Review Article
Roles of TRP Channels in Neurological Diseases

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Transient receptor potential (TRP) channels are a superfamily of cation channels that play critical roles in the responses to diverse environmental changes and stimuli. Mutations in TRP were originally related to an abnormal behavioral phenotype in response to light and characterized by an electroretinogram phenotype in Drosophila. The mutant strain of D. melanogaster showed a transient receptor potential to constant light rather than the continuous response recorded in the wild type, which leads to the origin of the name TRP [1]. The TRP channel superfamily is conserved in yeast, invertebrates, and vertebrates. On the basis of sequence homology, this superfamily can be subdivided into 7 subfamilies including TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), TRPA (ankyrin), and TRPN (NOMPC-like); TRPN exists only in invertebrates and fish, but not in mammals. TRP channels are widely expressed in multiple human organs, such as the brain, heart, kidneys, and lungs. TRP channels largely demonstrate permeability to both monovalent and divalent cations, as well as trace metal ions. Interestingly, they can be activated by a variety of gating mechanisms, including ligand binding, voltage and changes in temperature, and covalent modifications of nucleophilic residues [2]. Given the widespread distribution and complex cellular sensors of TRP channels, it is not surprising that TRP channels participate in the pathogenesis of diseases affecting different organ systems. In this review, we summarize the current knowledge on the pathological significance of TRP channels in the brain and give an outlook on potentially promising therapeutics targeting TRP.

1. Introduction

The transient receptor potential (TRP) channels are a superfamily of cation channels that play critical roles in the responses to diverse environmental changes and stimuli. Mutations in TRP were originally related to an abnormal behavioral phenotype in response to light and characterized by an electroretinogram phenotype in Drosophila. The mutant strain of D. melanogaster showed a transient receptor potential to constant light rather than the continuous response recorded in the wild type, which leads to the origin of the name TRP [1]. The TRP channel superfamily is conserved in yeast, invertebrates, and vertebrates. On the basis of sequence homology, this superfamily can be subdivided into 7 subfamilies including TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), TRPA (ankyrin), and TRPN (NOMPC-like); TRPN exists only in invertebrates and fish, but not in mammals. TRP channels are widely expressed in multiple human organs, such as the brain, heart, kidneys, and lungs. TRP channels largely demonstrate permeability to both monovalent and divalent cations, as well as trace metal ions. Interestingly, they can be activated by a variety of gating mechanisms, including ligand binding, voltage and changes in temperature, and covalent modifications of nucleophilic residues [2]. Given the widespread distribution and complex cellular sensors of TRP channels, it is not surprising that TRP channels participate in the pathogenesis of diseases affecting different organ systems. In this review, we summarize the current knowledge on the pathological significance of TRP channels in the brain and give an outlook on potentially promising therapeutics targeting TRP.

2. Structure, Expression, and Function of TRP Channels in the Brain

2.1. Structure of TRP Channels. TRPs form functional channels as either homotetramers or heterotetramers within the confines of the same or different subfamilies [3]. A typical TRP protein shares a common topology of six transmembrane helical segments (S1–S6), an intracellular amino (N), and a carboxy (C) terminal extension (Figure 1). The transmembrane domain can be divided in two building blocks: the voltage-sensing block formed by S1–S4 and the pore formed by S5 and S6. The pore forms an ion-conducting hole, which is hypothesized to shape the selectivity filter in TRP channels. The sensor block perceives the stimuli, transmits information to the gate, and causes a conformational
change [4]. The transmembrane domain shares greater homology within a particular subfamily, and amino acid sequences of the pore block are the most strongly conserved across the TRP channels, which highlights the significance of the core channel structure. Intracellular N- and C-termini have less homology between subfamilies, and they are variable in length and sequence with a variety of domains and motifs. These diverse cytosolic domains play a role in channel assembly, activation, and regulation, which is one of the most fascinating structural aspects of TRP channels [5].

2.2. Expression and Functions of TRP Channels in the Brain. It is widely thought that TRPs play a significant role in the brain, considering their widespread expression and physiological functions. The activation of TRP channels by various stimuli and ligand binding contributes to changes in several monovalent and divalent cations, especially calcium. These contributions are important for several physiological functions, including sensitivity to stimuli (i.e., pheromone signaling cascades, thermosensation, and mechanosensation), ion homeostasis (i.e., calcium and magnesium reabsorption and osmoregulation), and motility (i.e., muscle contraction and vasomotor control) [2].

