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Transient receptor potential melastatin 2 channels in neurological disorders: Mechanisms and animal models

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Abstract

Transient receptor potential melastatin 2 (TRPM2) is a calcium-permeable ion channel implicated in neurodegenerative disorders and conditions. It is activated in response to reactive oxygen species (ROS) and thereby alters Ca^{2+} homeostasis and initiates pathways that lead to apoptosis and cell dysfunction. This review summarizes the current role of TRPM2 in neurological disorders, including Parkinson's disease, Alzheimer's disease, ischemia, traumatic brain injury, and depressive disorders (bipolar disease and depression). It describes the distribution and function of the TRPM2 channel across the brain and highlights common mechanisms between diseases. Specific animal and cell culture studies using TRPM2 inhibitors or genetic knockouts are discussed, including strategies to reduce the effect of ROS in disease through TRPM2 inhibition.

Keywords: Transient receptor potential melastatin 2; Ion channel; Neurological disorders; Brain injury; Stroke

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1. Introduction

Understanding of the molecular mechanisms underlying cell damage in neurological diseases is improving; however, challenges remain in therapeutic development. In Alzheimer's disease (AD), therapies targeting amyloid or tau pathology have not been successfully translated from animal studies (mice) to humans[1]. Similarly, therapeutic options remain limited in ischemia and brain injury[2].

There are a variety of reasons for poor clinical translation. Numerous independent and interrelated molecular mechanisms are altered during disease or injury. Consequently, targeting a single mechanism may not be sufficient to minimize tissue damage. For example, in traumatic brain injury (TBI), microvascular remodeling and angiogenesis occur to restore blood flow[3]. This process, however, occurs concurrently with gliosis, widespread neural degeneration, and axonal injury[4]. Animal models, typically used

to elucidate the pathophysiology of neurological disease, may not recapitulate the complexity of human diseases. This has been an issue in clinical translation of AD mouse model findings where strategies to remove plaques in mice do not cure AD in humans[5]. In some cases, therapeutic treatments for ischemia, such as administering growth factors, have had side effects such as blood–brain barrier (BBB) leakage[6].

The transient receptor potential melastatin 2 (TRPM2) ion channel is an important member of the calcium-permeable, non-selective, cation conducting TRP family. It is sensitive to perturbations in the cellular environment and is essential to both cell survival and the induction of cell death. TRPM2 is located at the plasma membrane and/or lysosomal compartments, with a broad tissue distribution profile indicative of its involvement in multiple physiological processes[7,8].

TRPM2 is highly expressed in a variety of cells in the brain and is, therefore, an attractive target for improving brain function. Modulation of TRPM2 has the potential to prevent apoptosis, minimize BBB leakage, and reduce the inflammatory response. Activated in response to oxidative stress and reactive oxygen species (ROS), which are common among different diseases, TRPM2 is involved in many neurological disorders, such as Parkinson's disease (PD), AD, ischemia, brain tumors, and aging[9,10]. TRPM2 is also implicated in the evolution and development of neuropsychiatric disorders. Our own studies in neonatal hypoxic-ischemic-induced mice demonstrate reduced infarction volume and glial cell activation in response to TRPM2 gene knockout or administration of a TRPM2 inhibitor[11,12]. This suggests that TRPM2 inhibition confers neuroprotective effects in neurological diseases that share common underlying molecular mechanisms.

This review begins with an introduction describing the expression, distribution, and function of the TRPM2 channel. We use data from the Allen Mouse Brain Atlas[13-15] to highlight TRPM2 expression across the brain and discuss the common mechanisms by which TRPM2 activation induces neural dysfunction or injury. In a previous review[16], we focused on the role of the TRPM2 channel in ischemia/hypoxia. Here, we discuss TRPM2 in a number of neurological conditions or disorders, including PD, AD, ischemia, TBI, and psychiatric disorders, highlighting the common mechanisms and pathways between the conditions. We primarily focus on the use of animal (rodent) disease models as well as *in vitro* studies to better understand the role that TRPM2 activation plays in mediating brain dysfunction or injury. The review concludes by summarizing the current status of TRPM2 research and potential future developments in the field.

2. Expression, distribution, and function of the TRPM2 ion channel

Real-time quantitative reverse transcription polymerase chain reaction reveals TRPM2 expression in all peripheral regions analyzed aside from cartilage and bone[17]. This includes expression in bone marrow, lung, spleen, heart, and pancreas, with highest relative expression levels apparent in the brain[17]. Within the central nervous system (CNS), TRPM2 is among the most abundant of all the TRPM channels[17]. Regarding regional distribution patterns within the human CNS, a major 6.2 kb *trpm2* transcript was demonstrated by northern blotting in various regions, including the cerebral cortex, hippocampus, thalamus, cerebellum, and substantia nigra, while a minor 5.5 kb transcript was detected only in the striatum[18,19]. *Trpm2* mRNA and TRMP2 protein are also detected in corresponding brain regions in murine models[18,20,21].

The Allen Mouse Brain Atlas has been an instrumental tool in mapping *Trpm2* gene expression within a three-dimensional reference framework[13-15]. The available high-resolution *in situ* hybridization (ISH) map of *Trpm2* expression in a male postnatal day 56 mouse, corresponding to the adult stage, provides a transcriptomic profile of the channel. Representative images of *Trpm2* expression in a sagittal section and three-dimensional reconstruction of the mouse brain are shown in Figure 1A and 1B, respectively, with the background signal subtracted and the relative expression level displayed in cool colors (low expression) to hot colors (high expression). Quantification of this dataset demonstrates that at this developmental stage, the level of *Trpm2* mRNA is greatest in the thalamus followed by the medulla, midbrain, and cortical subplate (Figure 1C)[13-15]. It is important to note that the ISH data are semi-quantitative because of the signal amplification process, but nevertheless it enables the visualization of *Trpm2* mRNA localization coupled with intensity, which helps to guide the study of neurological processes in which TRPM2 is implicated. For example, *Trpm2* is expressed in the preoptic area of the hypothalamus, with its function confirmed by electrophysiological recordings. Cultured preoptic neurons from TRPM2-deficient (*Trpm2*$^{-/-}$) mice had reduced responses to high temperatures above 37°C, compared with wild-type cultures, indicating that TRPM2 serves as a hypothalamic heat sensor[22,23]. TRPM2 is also involved in hippocampal synaptic plasticity and long-term depression (LTD), with hippocampal TRPM2 ablation conferring impaired LTD[24]. Similarly, knowledge of TRPM2 regional localization paired with an understanding of its modulation and signaling patterns implicates this channel in a variety of neurological disorders.

