[80] which is consistent with the finding that $Mg^{2+}$ deficiency in rats for over a number of generations significantly showed decreased DA neurons in the SN.[81] Thus as, TRPM7 channel are tightly linked with $Mg^{2+}$ transport, they may play a role in various neurodegenerative disease onsets under some circumstances. Consistent with these observations, TRPM7 channels are expressed in SN neurons. Recently, TRPM7 mutant Zebrafish showed defects in the production or release of dopamine which lead to hypomotile and a failure to make a dopamine-dependent developmental transition. Importantly, both of these deficits were partially rescued by the application of dopamine.[82] In SH-SY5Y cells, which models aspects of human DA neurons, forced expression of a channel-dead variant of TRPM7 causes cell death.[82] Further reports indicate that mRNA levels of TRPM7 also significantly decreased in SN area of PD patients.[83] Together, these suggest that DA neurons depend on the TRPM7 expression and loss of TRPM7channel function may be involved in PD.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the progressive degeneration of motor neurons.[84] Parkinsonism dementia is also related to ALS, but is a distinct, neurodegenerative disease. ALS and PD can share overlapping clinical symptoms and frequently occur together in the same families, as well as even in the same individual. Further, the basic pathogenic mechanisms underlying these disorders are similar.[85-89] Extensive studies conducted over the years strongly suggest that ALS and Parkinsonism Dementia are connected with low levels of $Ca^{2+}$ and $Mg^{2+}$, which create a condition that could affect the proper function of TRPM7 channels.[89-91] Importantly, a heterozygous variant of TRPM7 encoding a channel protein with a missense mutation was found in a subset of ALS/PD cases in Guam but not in the Kii peninsula of Japan.[89,92,93] Notably, the mutation did not affect TRPM7 kinase activity but increased the channel's sensitivity to an intracellular $Mg^{2+}$ block, resulting in imbalance in $Mg^{2+}$ and $Ca^{2+}$ homeostasis that could affect vital cellular processes including those responding to increased oxidative stress and those causing activation of proinflammatory pathways.[89] TRPM7 also resides in the membrane of synaptic vesicles and interacts with snapin altering acetylcholine release. Thus, indicating that vesicular TRPM7 channel activity is critical to neurotransmitter release in sympathetic neurons.[57,58] Importantly, disruption and loss of neuromuscular synapse has been reported as one of earliest pathological events in ALS and occurs long before the appearance of clinical symptoms.[94] Thus, TRPM7 mutation may play a crucial role in neurotransmitter release in ALS.

Another neurodegenerative disease where TRPM7 can play a vital role is stroke. Stroke is a sudden loss of brain function due to an interruption of the brain's blood supply. Loss of oxygen leads to a decrease in ATP levels and as neuronal cells are dependent on glucose metabolism, inhibition of mitochondrial function could lead to neuronal cell death and loss of brain function. Additionally in strokes, cell death is triggered by membrane depolarization, $Ca^{2+}$ overload, and the production of ROS. As indicated above, TRPM7 could lead to $Ca^{2+}$ toxicity and are activated by free radical which could amplify neuronal degeneration during ischemia.[62] Consistent with this inhibition of TRPM7 activity and siRNA knockdown has proven to be neuroprotective after prolonged oxygen glucose deprivation (an in vitro model of stroke), suggesting that its activity may be responsible for the delayed cell death and $Ca^{2+}$ overload that inevitably accompany stroke.[72] In addition, TRPM7 has also been proposed as a downstream targets since it was first implicated in the cell death that follows stroke.