2.2.1. TRP Channels in Neurons. The TRPC subfamily in mammals is the closest homolog to the Drosophila TRP. There are six mammalian TRPC proteins (TRPC1–6) widely distributed in the brain throughout embryogenesis to adulthood [6]. Extensive evidence has been provided for a critical role of TRPC1 in store-operated Ca\(^{2+}\) entry by interacting with stromal interaction molecule and Orai [7]. TRPC1 is involved in glutamate release, growth cone turning, and neurite outgrowth. TRPC2 is a pseudogene in human. As it is abundantly expressed in Purkinje cells, TRPC3 mediates metabotropic glutamate receptor- (mGluR-) dependent synaptic transmission [8]. TRPC4 and TRPC5 have an inhibitory role in neurate growth and morphogenesis and are thereby important for proper and balanced development of the brain [9, 10]. Together with TRPC3, TRPC6 plays an essential role in brain-derived neurotrophic factor- (BDNF-) induced axon guidance and neuron survival via Ca\(^{2+}\) signaling activation [11]. Overexpression of TRPC6 increases the number of spines in hippocampal neurons, leading to better spatial learning and memory. Thus, TRPC6 plays a role in synaptic and behavioral plasticity [12].

With widespread distribution in neurons throughout the brain, TRPV1 plays an important and versatile “nonsensory role” in neuronal activity and synaptic plasticity [13]. In the hippocampus, long-term depression (LTD) at excitatory synapses is induced by TRPV1 activation, and long-term potentiation (LTP) is reduced in Trpv1 and Trpv3 knockout mice [14, 15]. Furthermore, hippocampal endogenous cannabinoids such as the TRPV1 ligand anandamide could even reverse cognitive and learning impairments caused by chronic stress [16]. Moreover, this influence on synaptic plasticity is also found in the nucleus accumbens and dentate gyrus [17, 18]. TRPV2 expression is detected in the developing sensory and motor neurons, where it regulates axon outgrowth after activation by membrane stretch [19]. Additionally, TRPV2 is reportedly expressed in cultured hippocampal neurons and colocalizes with TRPV1 in a rat cortex, which may increase the functional diversity of this receptor family [20]. The thermosensor protein TRPV4 is activated at the physiological temperature in hippocampal neurons and regulates neuronal excitability and behaviors in vitro [21]. Unlike the other TRPs, TRPV5 and TRPV6 are the only highly selective Ca\(^{2+}\) channels and are rarely expressed in the brain.
TRPM2, formerly known as LTRPC2 or TRPC7, is a redox-sensitive TRP channel and is expressed in neurons of the hippocampus and substantia nigra [22, 23]. In particular, it is involved in the response to oxidative stress mediated by reactive oxygen species (ROS) and is associated with spontaneous firing rate, burst activity, and neuronal death [24, 25]. In addition, Trpm2 knockout mice show active axonal growth and impaired LTD, implicating a role in neuronal development and synaptic plasticity [22]. TRPM3 channel, which is abundantly expressed in hippocampus and cerebellar neurons, is activated by pregnenolone sulfate to modulate glutamatergic transmission [26]. TRPM4 and TRPM5 are Ca2+-impermeable monovalent channels, but they can be activated by intracellular Ca2+ to regulate inspiratory burst activity in the inspiratory neurons of the neonatal murine brainstem [27]. Primarily expressed in the small intestine and kidney, TRPM6 function in the nervous system is unclear now. TRPM7 is detected in the hippocampus, where it has a role in neuroprotection [28].

The function of TRPML in neurons is not completely known. TRPML1 is widely localized in the lysosome as the principle Ca2+ channel, where TRPML2-3 are involved in TRPML1 distribution and trafficking [29]. Disruption of the TRPML1 channel leads to a neurodegenerative disorder, which can be rescued by expression of TRMPL in neurons, glia, or hematopoietic cells [30].

The TRPA subfamily consists of only one mammalian member, TRPA1, which is expressed in the dorsal root, trigeminal ganglion neurons, and hair cells. It is known as a sensor for environmental stimuli and endogenous noxious substances.

2.2.2. TRP Channels in Glial Cells. TRP expression has been detected in glial cells, though most of their functions remain unelucidated and under investigation.

In astrocytes, which are the most abundant cells in the brain, several isoforms of TRP are expressed. TRPC1-6 have been detected in cultured astrocytes with quantitative differences [31]. In fact, knockdown of the TRPC6 gene markedly reduced receptor-operated Ca2+ entry [32]. Besides, TRPC1 and TRPC3 are likely involved in store-operated Ca2+ entry, suggesting an important role for these proteins in the activation of excitatory astrocytes [33]. TRPV1 is localized in the plasma membrane of astrocytes to detect bloodborne molecules in the sensory circumventricular organs of adult mouse brains [34]. TRPV2 expression is detected in plasma membrane and activated by very high temperature and endogenous lysophosphatidylcholine, the latter of which suggests that astrocytic TRPV2 might regulate neuronal activities in response to lipid metabolism [35]. TRPV4 activation in astrocytes is related to control of cell volume alongside aquaporin-4, amplification of neurovascular coupling responses via Ca2+-induced Ca2+ release, and regulation of neuronal excitability by release of gliotransmitters [36-38]. TRPM2 could be activated and upregulated by oxidative stress to induce a neuroinflammatory response [39]. Silencing TRPM7 decreases intracellular basal Mg2+ concentration without affecting Ca2+ concentration, leading to impaired proliferation and migration of astrocytes [40].