TRPM2 has been detected in various cell types, including neurons and glial cells of the CNS, other

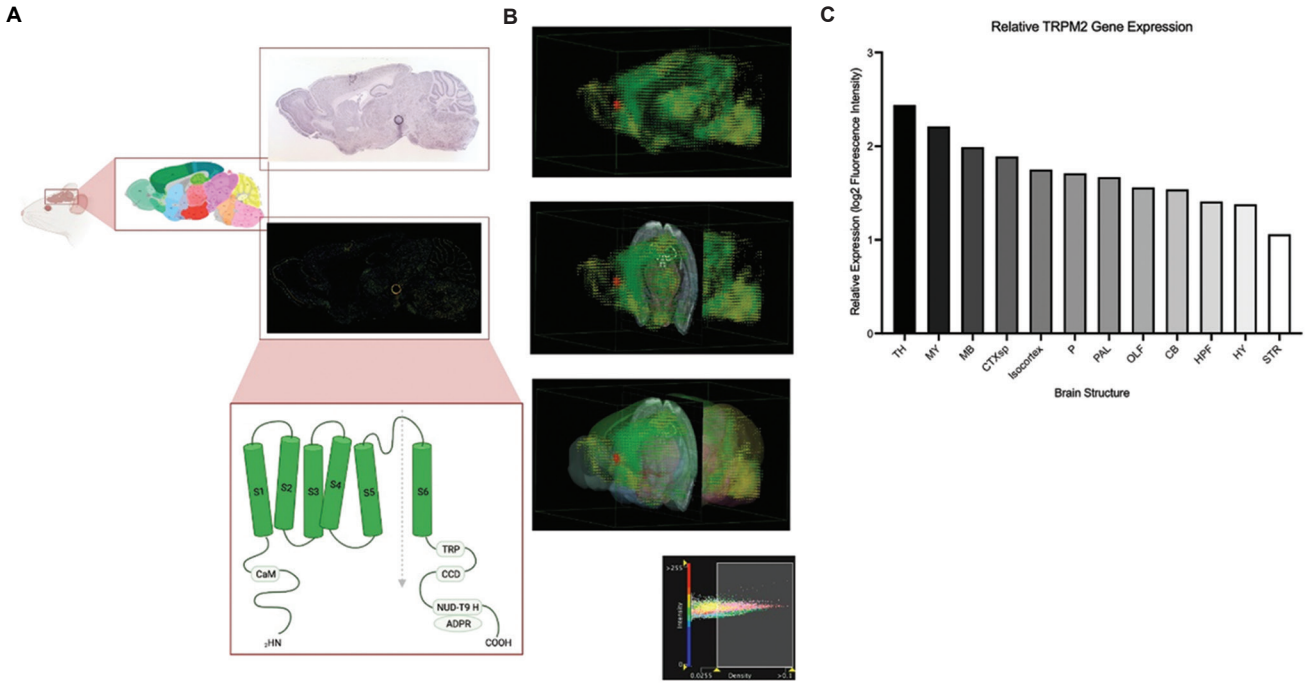

Figure 1. Allen Mouse Brain Atlas *in situ* hybridization and brain explorer database for TRPM2 gene expression. (A) Representative anatomical reference atlas of the mouse at postnatal day (P) 56, in a sagittal section (left panel). Representative *in situ* hybridization image at the corresponding sagittal section of the brain showing the relative location and intensity of *Trpm2* mRNA (upper panel). Representative expression mask at the corresponding sagittal section with background signal subtracted showing low expression in cool colors and high expression in warm colors (middle panel). Representative TRPM2 protein structure comprising six transmembrane helices, labeled S1 – S6. The amino terminus contains a Ca^{2+}-calmodulin (CaM)-binding motif that participates in channel activation. The carboxyl terminus contains a TRP domain (TRP), a coiled-coil domain, and a ~270 residue nucleoside diphosphate-linked moiety X-type homology motif (NUDT9) that interacts with adenosine diphosphate ribose (lower panel). Allen Reference Atlas – Mouse Brain, https://atlas.brain-map.org/and Allen Mouse Brain Atlas, https://mouse.brain-map.org/experiment/show/69288417. (B) Construction of a three-dimensional image of the mouse brain at P56 displaying the *in situ* hybridization gene expression data of *Trpm2*. *Trpm2* expression intensity (sum of expression pixel intensity/sum of expression pixels) is first shown alone, then with a coronal section, and then with a coronal section and outer structures. Low expression is indicated in cool colors of blue to green, while high expression in indicated in warm colors of yellow to red hues. Allen Mouse Brain Atlas, 3D brain explorer. (C) Relative *Trpm2* expression in specific analyzed brain structures. Allen Mouse Brain Atlas, https://mouse.brain-map.org/experiment/show/69288417. TH: Thalamus; MY: Medulla; MB: Midbrain; CTXSP: Subcortical plate; P: Pons; PAL: Pallidum; OLF: Olfactory areas; CB: Cerebellum; HPF: Hippocampal formation; HY: Hypothalamus; STR: Striatum. Figure generated with BioRender.

immune cells, and endothelial cells. As a Ca^{2+}-permeable channel activated by oxidative stress, TRPM2 has been investigated in pathological conditions characterized by Ca^{2+}-induced cytotoxicity and high levels of ROS and hydrogen peroxide (H_2O_2). TRPM2 is abundant in hippocampal pyramidal neurons, dopaminergic neurons of the substantia nigra, and cortical neurons[21,25,26]. In glial cells, TRPM2-mediated Ca^{2+} currents in response to H_2O_2 have been observed in cultured microglia heterogeneously expressing TRPM2[27]. TRPM2 at mRNA and protein levels has been detected in astrocytes, with siRNA transfection leading to a significant reduction in astrocyte-mediated interleukin (IL)-6 release[28]. These studies indicate that TRPM2 is present in both microglial cells and astrocytes, where it plays a key role in the inflammatory response and promotion of cytokine release under pathological conditions. This role is supported by TRPM2 being present in the cells of the peripheral immune system, including neutrophils, macrophages, monocytes, and lymphocytes[29-32]. Finally, TRPM2 has been implicated in cerebrovascular integrity because of its expression in endothelial cells. ROS production stimulates excessive TRPM2-mediated Ca^{2+} entry through the endothelial plasmalemma, which, in turn, activates caspase-3-mediated apoptosis[33]. Meanwhile, TRPM2 inhibition prevents thrombin-induced BBB permeability through the blockade of Ca^{2+} influx in brain capillary endothelial cells[34]. These results highlight the role of TRPM2 in modulating BBB integrity under physiological and pathological conditions.

In regard to subcellular localization, TRPM2 is primarily a plasma membrane channel. However, immunofluorescence of TRPM2 in pancreatic β- cells has revealed intracellular localization, including in lysosomes.