Carvacrol, a pungent natural compound, has been reported to block TRPM7 current in hippocampal neuron, as well as provide neuroprotection in adult mice subjected to focal ischemia TRPM7 inhibitor.[95,96] Carvacrol pre-treatment protects against neonatal hypoxic-ischemic brain injury by reducing brain infarct volume, promoting pro-survival signaling and inhibiting pro-apoptotic signaling, as well as improving behavioral outcomes.[97] This suggest that the neuroprotective effect may be mediated by the inhibition of TRPM7 channel function and TRPM7 may be a feasible target for pharmacological intervention during stroke. Sun et al showed that suppression of TRPM7 activity in hippocampal neurons made them resistant to ischemic death and it also preserved neuronal morphology and function. Moreover, TRPM7 suppression prevented ischemia-induced deficits in long-term potentiation (LTP) and preserved the performance in fear associated and spatial-navigational memory tasks.[98] Recent studies by Chen et al also showed that carvacrol pre-treatment protects against neonatal hypoxic-ischemic brain injury and this neuroprotective effect may be mediated by the inhibition of TRPM7 channel function.[99] Both in vitro and in vivo studies indicate the involvement of TRPM7 channels in ischemic neuronal injury [100] but further extensive preclinical testing is obligatory to evaluate the therapeutic potential of the TRPM7 blockade in stroke.

In addition, TRPM7 also interacts with several proteins such as PLC, Fas-associated death domain protein (FADD), and eEF2K, which are all associated with neurodegenerative disease. PLC enzymes are crucial signaling elements and can convert the membrane-bound $PIP_2$ to the second messengers Diacylglycerol (DAG).[101] AD related Aβ peptide significantly altered muscarinic cholinergic receptor (mChR) signaling on the level of G protein regulated PLC leading to the lower formation of inositol-1,4,5-triphosphate (IP3) and DAG.[102] TRPM7 Ser/Thr-kinase can interact with PLCβ1 -β2 -β3, and -γ1eEF2 controlling PLC activity.[44,101] eEF2K are key downstream effectors that mediate the detrimental effects of hyperactive AMPK in AD.[103] Levels of p-eEF2K were significantly increased and total eEF2 is significantly decreased in AD.[104] TRPM7, via its kinase, mediates enhanced phosphorylation of eEF2, which does not directly phosphorylate eEF2, but rather to influence the amount of eEF2s cognate kinase eEF2k to regulate eEF2.[105] The FAS gene plays a role in apoptosis and is associated with AD by modulating the apoptosis and

neuronal loss secondary to AD neuropathology.[106,107] PD patients also show mitochondrial, ubiquitin-proteasome system dysfunction, associated to high expression of the Fas molecule, activation of caspase-3 and -9 and proneness to apoptosis.[108] A recent study indicated TRPM7 regulates endocytic compartmentalization of the Fas receptor and knockdown TRPM7 considerably reduced incidence of Fas receptor internalization after receptor stimulation,[52] an important process for apoptotic signaling through Fas receptors. Thus, functional interaction of TRPM7 with these proteins maybe one of the additional mechanisms of TRPM7 involved in neurodegenerative disease.

## Conclusion and Future Directions

The activity of TRPM7 channel is crucial for maintenance of appropriate levels of intracellular $Ca^{2+}$ and $Mg^{2+}$ levels and alterations in this homeostasis will change cell function. This can lead to elevated oxidative stress reasonably which disrupt the function, differentiation, and survival of neurons. Hence, genetic variations in TRPM7 channels may influence susceptibility to neurodegenerative diseases. However, whether TRPM7 channel is linked to intracellular signal cascades via its kinase domain or associated proteins remains to be determined.[109] Phosphorylation by TRPM7 kinase within the N-terminal $\alpha$-helix is stimulated by $Ca^{2+}$ influx through the channel domain and allude to an interaction between channel and kinase functions. TRPM7

channel kinase domain is also required for embryonic development making the TRPM7 knockout mice lethal and thereby restricting the knockout studies.[59] Importantly, recent reports have also shown that the kinase domain of TRPM7 is essential for regulating the epigenome. Although these studies were performed in non-neuronal cells, it is exciting and opens new direction as to how TRPM7 can regulate neuronal functions. Thus, further studies will lead to fully evaluating the significant role of TRPM7 channel in neuronal functions and how loss of these vital functions may be involved in different types of neurodegeneration. In conclusion regulating TRPM7 channel functions may uncover new strategies in the future to prevent the progression of neurodegenerative diseases.

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