In microglia cells, the resident immune cells of the brain, only a few studies have been conducted about TRPs. TRPC3 in activated microglia contributes to the maintenance of BDNF-induced sustained intracellular Ca2+ elevation to suppress NO production [41]. Additionally, TRPV1 activation contributes to microglial migration and cell death via Ca2+-mediated mitochondrial damage [42, 43]. Furthermore, downregulation of TRPV1 and TRPV2 induced by cannabidiol enhances microglial phagocytosis [44]. Stimulation of TRPV4 suppresses abnormal activation of microglia by attenuating the driving force for extracellular Ca2+ [45]. TRPM2-mediated Ca2+ signaling in microglia contributes to neuronal degeneration via NO, as well as microglial migration and invasion during anti-inflammatory states [46, 47].

Single-cell transcriptomic data suggests that TRPC, TRPV and TRPM channels can be found in mouse oligodendrocyte lineages, though their functions, to date, largely remain unknown [48]. Among them, TRPC1-mediated Ca2+ influx is known to be involved in the proliferation of oligodendrocyte precursor cells by the golli products of the myelin basic protein gene [49].

In ependymal cells, TRPV1, TRPV3, and TRPA1 are found in the developing rat brain. TRP channel expression is found to be higher in choroid plexus than the ventricular lining ependyma. At the 19th day of gestation, all the expression is found to be decreased, which suggests different functions of regulating cerebral spinal fluid during development. Changes in TRP expression in gestation coincide with a period of ventricular shrinkage, which implies a possible role in the need to make space for the growing brain structure [50].

2.2.3. TRP Channels in the Cerebral Blood Vessels. It has been reported that many TRP channels play functional roles in the cerebral blood vessels, including vascular endothelium and smooth muscle. TRPV3 is expressed in the endothelium of cerebral arteries, and its activation elicits vasodilation with a concurrent decrease of intracellular Ca2+ in arterial myocytes and smooth muscle hyperpolarization [51]. TRPA1 is specifically localized to the endothelial cell membrane projections proximal to smooth muscle layer. TRPA1-mediated Ca2+ influx elicits vasodilation involving endothelial cell Ca2+-activated K+ channels, thus inwardly rectifying K+ channels in arterial myocytes [52]. It is reported that TRPV4 and TRPM4 are detected differently in endothelial cells and smooth muscle cells, thus contributing to myogenic vasoconstriction of cerebral arteries via a Ca2+ influx induced by various factors [53, 54].

3. Roles of TRP Channels in Neurological Diseases

Considering the widespread expression and diverse functions of TRP channels in the brain, it is conceivable that dysfunction of these channels can have a profound effect on various pathological events of neurological and psychiatric disorders in animals (Table 1) and humans (Table 2) and their pharmacological interventions targeting TRP channels for corresponding diseases (Table 3).
| TRP channels | Evidence of expression | Proposed functions | Related disorders | References |
|-------------|------------------------|--------------------|------------------|------------|
| TRPC1       | Dog brain and basilar artery | Vasospasm induced by endothelin-1 after SAH | SAH | [80] |
|             | Rat cortical astrocytes | Activation and perihematol accumulation of astrocytes; contribution to brain damage after ICH | Hemorrhagic stroke | [76, 77] |
| TRPC3       | Rat immature and dysplastic cortex; rat pyramidal cells and dentate granule cells | Low Ca⁺ and low Mg⁺-induced depolarization and epileptiform activity; contribution to neuronal death and epileptogenic insults after SE | Epilepsy | [100, 101] |
|             | Rat striatal and hippocampal neurons | Upregulated expression with unknown function after ischemia | Ischemic stroke | [59] |
| TRPC4       | Dog brain and basilar artery | Vasospasm induced by endothelin-1 after SAH | SAH | [80] |
| TRPC6       | Rat/mouse cortical neurons | Protection against neuronal death after ischemia | Ischemic stroke | [55–58] |
|             | Rat pyramidal cells and dentate granule cells | Inhibition of seizure susceptibility and neuronal vulnerability | Epilepsy | [101] |
| TRPV1       | Mouse brain | Reduced neurological and motor deficits and infarct volume in Trpv1 knockout mice after ischemia | Ischemic stroke | [70] |
|             | Rat substantia nigra pars compacta astrocytes | Rescue of the active degeneration of dopamine neurons via endogenous production of ciliary neurotrophic factor | PD | [96, 97] |
|             | Mouse hippocampal glia and neurons | Contribution to epileptiform activity and electrographic seizures | Epilepsy | [102, 103] |
| TRPV4       | Rat hippocampal astrocytes and neurons | Schizophrenia-like changes in the brain via intrinsic sensory deprivation induced by a TRPV1 activator | Schizophrenia | [107] |
|             | Rat brain | Contribution to astrogliosis and neuronal death after ischemia | Ischemic stroke | [72–75] |
| TRPM2       | Rat microglia; mouse microglia and cortical neurons | Activation of microglia and the consequent injury and inflammation after ischemia; contribution to neuron and brain damage specifically in male after ischemia | Ischemic stroke | [61, 62] |
|             | Rat cortex and hippocampus | Upregulated expression with unknown function after TBI; possible involvement in TBI-induced oxidative stress, apoptosis, and calcium entry | TBI | [81, 82] |
|             | Mouse brain | Contribution to Aβ- and H₂O₂-induced neuronal toxicity and cell death | AD | [90] |
|             | Rat nigral dopaminergic neurons | Changes in neuronal excitability and calcium homeostasis | PD | [94, 95] |
|             | Mouse hippocampal neurons and ventricle cells | Contribution to the expression of JME phenotypes by mediating cell death | Epilepsy | [106] |
|             | Mouse | BD-like changes in behavior and mood in TRPM2-deficient mice | BD | [109] |
3.1. Stroke