Emptying of lysosomal Ca^{2+} stores suppresses adenosine diphosphate ribose (ADPR)-mediated Ca^{2+} release, indicating that ADPR-dependent TRPM2 channels function as lysosomal Ca^{2+} channels[7]. Cytoplasmic distribution of TRPM2 has also been observed in dendritic cells, with TRPM2 mostly localized on the lysosomal membrane. Furthermore, TRPM2-deficient dendritic cells exhibit impaired chemotaxis in response to chemokine stimulation[35]. These findings highlight the importance of TRPM2 in responding to both extracellular and intracellular perturbations[35].

3. TRPM2 in neurological disease and acute brain injury

3.1. PD

PD is a neurodegenerative disorder encompassing a range of motor and non-motor deficits, such as resting tremor and cognitive changes[36]. Numerous risk factors including mitochondrial dysfunction and inflammation are associated with PD pathology and contribute to its progression[36].

Animal and cell models have been developed to simulate features of PD. Commonly used models involve administering toxins to animals or cell cultures, such as 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). 6-OHDA needs to be injected into the brain because it does not cross the BBB, and it leads to degeneration of dopaminergic neurons in regions such as the striatum, medial forebrain bundle, and substantia nigra[37]. The mechanism of action underlying this effect is likely through auto-oxidation of 6-OHDA leading to H_2O_2, superoxide radicals, and ROS production[37]. MPTP crosses the BBB and is converted to 1-methyl-4-phenylpyridinium ions (MPP^+) that are taken up by dopaminergic neurons through dopamine transporters (DATs)[38]. This leads to the inhibition of the electron transport chain (ETC), decreased mitochondrial membrane potential, and altered calcium homeostasis, ultimately leading to neuronal death[38].

An important mechanism of MPTP-generated neurotoxicity is oxidative stress[39]. MPTP accumulation in dopaminergic neurons generates ROS through the mitochondria[39]. These species may damage cells through reactions that lead to lipid peroxidation, DNA damage, changes to membrane fluidity, and endothelial dysfunction[38,39]. Molecules with similar structures to MPTP, such as rotenone (insecticide) and paraquat (a herbicide), also induce degeneration of dopaminergic neurons[39]. Neurotoxin models are relatively simple, merely requiring an injection of the substance. However, such models only mimic pathological symptoms and not the underlying pathology, and may only approximate the late state of the disease[37]. Consequently, alternative genetic models have been explored, such as transgenic mice with alterations to the α-synuclein gene[37].

The interaction between oxidative stress and PD means that understanding the molecular mechanisms and proteins that contribute to ROS-induced cellular dysfunction is important in developing therapeutics. ROS induces TRPM2 channel activation through the generation of ADPR in the cell nucleus[40]; therefore, TRPM2 activation may play a role in PD. In microglial cells, TRPM2 activation leads to the production of pro-inflammatory mediators that contribute to reduced blood flow and hypoxic-ischemic injury, neuropathic pain, and neurodegeneration[40]. TRPM2 is also localized in the cell membrane of dopaminergic neurons in the rat substantia nigra and is activated in response to H_2O_2, which indicates a possible contribution of TRPM2 to PD pathology[25].

There are indicators of a TRPM2 contribution to PD progression. Amyotrophic lateral sclerosis and PD share overlapping symptoms and occur at a relatively high rate on three separate Western Pacific islands[41]. Hermosura *et al.* identified in a Guamanian population a variant in the TRPM2 channel that increases susceptibility to PD and amyotrophic lateral sclerosis[42]. This variant is a missense mutation that inactivates the channel[42].

In an MPTP-induced PD rat model, administration of 2-APB (a TRPM2 and general Ca^{2+} channel blocker) and PJ-34 (a PARP inhibitor that impairs TRPM2 function) improved cognition and locomotion, with decreased TRPM2 levels in the striatum and midbrain in the PD rat[43]. In a 6-OHDA rat model, TRPM2 was upregulated in the substantia nigra[44]. When dorsal root ganglion neurons were isolated from a rat and exposed to rotenone, TRPM2 currents, which were blocked by TRPM2 inhibitors, were generated[45].

Further support for the involvement of TRPM2 in PD has been demonstrated in cell culture studies. The neuroblastoma SH-SY5Y cell line is often used in these studies because these cells are of human origin and are easy to maintain. In addition, they possess catecholaminergic properties, such as the ability to produce dopamine[46]. In PD patients administered with dopamine synthesis-enhancing drugs, homocysteine is produced as a byproduct, which may cause side effects, such as apoptosis and oxidative stress, contributing to PD development[47]. This is replicated in SH-SY5Y cells exposed to MPP^+ and homocysteine, which display high levels of ROS, mitochondrial membrane depolarization, and activation of caspases (enzymes involved in apoptosis)[47]. This effect was reduced by selenium, an antioxidant, and 2-APB,

a TRPM2 inhibitor, which decrease apoptosis and Ca^{2+} influx[47]. In SH-SY5Y cells overexpressing TRPM2, cell viability was reduced relative to wild-type cells in response to H_2O_2 exposure, which was prevented by TRPM2 and PARP inhibition[48]. Overall, MPP^+ increases TRPM2 expression in SH-SY5Y neurons, increasing caspase activation, and reducing cell viability[48-50].

Results from human, animal, and *in vitro* studies are complementary. Sun *et al.* showed that TRPM2 levels are increased in the substantia nigra in both an MPTP-induced mouse model and human PD patients[38]. ROS-mediated TRPM2 activation also induced cell death or apoptosis in SH-SY5Y cells through elevation of Ca^{2+}[38].

These findings in PD animal models, cell cultures, and humans indicate a role for TRPM2 in neuronal dysfunction through ROS-mediated activation of TRPM2 and loss of intracellular Ca^{2+} homeostasis, leading to apoptosis.

3.2. AD

Similar to PD, oxidative stress contributes to AD development. ROS may be generated through mitochondrial dysfunction and autophagy[51], activation of microglia[51], and amyloid-β (Aβ) (1 – 42) through binding iron[51].

According to the amyloid hypothesis, there is an overproduction of amyloid precursor protein (APP), or problems in clearing APP, leading to increased amyloid concentration in tissue[1]. Drugs developed to target amyloid have generally been unsuccessful when translated from mice to humans. This is possibly because Aβ antibodies do not clear toxic soluble oligomers, removing amyloid too late in the disease process when permanent tissue damage has already occurred, or because of failure to target other elements of AD pathology such as phosphorylated tau or inflammatory mediators[1].

Mouse models have been developed to study features of the disease. Mice do not spontaneously develop AD; therefore, the most common models overexpress familial human AD genes. This leads to amyloid plaque formation, cognitive deficits, and abnormal synaptic plasticity in the mice[5,52]. One model is the TgCRND8 mouse, which overexpresses mutant human APP at a rate 5 times higher than murine APP, causing plaque deposits and neuritic pathology by 3 and 5 months, respectively[53]. Transgenic APP mice, however, do not often develop other important features of the pathology, such as neurofibrillary tangles and extensive neuronal and synaptic loss[5]. For example, by 8 months, the APP/presenilin 1 (PS1) mouse does not display cortical neuron loss outside the dentate gyrus[54]. Although neuritic processes in APP/PS1 mice contain hyperphosphorylated tau, these do not present as tangles equivalent to those in human pathology[54].