3.1.1. Ischemic Stroke. In ischemic stroke, which is caused by the blockage of a cerebral blood vessel, excitotoxicity induced by Ca\(^{2+}\) overload is considered to be the most important mechanism of cell death. There is some accumulating evidence that TRPC6 expressed in neurons can protect from excitotoxicity after ischemia by suppressing intracellular Ca\(^{2+}\) elevation induced by N-methyl-D-aspartate (NMDA). It has been reported that downregulation or inhibition of TRPC6 during ischemia contributes to brain damage in rodent models, and upregulation or activation by hyperforin and resveratrol attenuates this damage [55, 56]. For example, in a transient model of middle cerebral artery occlusion (tMCAO), TRPC6 protein levels in neurons are found to be greatly reduced in ischemia as a result of NMDA receptor-dependent calpain proteolysis. This downregulation precedes and is responsible for ischemic neuronal cell death. Inhibiting TRPC6 degradation prevents ischemic brain damage, with a reduction in infarct volume at 24 hours after reperfusion, an improvement in behavior performance, and a lower mortality within 35 days after ischemia [57]. Thus, TRPC6 expression in neurons plays a beneficial role for neuronal survival and can be a potential therapeutic target after ischemic stroke. Additionally, an increase of TRPC4 protein is found in the striatum and hippocampus from 12 hours to 3 days after tMCAO operation, which suggests a role for this protein in acute and delayed neuronal injury after focal ischemia [59]. However, the role of TRPC4 in a positive or negative manner is still unknown after ischemia.

Studies have shown that TRPM2 and TRPM7 gating lies downstream of several signaling pathways in response to oxidative stress induced by cerebral ischemia and reperfusion injury, which is considered to be an important event leading to neuronal death. TRPM2 is considered a connection point that mediates Ca\(^{2+}\) overload in response to ROS. This sensitivity to ROS is attributable to the production of nicotinamide adenine dinucleotide and its metabolites such as adenosine diphosphoribose (ADPR) [60]. The inhibitors and RNA interference targeting TRPM2 efficiently suppress Ca\(^{2+}\) influx and ROS-induced neuronal death in cultured neurons or HEK cells. Using an in vivo stroke model, Trpm2

Table 1: Continued.

| TRP channels | Evidence of expression | Proposed functions | Related disorders | References |
|--------------|------------------------|--------------------|-------------------|------------|
| TRPM4        | Rat (ectopic expression in capillaries) | Upregulated expression in vascular endothelium to contribute to capillary death after ischemia | Ischemic stroke | [69]       |
|              |                        | Disruption of capillary structural integrity and initiation of secondary hemorrhage after SCI | SCI | [83]       |
| TRPM7        | Mouse brain            | Contribution to excitotoxic cell death after ischemia | Ischemic stroke | [67]       |
| TRPA subfamily | TRAP1                     | Mouse brain                     | Impediment to AD progression | AD | [93]       |

Table 2: Evidence of proposed functions of TRPs and possible relationships to neurological disorders in humans.

| TRP channels | Evidence of expression | Proposed functions | Related disorders | References |
|--------------|------------------------|--------------------|-------------------|------------|
| TRPC1        | Human glioma cell lines | Impaired cytokinesis and facilitated glioma cell migration | Malignant gliomas | [85, 86] |
| TRPC3        | Human cerebral vascular tissue after hypertensive ICH | Decreased expression from hypertensive patients after intracerebral hemorrhage with unknown function | Hypertensive ICH | [79] |
| TRPC1, 3, 5, 6 | Human glioma cell lines | Impaired cytokinesis to become nuclear atypia and enlarged cells induced by TRPC inhibition | Malignant gliomas | [85] |
| TRPV2        | Human glioma cell lines | Increased chemotherapeutic drug uptake and cytotoxic activity | Glioblastoma multiforme | [87] |
| TRPML2       | Human gliomas of different levels and high-grade glioma cell lines of astrocytic origin | Increased survival and proliferation in glioma cell lines | Glioma | [88] |
knockout mice exhibit smaller infarct volume at 48 hours after tMCAO operation when compared with wild-type mice. In hippocampal slices, sublethal concentrations of H2O2 increase baseline synaptic excitability in Trpm2 knockout but not wild-type neurons. This difference depends on the changed expression ratio of NMDA receptor subunits induced by the absence of TRPM2, which may then selectively upregulate survival signals and provide neuroprotection against ischemic cell death [61]. Interestingly, a TRPM2 inhibitor, tat-M2NX, provides protection from ischemic stroke with a smaller infarct volume in aged male mice but not female, suggesting a sexually dimorphic mechanism [62].