To study tau pathology, transgenic mice were developed that express human tau through different promoters[5]. When the P301L mutation is present in the human *microtubule-associated protein tau* gene, which encodes tau protein, mice homozygous for this transgene develop neurofibrillary tangles by 4.5 months and experience neuronal loss, particularly in the spinal cord[55]. To develop mouse models that encompass both plaques and tangles, transgenic tau and APP mice have been crossed. These mice develop Aβ pathology as per the transgenic APP model, with enhanced neurofibrillary tangle pathology in the olfactory cortex and limbic system relative to single transgenic tau mice[56,57], indicating that Aβ exacerbates tau pathology[57].

Mechanisms of TRPM2 action on AD progression have been detailed in cell culture and animal studies. In hippocampal neurons extracted from mouse brain tissue and exposed to Aβ, ROS were generated through protein kinase C and nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidases[58]. In cultured rat striatal cells exposed to Aβ and H_2O_2, blocking TRPM2 function (through transfection with a splice variant) or downregulating its expression (through siRNA) prevented intracellular increases in Ca^{2+} and resultant cell death[59]. In addition to calcium overload, increases in cytosolic and mitochondrial Zn^{2+} may also induce apoptosis. The increase in cytosolic Zn^{2+} occurs through TRPM2-mediated Ca^{2+} increases that lead to the release of Zn^{2+} by lysosomes[60]. Mitochondria are affected by lysosome-released Zn^{2+}, which inhibits the ETC and reduces the membrane potential[60]. This recruits dynamin-related protein 1 to mitochondria, initiating apoptosis[1,60].

The role of TRPM2 in AD progression was highlighted in a study with cultured neurons and the APP/PS1 mouse model. Ostapchenko *et al.* demonstrated increased TRPM2 current in cultured hippocampal neurons in response to Aβ oligomers[61]. $TRPM2^{-/-}$ APP/PS1 mice possessed decreased endoplasmic reticulum (ER) stress in brain tissue and avoided the extensive synapse loss present in APP/PS1 mice. Finally, microglial activation was decreased in $TRPM2^{-/-}$ AD mice. These changes were not attributable to altered amyloid processing in response to TRPM2 absence because the percent of amyloid plaque per tissue area did not differ between $TRPM2^{-/-}$ APP/PS1 and APP/PS1 mice. This finding in animals is paralleled in microglial cell cultures, where $TRPM2^{-/-}$ microglial cells, or those in which the TRPM2 channel is inhibited, are not activated and do not generate tumor necrosis factor alpha (TNF-α, a pro-inflammatory cytokine) in response to Aβ[62].

Although not directly related to AD, $TRPM2^{-/-}$ aged mice (20 – 24 months old) did not demonstrate the working

and cognitive memory impairment present in wild-type mice relative to their younger (2 – 3 and 12 – 16 months old) counterparts. These functional improvements corresponded to reduced white matter and hippocampal damage and reduced levels of microglia/macrophages and pro-inflammatory cytokines relative to TRPM2$^{+/+}$ mice[63].

TRPM2 is present in multiple cell lines; therefore, Aβ-generated ROS may act on several cell types, including microglia, neurons, and endothelia, in neurovascular dysfunction[64]. Therapeutic targeting of TRPM2 may thus alter multiple pathways involved in AD progression and overcome limitations of current strategies targeting only a single pathway.

3.3. Ischemic stroke

Stroke is the second leading cause of death globally according to the World Health Organization. Ischemic stroke, often caused by obstructed blood supply to the brain, accounts for approximately 87% of all strokes[65]. Due to the complex nature of ischemic stroke, various *in vivo* experimental models have been developed in the past few decades to mimic the clinical pathology of human strokes. These models are critical for understanding pathophysiological processes involved in ischemic stroke and to develop or test therapeutic strategies.

Animal models of ischemic stroke are generally classified as focal or global ischemia. One of the most widely used focal stroke models is the intraluminal middle cerebral artery occlusion (MCAO) model, where a suture is first introduced into either the common carotid artery or external carotid artery and advanced further into the MCA to interrupt blood supply[66,67]. This model mimics the majority of ischemic strokes in humans and generates highly reproducible infarction in the MCA territory. Intraluminal MCAO models can be used to model either permanent or transient ischemic strokes. In the transient MCAO (tMCAO) model, the suture is withdrawn after typically 60 – 120 min to allow reperfusion. In contrast, reperfusion is absent in the permanent MCAO (pMCAO) model. Embolic stroke models are another commonly used experimental model of stroke, where an autologous blood clot or thrombin is injected into the internal carotid artery or MCA[68]. The embolic model is typically used to study novel thrombolytic agents or the combined therapy of neuroprotective agents and tissue plasminogen activator, with micro- and nano-particles recently being investigated in thrombolytic research[69]. Other focal ischemic stroke models include the photothrombotic model, which uses a photosensitive dye followed by illumination of the targeted brain regions, and the vasoconstrictor endothelin-1 model. Although less commonly used, these models allow the induction of focal ischemia in virtually any brain region and are more suitable for modeling lacunar stroke[67,70].

Global ischemia models are characterized by reduced blood supply to most regions or the entire brain. The 2-vessel occlusion (2-VO) model is one of the easiest methods to induce global ischemia in rodents[71,72] and involves the transient occlusion of the bilateral common carotid artery (typically 5 – 15 min) to reduce global blood supply. Due to the simplicity of the surgical procedure, it has been increasingly used as an alternative to the 4-VO model developed earlier. Global ischemia can also be induced using the cardiac arrest/cardiopulmonary resuscitation (CA/CPR) model, which is specifically used to study transient ischemic brain injury following a sudden cardiac arrest[71]. In the CA/CPR model, CA is first induced by potassium chloride injection. After typically 8 – 10 min of CA, CPR is provided to the animals to restore circulation[73]. This model induces clear injury in regions such as the hippocampi that are more sensitive or vulnerable to ischemic insult.

TRPM2 has been increasingly studied in experimental models of ischemic stroke. TRPM2 plays a detrimental role and contributes to cell death after ischemic stroke, whereas inhibition or genetic ablation of TRPM2 is generally protective. In focal ischemia models, *Trpm2* mRNA levels were significantly increased in a time-dependent manner after tMCAO in the rat cortex[74]. This upregulation was observed at 24 h, peaked at 7 d (3 – 4-fold increase), and remained increased at 4 weeks post-stroke. Consistent with this finding, TRPM2$^{-/-}$ mice show an approximately 40% reduction in infarction volume at 48 h after tMCAO when compared with wild-type controls[75]. A similar effect was observed in mice treated with the TRPM2 inhibitor, duloxetine, after tMCAO[76]. However, there were no differences in infarct volumes between wild-type and TRPM2$^{-/-}$ mice when they were subjected to pMCAO, indicating that the absence of TRPM2 is neuroprotective against ischemic stroke only when followed by reperfusion[75]. One explanation is that the injury induced by pMCAO is so severe that genetic ablation of TRPM2 alone is not sufficient to rescue damaged tissue. Another possible explanation is that TRPM2 is involved in reperfusion, where there is an increased production of ROS and subsequent activation of TRPM2 by H_2O_2; therefore, TRPM2$^{-/-}$ mice might be protected more from H_2O_2-induced cell death during the period of reperfusion[75]. Interestingly, the same study also found that the hippocampal expression of N-methyl-D-aspartate receptor subunits GluN2A and GluN2B was significantly altered in neurons of TRPM2$^{-/-}$ mice. Specifically, after MCAO, GluN2A expression was increased by ~43% while GluN2B expression was decreased by ~46% in TRPM2$^{-/-}$ mice[75]. As GluN2A is involved in cell survival and GluN2B is involved in cell death, the neuroprotection observed in

TRPM2$^{-/-}$ mice may not be solely attributed to TRPM2. The mechanisms underlining the neuroprotection in TRPM2$^{-/-}$ mice are mediated by increased phosphorylation of ERK 1/2 and AKT and by the inhibition of glycogen synthase kinase 3 (GSK3)-β by Akt.

In addition to promoting neuronal death, TRPM2 has also been implicated to act in peripheral immune cells and glial cells post-stroke. Using bone marrow chimeric mice, Gelderblom *et al.* demonstrated a contribution of TRPM2 to immune cell invasion after tMCAO[77]. They found that besides reduced infarction and improved cognitive outcome, TRPM2$^{-/-}$ mice exhibited reduced invasion of peripheral neutrophils and macrophages to the injury site and reduced inflammation[77]. Similar effects were observed using the TRPM2 inhibitor, N-(p-amylcinnamoyl)anthranilic acid. In microglia, TRPM2 activation has been suggested to induce inducible nitric oxide synthase post-stroke, and the time course of TRPM2 mRNA upregulation in the cortex is consistent with the temporal profile of microglial activation after tMCAO. This indicates a potential contribution of TRPM2 to post-ischemic inflammation[74,78-80].

A sex-dependent role of TRPM2 has been reported in ischemic stroke[81]. Jia *et al.* first demonstrated that the TRPM2 inhibitor, clotrimazole, was effective in reducing infarction volume after tMCAO only in male mice[20]. Accordingly, *in vivo* shRNA-targeted TRPM2 knockdown reduced neuronal survival in male mice, indicating that TRPM2 activation contributes to ischemic injury selectively in males[20]. Similar findings were described by Shimizu *et al.* using aged animals with a more specific TRPM2 inhibitor, tatM2NX[82]. This male-specific TRPM2 activation is potentially caused by androgen signaling, which can promote the activation of poly (ADP-ribose) polymerase 1 (PARP1) and the formation of ADPR, which directly activates TRPM2. A 5-fold increase in ADPR activity and increased PARP1 activity were observed in male mice after tMCAO compared with either female mice or castrated male mice, while PARP knockout male mice exhibited reduced infarction[83]. In contrast, both ovariectomized and PARP1$^{-/-}$ female mice show exacerbated ischemic injury after tMCAO compared with intact female mice[84,85]. However, female mice treated directly with the androgen dihydrotestosterone do not show activation of PARP and no increase in the level of ADPR, indicating that circulating androgen alone is insufficient to promote TRPM2 activation and mediate TRPM2-mediated ischemic injury in females[85].

A similar detrimental role of TRPM2 has been proposed in the global ischemia models, 2-VO and CA/CPR. Specifically, TRPM2$^{-/-}$ mice were protected from 2-VO-induced global ischemia in terms of reduced hippocampal cornu ammonis 1 (CA1) pyramidal neuronal death and memory impairment compared with wild-type controls[86]. Neuroprotection in TRPM2$^{-/-}$ mice is associated with the absence of a delayed, ROS-induced, TRPM2-dependent accumulation of cytosolic Zn^{2+}, which promotes CA1 neuronal death[86]. This is consistent with a more recent study showing that modulation of TRPM2 prevents 2-VO-induced cell death[87].

Last, genetic ablation and inhibition of TRPM2 with tatM2NX both prevent hippocampal CA1 cell death in mice after CA/CPR-induced global ischemic stroke[88]. The effect was again only observed in males, which is consistent with the previous studies[88,89]. Surprisingly, TRPM2 inhibition with tatM2NX at delayed time points post-stroke reversed synaptic plasticity and hippocampal-dependent memory impairments in males and females 1 week after CA/CPR[88]. Electrophysiology confirmed that delayed inhibition of TRPM2 reverses the ischemia-induced long-term potentiation deficits in the hippocampus. Using a pharmacological approach, TRPM2 was shown to mediate synaptic impairment through calcineurin-GSK3-β signaling following CA/CPR[88]. These findings demonstrate that the TRPM2 channel mediates cell death in neurons, glia, and immune cells in models of both focal ischemic-reperfusion injury and global ischemia.

3.4. TBI

TBI represents the primary cause of mortality and neurological morbidity globally in individuals under the age of 45[90]. The estimated incidence of TBI is over 69 million per year worldwide and the most common reasons for TBI include road traffic accidents, falls, and sports-related concussions[91]. TBI is characterized by a primary injury and manifests immediately after the mechanical insult, followed by a delayed long-lasting secondary injury. TBI-induced brain damage has been associated with excitotoxicity, oxidative stress, BBB dysfunction, edema, inflammation, hematoma, and diffuse axonal injury[90].

Animal models recapitulate different aspects of TBI. Controlled cortical impact is commonly used to study focal injury. In the controlled cortical impact model, a craniotomy is performed and TBI is typically delivered through a piston onto the exposed dura with a user-specified time, speed, and depth of the impact[92]. In the fluid percussion injury model, a pressure pulse generated from a fluid percussion device is delivered onto the exposed dura[92]. Fluid percussion injury, either lateral or midline, produces a mixed injury with combined focal cortical contusion and a diffused subcortical injury[93]. In the weight drop injury model, injury is induced by a

free-falling weight and injury severity largely depends on the mass and the height of the weight[92]. Of the three major weight drop injury variations, Marmarou's impact acceleration model differs in that it involves linear and rotational acceleration to cause diffuse head injury. This model represents TBIs that occur due to traffic accidents and falls, generating widespread neuronal damage and diffuse axonal injury in cortical and subcortical regions[92]. Last, sports injury can be modeled with repeated mild TBI, and combat-related brain injury can be modeled with blast-induced or penetrating ballistic-like brain injury.