In addition to being expressed in neurons, several studies have highlighted the link between consequent injury and TRPM2 activation in nonneuron cells. The upregulation of TRPM2 has been observed to correlate with microglial activation from 1 to 4 weeks in a tMCAO stroke model, and the functional expression of a TRPM2-like conductance is confirmed in cultured microglia. Patch-clamp recordings from microglia demonstrate that increased intracellular ADPR or extracellular H2O2 induces an inward current, accompanying with activation of TRPM2 [63]. Besides, the TRPM2-mediated Ca2+ influx induces the production of proinflammatory chemokines in monocytes to aggravate inflammation [64]. Consistent with these findings, TRPM2 deficiency attenuates migratory capacities of neutrophils and macrophages into an ischemic brain thereby secondarily perpetuating brain injury [65]. Taken together, the above results indicate that TRPM2-mediated Ca2+ influx may be activated by intracellular messengers such as ADPR in response to oxidative stress after stroke, which may result in neuronal death and detrimental inflammation.

TRPM7 and TRPM2 channels share similar property of modulation by oxidative stress. RNA interference targeting TRPM7 also inhibits TRPM2 mRNA in primary cortical neurons, suggesting that the expression of the two proteins is interdependent [66]. TRPM7 activity is greatly enhanced after oxygen glucose deprivation, and TRPM7 inhibition blocks TRPM7 currents, anoxic Ca2+ uptake, ROS production, and anoxic death. This process is a pH-dependent channel potentiation resulting from an acidic environment due to ischemic stroke [67]. TRPM7 inhibitor carvacrol protects the brain from neonatal hypoxic-ischemic injury by reducing infarct volume, inhibiting apoptosis, and improving behavioral outcomes [68].

| TRP channels | Ion permeability | General physiological functions | Pharmacological interventions | References |
| ------------ | ---------------- | ------------------------------- | ----------------------------- | ---------- |
| TRPC subfamily | TRPC3 Nonselective cation | Neuronal differentiation, growth cone guidance, vasomotor | Pyr3 for stroke, epilepsy | [77, 100, 101] |
| TRPC6 Nonselective cation | Axon guidance, vasomotor, smooth muscle, mechanosensor | Hyperforin for stroke, epilepsy | Resveratrol for stroke | [55–58, 89, 101] |
| TRPV subfamily | TRPV1 Ca2+ permeable | Sensing spicy (hot) peppers, pain sensation, noxious temperature sensing | Dihydrocapsaicin for stroke | [70, 71, 97–99, 102, 103, 107] |
| TRPV2 Weakly Ca2+ selective | Thermal pain sensing, mechanosensor | Capsaicin for PD, schizophrenia | Cannabidiol for glioblastoma, epilepsy | [87, 105] |
| TRPV4 Ca2+ permeable | Osmosensing, warm sensing, nociception, pressure sensing | HC-067047 for stroke, AD, epilepsy | | [73, 78] |
| TRPM subfamily | TRPM2 Nonselective cation | Oxidant stress sensing | Tat-M2NX for stroke | [62, 90, 91, 95] |
| | | | 2-Aminoethoxydiphenyl borate for AD | |
| | | | N-(p-Amyl)anthranilic acid for AD, PD | |
| | | | Flufenamic acid for PD | |
| | TRPM4 Ca2+ impermeable | Mechanosensor | 9-Phenanthrol for stroke | [69] |
| | TRPM7 Mg2+ permeable | Mg2+ homeostasis, entry pathway for trace metals | Carvacrol for stroke | [68] |
| TRPA subfamily | TRPA1 Nonselective cation | Pungent painful stimuli sensing, noxious cold sensing, mechanosensor | HC-030031 for AD | [93] |
Moreover, TRPM4 is upregulated in vascular endothelium within the penumbra region after tMCAO. Blocking TRPM4 with 9-phenanthrol promotes tube formation on matrigel and improves vascular integrity after oxygen/glucose deprivation in vitro [69]. TRPVs play a complex role in cerebral ischemia. Trpv1 knockout mice show a lower neurological and motor deficits and infarct volume than wild-type mice in a tMCAO model. Furthermore, intracerebroventricular injection of capsaicin, a TRPV1 antagonist, leads to a reduction in infarct size and behavior deficits [70]. However, another study shows a contradictory role of TRPV1 in stroke. Hypothermia via a TRPV1 agonist, dihydrocapsaicin, provides neuroprotection following focal cerebral ischemia [71]. These findings indicate a promising but intricate target for ischemic stroke.