The role of TRPM2 in TBI has been investigated in rodents in two studies[94,95]. Both used the impact acceleration model in male rats. Compared with sham-operated rats, TRPM2 was transcriptionally and translationally upregulated in the cortex and hippocampus of rats subjected to TBI[95]. The upregulation of TRPM2, however, was not observed until 3 days post-TBI while the expression remained elevated at 5 days post-TBI[95]. These findings indicate that delayed and prolonged activation of TRPM2 contributes to injury following TBI. Another study reported that modulation of TRPM2 by the antioxidant melatonin reduced caspase-3-dependent apoptosis and ROS accumulation in hippocampal neurons through the regulation of (TRPM2-mediated) Ca^{2+} entry[94].

Further studies are required to investigate TRPM2 action over multiple time points following TBI. Since differences in males and females have been demonstrated in TRPM2-mediated acute brain injury, with a trend of increased susceptibility in males after experimental TBI[96], it will be interesting to include both sexes in future TBI studies to examine sex-dependent TRPM2 responses.

The studies discussed in section 3 are summarized in Table 1.

4. TRPM2 in psychiatric disorders

Recent genome-wide association studies have implicated TRPM2 in psychiatric disorders. The responsiveness of TRPM2 to oxidative stress and the key role this channel plays in mediating intracellular calcium homeostasis and neuroinflammation makes it an attractive candidate in disease etiology and supports its relevance in mood disorders and mental illness. Specifically, TRPM2 is a potential therapeutic target in bipolar disorder (BD) and major depressive disorder (MDD). Current models used to study these disorders and the contribution of TRPM2 to their distinct pathology are discussed below.

4.1. BD

BD is a complex psychiatric disorder with clinical heterogeneity characterized by recurrent manic and depressive episodes. These states vary in duration from weeks to several months and are accompanied by changes in energy levels as well as cognitive, behavioral, and physical symptoms[102]. A manic episode may be accompanied by an elevated or irritable mood, psychomotor agitation, grandiosity, racing thoughts, and sleep loss. Depressive symptoms include reduced interest in all activities, psychomotor retardation, fatigue, impaired concentration or indecisiveness, and suicide ideation[102,103]. Globally, BD has a median age of onset of ~25 years, a lifetime prevalence of 0.4 – 0.6%, and is associated with high morbidity, mortality, and socioeconomic burden[104].

Although etiological roles for common variant alleles are well-established, rare variants and epigenetic factors may also contribute to underlying BD pathophysiology and phenotypic presentation of the disorder[105]. Various interrelated molecular mechanisms have been postulated to underlie BD. These include cyclic dysregulation of dopaminergic transmission, altered ionic homeostasis and calcium metabolism, and chronic inflammation in both the periphery and brain with increased levels of IL-1β, IL 1 receptor, nuclear factor kappa B, and glial fibrillary acidic protein mRNA and protein in the post-mortem frontal cortex of BD patients. Mitochondrial dysfunction and oxidative stress have also been suggested to play important roles as indicated by reduced expression of mitochondrial ETC complex I subunits and increased oxidative and nitrosative damage in BD brains[106-109]. Given its role in regulating intracellular Ca^{2+} homeostasis and oxidative stress, TRPM2 has been implicated in mediating BD-related pathophysiological disturbances[110].

To study the role of TRPM2 in BD using rodent models, genetic, pharmacological, and environmental manipulation may be employed. Mutations in the circadian locomotor output cycles kaput gene have induced manic- and depressive-like behaviors in mice, as has genetic ablation of DAT[111,112]. DAT knockdown mice exhibit photoperiod length-driven manic- and depression-relevant behaviors including enhanced risk preferring behavior (manic) in long-active photoperiods and enhanced punishment sensitivity and despair-related behavior (depression) during short-active photoperiods[113]. This mimics seasonally induced switching of states – summer-onset mania and winter-onset depression – that parallel the switch between mania and depression characteristic of BD. Viral-mediated over- and under-expression of the dopamine D1 receptor is also associated with manic and depressive phenotypes, respectively[114]. Furthermore, administration followed by subsequent withdrawal of psychostimulants, including amphetamine, fenproporex, and cocaine[115-117], may be used to mimic BD in mice, while compounds such as monensin that acts to elevate intracellular Na^+ concentration to levels comparable

Table 1. Summary of results pertaining to animal and cell models discussed.

Neurological disorder	Model	TRPM2-mediated mechanisms	Reference
Parkinson's disease	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine	Increased TRPM2 expression in substantia nigra; TRPM2 and PARP inhibition improve cognition and locomotion	[38,43]
	6-hydroxydopamine	Upregulation of TRPM2 in substantia nigra	[44]
	Rotenone (insecticide) Exposure	Induced TRPM2-mediated currents	[45]
	MPP^+ and homocysteine exposure in SH-SY5Y cells	TRPM2 inhibition with antioxidant, selenium, reduced apoptosis, and Ca^{2+}-influx	[47]
	MPP^+ exposure in SH-SY5Y cells	Increased TRPM2 expression associated with increased caspase activation and reduced cell viability	[48-50]
Alzheimer's disease	APP/PS1	$TRPM2^{-/-}$ APP/PS1 mice possessed decreased ER stress and reduced synaptic loss	[61]
	$TRPM2^{-/-}$	$TRPM2^{-/-}$ mice exhibit decrease microglia activation; $TRPM2^{-/-}$ microglial cells are not activated and do not generate TNF-α in response to Aβ	[61,62]
	Aβ and H_2O_2 exposure in rat striatal cells	TRPM2 downregulation inhibits the elevation of intracellular calcium levels and cell death	[59]
	Aβ exposure in hippocampal neurons	Increased TRPM2-mediated currents	[61]
Ischemic stroke	Transient middle cerebral artery occlusion	Inhibition and genetic ablation of TRPM2 promote phosphorylation of ERK 1/2 and Akt and the inhibition of GSK3-β by Akt; $TRPM2^{-/-}$ mice might be protected from H_2O_2-induced cell death during reperfusion; TRPM2 activation promotes peripheral immune cell invasion and induces inducible nitric oxide synthase in microglia; sexually dimorphic response in TRPM2 activation is related to PARP-1 activation and ADPR formation	[74-76]
	Permanent middle cerebral artery occlusion	No significant protection was observed in $TRPM2^{-/-}$ mice	[75]
	2-vessel occlusion	TRPM2 mediates the delayed, ROS-induced accumulation of cytosolic Zn^{2+} and promotes CA1 neuronal death	[86,87]
	Cardiac arrest/cardiopulmonary resuscitation	TRPM2 mediates synaptic impairment through the calcineurin-GSK3-β signaling	[88,89]
Traumatic brain injury	Weight drop injury	TRPM2 mediates the delayed phases after TBI; negative modulation of TRPM2 reduces caspase-3-dependent apoptosis and ROS accumulation in hippocampal neurons through the regulation of (TRPM2-mediated) Ca^{2+} entry.	[94,95]
Bipolar disorder	BD-derived B lymphoblast cell line	Reduced TRPM2 mRNA expression; increased intracellular calcium levels	[97]
	Monensin (Na^+ ionophore) treatment	Increased TRPM2s (short form) expression and decreased TRPM2L (long form) expression at mRNA and protein level; altered TRPM2 expression is associated with increased caspase-3, caspase-7, and PARP at the protein level	[98]
	$TRPM2^{-/-}$	$TRPM2^{-/-}$ mice exhibit BD-related behavior (increased anxiety and decreased sociability) associated with abnormal GSK3-β regulation; lithium is ineffective in attenuating BD-related phenotype in $TRPM2^{-/-}$ mice	[99]
Depression	Chronic unpredictable stress	CUS $TRPM2^{-/-}$ mice exhibit reduced lipid peroxidation and PARP levels in the hippocampus compared with CUS $TRPM2^{+/+}$ mice; CUS $TRPM2^{-/-}$ mice exhibit reduced depressive behavioral phenotype compared with CUS $TRPM2^{+/+}$ mice; upregulated TRPM2 mRNA in CUS WT mice	[100]
	Duloxetine (SSNRI) treatment	Inhibited H_2O_2-induced TRPM2 calcium transients; reduced TRPM2 signaling decreases intracellular lipid peroxidation and ROS levels; reduced TRPM2 signaling increases antioxidant glutathione levels	[101]

to those observed in BD patients can also be used[98]. Finally, environmental manipulation through behavioral interventions, such as isolation rearing, or early postnatal stress paradigms, such as maternal separation and communal nursing, has been used to induce depressive-like phenotypes characteristic of BD once mice reach adulthood[118,119]. TRPM2 has not been extensively investigated in *in vivo* BD models; however, the outlined mouse models may be employed in future to elucidate its contribution.

Nevertheless, TRPM2 remains a priority candidate for BD because it is located in a BD susceptibility locus at 21q22.3[120]. An independent fine mapping study of 21q22.3 revealed association between TRPM2 and BD which was confirmed by family-based association studies[120-122]. Ten single-nucleotide polymorphisms in TRPM2 have since been identified that confer increased risk of BD[122,123]. The relevance and specific contributions of these TRPM2 variants to BD are seemingly based on the channel's regulation of Ca^{2+} homeostasis and sensitivity to oxidative stress, both of which are dysregulated under BD conditions. Elevated oxidative stress in primary rodent neurons increases *Trpm2* mRNA levels and alters TRPM2 levels, while elevated intracellular Ca^{2+} levels were reported in B lymphoblast cell lines from BD patients[26,32,97]. Furthermore, monensin-treated human olfactory neuroepithelial-derived progenitors have upregulated TRPM2 expression, elevated intracellular calcium levels, as well as increased caspase-3, caspase-7, and PARP; effects were attenuated by lithium treatment, the first-line treatment for BD[98]. Interestingly, lithium protects against oxidative stress and also inhibits GSK3 activity. In relation to this, $TRPM2^{-/-}$ mice have increased protein levels of the inactivated phosphorylated GSK3α and GSK3β, while the stimulation of TRPM2 leads to a downregulation of GSK3 phosphorylation. Furthermore, $TRPM2^{-/-}$ mice exhibited BD-related behavior, including increased anxiety and decreased sociability, and treatment with lithium was ineffective in attenuating these behavioral deficits[99]. Together, these results indicate that genetic variants of TRPM2 may lead to abnormal regulation of GSK3, a primary target of the BD treatment, lithium, thereby inducing behavioral abnormalities associated with manic and depressive states. Further study is required, however, to identify whether targeting TRPM2 alone or in conjunction with other BD-relevant interventions can protect against both manic and depressive episodes in the long term.

4.2. Depression

Depression is a leading cause of disability worldwide. It adversely affects workplace productivity and has a profound socioeconomic impact at both personal and organizational levels[124]. Depression is heterogeneous with ~256 unique symptoms meeting the diagnostic and statistical manual of mental disorders criteria for a MDD diagnosis, and the duration and frequency of both depressive episodes and states of remission vary greatly among affected individuals[125,126]. Depression affects approximately 3.8% of the population and is associated with an increased risk of over 50% of developing a cardiovascular or metabolic disease[124]. As a phenomenon characterized by symptoms ranging from low mood, anhedonia, and fatigue to psychomotor disturbances, psychotic delusions, and disrupted circadian rhythms, the underlying etiology is multifactorial and incompletely understood[125]. The initial and perhaps most common mechanism suggested for depression is the monoamine hypothesis, which posits that an imbalance of monoamine neurotransmitters, including serotonin, norepinephrine, and dopamine, leads to the development of depression[127,128]. Thus, commonly prescribed antidepressants include monoamine oxidase inhibitors and selective serotonin reuptake inhibitors. More recent investigation into the pathophysiology of depression, however, has implicated abnormal functioning of the hypothalamic-pituitary-adrenal (HPA) axis, deficiency of neurotrophic factors, such as brain-derived neurotrophic factor, neuroinflammation, and chronic stress, leading to decreased neurogenesis, suppressed cell proliferation, and an imbalance between antioxidant defense and free radical production within the cell[127,129,130].

To elucidate the contributions of these molecular mechanisms and to identify key contributing molecules in depression pathology, mouse models bred to induce depressive-like behavior are used. The chronic unpredictable stress (CUS) model is one of the most commonly employed and involves exposure of the rodent to a battery of mild, variable stressors daily for 4 – 12 weeks, ultimately leading to depressive-like behavior including reduced sucrose preference, and increased immobility on the forced swim test and learned helplessness test[131,132]. The social isolation, chronic social defeat stress, and learned helplessness models are also frequently used and involve exposure to psychosocial and physical stressors, respectively[132]. Mice with impaired glucocorticoid functioning to induce an overactive HPA axis, such as glucocorticoid receptor knockout mice, also exhibit depressive symptoms[133].