Besides, involvement of TRPV4 is found in both neuronal and glial pathophysiology associated with ischemia. In a hypoxic/ischemic model induced by a bilateral carotid occlusion combined with hypoxic conditions, TRPV4 expression was decreased in hippocampal pyramidal neurons with ongoing neuronal cell death, as well as an increase in reactive astrocytes with progression of reactive gliosis, suggesting a role for TRPV4 in neuronal loss and reactive gliosis following ischemic insult [72]. TRPV4 antagonist reduced the infarct size while its activation had an opposite effect in the tMCAO model [73]. Furthermore, there is increasing evidence to show that TRPV4 activation in astrocytes during ischemia results in a calcium influx into astrocytes and extracellular accumulation of glutamate, which causes Ca\(^{2+}\) overload of neurons and can trigger neuronal death [74, 75].

### 3.1.2. Hemorrhagic Stroke (Intracerebral Hemorrhage and Subarachnoid Hemorrhage)

In hemorrhagic stroke caused by the rupture of a cerebral blood vessel, the blood-derived factors can extravasate into the brain parenchyma to participate in the pathophysiology of brain injury. It has been reported that TRPC3 can be dynamically upregulated by thrombin in rat primary cortical astrocytes. Additionally, it has been shown that this process contributes to the pathological activation of astrocytes through a feedforward upregulation of its own expression [76]. Consistently, in an intracerebral hemorrhage model induced by an intracerebral infusion of collagenase or autologous blood, TRPC3 inhibition by Pyr3 is found to reduce the perihematomal accumulation of astrocytes and ameliorate brain injury [77]. The TRPV4 antagonist, HC-067047, dihydrocapsaicin, provides neuroprotection following focal cerebral ischemia [71]. These findings indicate a promising but intricate target for ischemic stroke.

By contrast, decreased expression of TRPC3, TRPC5, and TRPM6 is found in cerebral vascular tissue from patients after hypertensive intracerebral hemorrhage through unknown mechanisms. Among them, TRPC3 mRNA correlates well with expression of hypoxia inducible factor-1α, suggesting its association with hypertension and hypoxic conditions [79]. Of note, after subarachnoid hemorrhage, TRPC1 and TRPC4 proteins are upregulated in canine smooth muscle, and the increased Ca\(^{2+}\) influx through TRPC channels mediates endothelin-1-evoked vasospasm [80]. Even after evaluating complex pathogenic functions, the role of TRP channels in hemorrhage still remains largely unknown.

#### 3.2. Traumatic Brain Injury and Spinal Cord Injury

Traumatic brain injury (TBI) and spinal cord injury (SCI) can cause direct, immediate mechanical damage to tissue and indirect, delayed secondary damage that may continue from days to weeks. Recent studies have implicated TRPM channels in the pathophysiological processes of TBI and SCI. In an impact-acceleration model of diffuse TBI in adult male rats, TRPM2 mRNA and protein expression significantly increased in the cerebral cortex and hippocampus, susceptible regions to significant damage, following TBI, suggesting a role for TRPM2 in TBI [81]. It is also reported that TRPM2 may participate in TBI by regulating oxidative stress, apoptosis, and Ca\(^{2+}\) entry in a rat hippocampus by melatonin [82]. Additionally, after SCI, TRPM4 mRNA and protein were found to be upregulated in the capillaries and contribute to their fragmentation and formation of petechial hemorrhages [83].

In addition to Ca\(^{2+}\) overload, depletion of intracellular Mg\(^{2+}\) is associated with poor neurological outcomes after TBI. Specifically, TRPM6 and TRPM7 have been considered to potentially play a role in Mg\(^{2+}\) homeostasis as a result of neuronal injury, which is a topic that requires further study [84].

#### 3.3. Brain Tumors

Glioma accounts for the majority of primary malignant tumors in the brain and is associated with poor prognosis. Recent studies have described the involvement of TRPCs and TRPVs in the regulation of malignant cell growth and progression. Consistent expression of TRPC1, TRPC3, TRPC5, and TRPC6 has been found in glioma cell lines and acute patient-derived tissues, which gives rise to small, nonvoltage-dependent cation currents and contributes to the resting conductance of glioma cells. Chronic inhibition of TRPCs by SKF96365 inhibits cytokinesis and results in multinucleated and enlarged cells that are histopathological hallmarks for glioblastoma multiforme, suggesting that a defect in TRPC channels may contribute to cellular abnormalities in this tumor type [85]. Similar morphological changes have been associated with high invasiveness observed in human glioma cells, which is induced by Ca\(^{2+}\) entry via TRPC1 and activated Cl\(-\) currents [86]. Moreover, glioma cell proliferation is inhibited by cannabidiol-induced TRPV2 activation, resulting from TRPV2-dependent Ca\(^{2+}\) influx and increase in the uptake of cancer chemotherapeutic drug, which, in parallel, potentiates cytotoxic activity in human glioma cells [87].