Inflammation and oxidative stress have emerged as central mediators in psychopathology. Specifically, increased serum levels of IL-1β and TNF-α are positively correlated with the severity of depression in MDD patients, while a meta-analysis of clinical trials demonstrated that anti-inflammatory drugs concurrently confer antidepressant effects[134,135]. Further, markers of oxidative stress, including 8-hydroxy-2′-deoxyguanosine and NADPH oxidases, a family of ROS-generating enzymes, are significantly

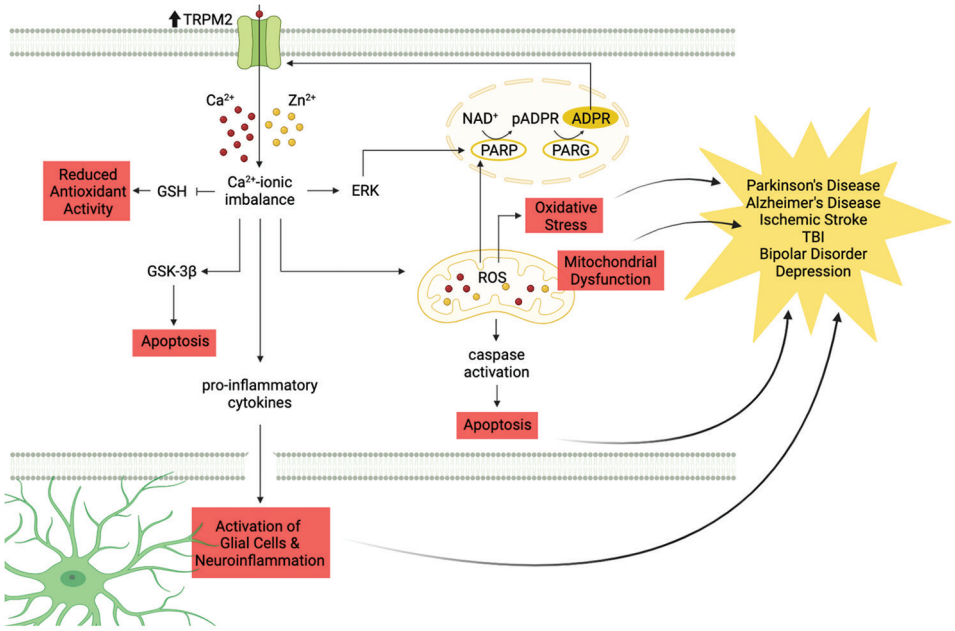

Figure 2. Interrelated molecular mechanisms by which TRPM2 activation induces neurological injury or disease. Activation of TRPM2 in the cell membrane or increased levels of TRPM2, both in response to oxidative stress, cause the excessive influx of ions such as Ca^{2+} or Zn^{2+} into the cell. The resultant Ca^{2+}-ionic imbalance induces a variety of intracellular processes, including augmented ROS production, which facilitates the production of ADPR, exacerbating TRPM2-mediated Ca^{2+} influx. This leads to the activation of key signaling molecules which ultimately induce apoptosis, activate glial cells and neuroinflammation, cause mitochondrial dysfunction, and reduce antioxidant activity. These pathological mechanisms have been highly implicated in the etiology of neurological disorders including PD, AD, ischemic stroke, TBI, BP, and depression.

upregulated in the brains of socially isolated mouse models of depression[136,137]. Interestingly, the serotonin and norepinephrine reuptake inhibitor, duloxetine, reduces Ca^{2+} flux and inhibits oxidative stress and apoptosis. This indicates an important role for the Ca^{2+}-permeable TRPM2 channel in depression, particularly given its role in neuroinflammation and mediating neuronal death. Duloxetine increases antioxidant glutathione levels and reduces H_2O_2-induced TRPM2 calcium transients, which is associated with a reduction in lipid peroxidation and ROS levels[101]. Furthermore, in a CUS model of depression, CUS TRPM2$^{-/-}$ mice had reduced lipid peroxidation and PARP levels in the hippocampus compared with CUS TRPM2$^{+/+}$ mice[100]. TRPM2$^{-/-}$ mice were also protected against CUS-induced depressive-related behavioral deficits compared with CUS TRPM2$^{+/+}$ mice. Cultured TRPM2$^{-/-}$ hippocampal neurons also have reduced H_2O_2-induced ROS accumulation and cyclin-dependent kinase 5 (Cdk5) hyperactivation. Aberrant hyperactivation of Cdk5 is typically observed in depression and results in antioxidant enzyme inhibition and ROS accumulation[100]. This study also indicates that in depression, TRPM2 signaling is associated with ROS-induced Cdk5 activity, which induces a feed-forward signaling response, exacerbating oxidative stress within the cell and ultimately leading to neuronal injury and functional deficits. Finally, TRPM2 at the mRNA and protein levels is upregulated in the hippocampus of CUS-induced depressed mice, which is consistent with the upregulation of *Trpm2* mRNA in the post-mortem hippocampal tissue of MDD patients compared with healthy controls[100]. Therefore, TRPM2 is highly implicated in the pathology of depression at both the cellular and functional levels, warranting further investigation into its therapeutic potential for the treatment of MDD.

Table 1 presents a summary of the studies discussed in Section 4.

5. Summary and conclusions

This review discusses the mechanisms behind the contribution of TRPM2 to neurodegenerative diseases, injuries, and psychiatric disorders. As a Ca^{2+}-permeable ion channel that is also responsive to other ions such as zinc, its activation in response to ROS and tissue injury alters intracellular ion homeostasis. This activates pathways, leading to apoptosis, release of inflammatory mediators, and mitochondrial production of ROS (Figure 2). Consequently, although the various neurological diseases discussed here are different (i.e., PD vs. AD), some of the underlying mechanisms of cell death or dysfunction are

similar, with ADPR acting on the NUDT9-H domain of TRPM2 and initiating Ca^{2+} influx into the cytosol[10]. Furthermore, because TRPM2 is highly expressed in the brain in multiple cell types, inhibition of TRPM2 has the potential to modulate multiple pathways contributing to disease. An overview of the mechanisms by which TRPM2 activation induces brain injury or disease is illustrated in Figure 2.

As noted, our own findings concerning neonatal hypoxic-ischemic injury demonstrate that TRPM2 inhibition reduces infarct volume and microglial activation[11,12]. Inhibitors of TRPM2 exist, such as flufenamic acid, 2-APB, and clotrimazole; however, they are not specific to TRPM2[16,40]. For example, 2-APB activates TRPV1 – 3 in addition to TRPM2[138,139]. Specific TRPM2 inhibitors have been synthesized, as recently demonstrated by Luo *et al.* who generated two ADPR analogues (7i and 8a) that specifically inhibit the TRPM2 channel[138]. Zn^{2+} recruits DRP1 to mitochondria and induces mitochondrial fission and dysfunction[58,60,140]; therefore, zinc chelators are a possible option for preventing Ca^{2+}-mediated Zn^{2+} release by lysosomes[141]. Antioxidant therapy has also been proposed to treat neurodegenerative diseases such as AD[142]. Surprisingly, in Chinese hamster ovary cell cultures, antioxidants do not reduce TRPM2 cation current upon exposure to H_2O_2, indicating that there are mechanisms in addition to TRPM2 activation by which ROS effects cell function in neurodegenerative disorders[143].

Research on TRPM2 will continue to examine the mechanisms discussed in this review and to develop TRPM2-specific inhibitors that will lead to new treatments for a variety of diseases.

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Conflict of interest

The authors have no competing interest to declare.

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