Human TRPML2 is found both in normal astrocytes and in neural stem/progenitor cells, as well as in glioma tissues of different levels and high-grade glioma cell lines of astrocytic origin. Knockdown of TRPML2 inhibits viability and proliferation and triggers apoptosis of glioma cell lines [88]. Therefore, TRP channels are potential and promising targets that interfere with relentless glioma growth and invasion.

#### 3.4. Neurodegenerative Diseases

##### 3.4.1. Alzheimer’s Disease

Amyloid fragments, free radicals, and calcium imbalance are thought to be the pathological
hallmarks of Alzheimer’s disease (AD). Presenilin (PS) proteins, which are integral membrane proteins, are mainly located in the endoplasmic reticulum of neurons. Mutations in the PS genes alter proteolytic processing of the amyloid precursor protein (APP) by a gain-of-function mechanism, which is associated with the development of early-onset AD. Recently, the AD-linked PS2 mutants have been shown to influence TRPC6-enhanced Ca\(^{2+}\) entry into HEK293 cells. Transient coexpression of a loss-of-function PS2 mutant and TRPC6 enhanced angiotensin II- and 1-oleoyl-2-acetyl-sn-glycerol- (OAG-) induced Ca\(^{2+}\) entry [89]. Both A\(\beta\) and H\(_2\)O\(_2\) induce death in cultured striatal cells with endogenous TRPM2, while inhibition of TRPM2 suppresses A\(\beta\)- and H\(_2\)O\(_2\)-induced increase in intracellular Ca\(^{2+}\) and cell death [90]. Another study shows that A\(\beta\)-induced TRPM2 currents and Ca\(^{2+}\) levels can be reduced by TRPM2 antagonism [91]. Additionally, a lack of TRPM2 rescues age-dependent spatial memory deficits in AD [92]. Therefore, these results reveal that abnormal TRPM2 activation may contribute to A\(\beta\)-related neurotoxicity and memory impairment in AD.

In APP/PS1 transgenic mice, another mouse model of AD, knockout of TRPA1 impedes AD progression, as evidenced by improved behavioral function, decreased A\(\beta\) plaque deposition, and proinflammatory cytokine production. TRPA1 antagonism induced by HC-030031 reduces astrocyte hyperactivity that is linked with A\(\beta\) production, A\(\beta\)-stimulated inflammation and astrogliosis, and CA1 neuron hyperactivity [93].

3.4.2. Parkinson’s Disease. Parkinson’s disease (PD) is a neurodegenerative disorder that is strongly associated with the degeneration and death of dopaminergic neurons located in the substantia nigra. Using acute brain slices, functional expression of TRPM2 channels has been found in rat nigra dopaminergic neurons. Importantly, in a PD model induced by rotenone, TRPM2 activity has been observed in dopaminergic neurons, and this activation may be mediated by rotenone-induced ROS production of mitochondrion [94]. Pharmacological inhibition of TRPM2 shows an increased protection by preventing PD-linked Ca\(^{2+}\) increase and inhibited apoptosis [95].

Conversely, it has been suggested that astrocytic TRPV1 may be neuroprotective for PD. In rat models of PD, TRPV1 activity in astrocytes prevents the active degeneration of dopamine neurons and leads to behavioral recovery via endogenous production of ciliary neurotrophic factor. A similar increase is observed in human post mortem substantia nigra from PD patients by western blot and immunohistochemical analysis, implying a novel therapeutic target for PD [96]. TRPV1 activation by capsaicin can suppress spontaneous locomotion in normal rats and modulate some locomotion in reserpine-treated PD rats [97], while this suppression can be reversed by TRPV1 antagonist [98, 99].

3.5. Epilepsy. Epilepsy is a chronic, recurrent disorder of disturbed and synchronized electrical activity in the brain. As the important regulators of membrane potential, TRP channels contribute to neuronal depolarization, electrical activity, and firing patterns.

TRPC3 expression is highly enriched in the immature and dysplastic cortex but is only weakly expressed in a mature cortex. The combinations of low-Ca\(^{2+}\) and low-Mg\(^{2+}\) are found to induce larger depolarization in pyramidal neurons, which represents greater susceptibility to epileptiform activity in the immature and dysplastic cortex. Furthermore, TRPC3 inhibition significantly diminishes these effects, suggesting a role of enhanced TRPC3 in epileptiform activity [100]. Furthermore, TRPC3 and TRPC6 have opposite roles in neuronal death following pilocarpine-induced status epilepticus (SE). TRPC3 expression is elevated in CA1 and CA3 pyramidal cells and dentate granule cells, while TRPC6 expression is reduced in these regions. TRPC3 inhibition by Pyr3 and TRPC6 activation by hyperforin effectively protects neuronal damage due to SE [101].

Increasing evidence suggests an antiepileptic potential of TRPV1 inhibition in neuronal activity. TRPV1 antagonist capsazepine suppresses 4-aminopyridine-induced epileptiform activity in vitro and electrographic seizures in vivo, while TRPV1 agonist anandamide shows proconvulsant effects in vivo [102, 103]. Furthermore, this role in epilepsy is associated with the endocannabinoid system that controls neuronal excitability and regulates long-term synaptic plasticity. The levels of the endocannabinoid anandamide, a TRPV1 agonist, increase in the course of epilepsy in human neocortical brain tissue. Mice lacking the enzyme fatty acid amidase hydrolase, the enzyme that hydrolyses anandamide, dramatically augment the severity of chemically induced seizures but not wild-type mice [104]. However, another cannabinoid, cannabidiol as a TRPV2 agonist, has been investigated for anticonvulsant effects. Cannabidiol is found to significantly reduce spontaneous epileptiform activity in vitro and incidence of severe seizures and mortality in vivo [105].

TRPM2 is reported to have molecular and functional interaction with EF-hand motif-containing protein (EFHC1), mutation in which causes juvenile myoclonic epilepsy (JME) via neuronal apoptosis. EFHC1 enhances TRPM2-mediated susceptibility to H\(_2\)O\(_2\)-induced cell death in HEK293 cells, which is reversed by JME mutations. These results suggest that TRPM2 contributes to JME phenotypes by mediating disruptive effects of EFHC1 mutations [106].

3.6. Mental Disorders. Schizophrenia, which is considered to be a neurodevelopmental disorder with origins in either the prenatal or neonatal period, is characterized by delusions, hallucinations, disorganized speech, and behavior. It has been reported that intrinsic somatosensory deprivation induced by neonatal capsaicin treatment, a TRPV1 activator, causes changes in the brains of rats similar to those found in schizophrenia. These changes in the rat brain and behavior suggest a possible role for TRPV1 in this neurodevelopmental disorder [107].

Various TRPs have been associated with bipolar disorders (BD), a mental disorder that causes dramatic mood shifts including emotional highs (mania or hypomania) and lows (depression). Several linkage analyses and single-nucleotide polymorphisms have shown that Trpm2 is associated with BD [108]. TRPM2-deficient mice exhibit BD-like changes.
in behavior and mood such as increased anxiety and decreased social responses, along with impaired electroencephalogram activity [109].

3.7. Pain. As an unpleasant sensory and emotional experience, pain is associated with actual or potential, tissue damage or described in terms of such damage. There is evidence suggesting that several TRP channels play a role in pain under physiological and pathological conditions. Expressed in somatosensory neurons, TRPV1 can be activated by both endogenous and exogenous stimuli including heat, arachidonic acid derivatives, vanilloids, protons, and cannabinoids. Upon activation, the pore of TRPV1 opens and allows ions for transmembrane motion to deliver a noxious message. However, TRPV1 will become rapidly desensitized upon activation, a process in which Ca$^{2+}$ preferentially enters the cell and stimulates a series of Ca$^{2+}$-dependent activities that ultimately lead to desensitization of the channel. This desensitization renders the channel refractory to further stimulation, leading to the paradoxical analgesic effect of TRPV1 [110].

TRPA1 is activated by pungent chemicals found in garlic, mustard, and onion. Trpa1 knockout mice display behavioral deficits in response to mustard oil, to cool and to punctate mechanical stimuli [111]. This channel is also proved to be the target through which mustard oil and garlic activate primary afferent nociceptors to produce inflammatory pain. Besides, TRPA1 can also be activated by cannabinoids to mediate currents and Ca$^{2+}$ influx in nociceptors. However, peripheral cannabinoid compounds exert antinociceptive effects rather than analgesic effects in vivo [112]. Since TRPA1 is mostly colocalized with TRPV1 in peripheral sensory neurons, TRPV1 and TRPA1 may cross-desensitize one another when acted upon by cannabinoids or other respective agonists. An aminoalkylindole cannabinoid, WIN 55,212-2, activates TRPA1 to trigger desensitization of TRPV1 [113], whereas another TRPV1-selective cannabinoid agonist desensitizes TRPA1 [114]. These findings suggest that specific and selective modulation of TRP channel activity will be of use in alleviating pain.

4. Conclusions and Perspectives

A recent work in animals and humans has increased the understanding of TRPs in the brain with their widespread distribution and varying functional roles. TRP channels play important roles not only as multifunctional cellular sensors but also as modulators in growth cone guidance, synaptogenesis, spine forming, synaptic plasticity, and synaptic transmission. Additionally, the involvement of TRP channels in the pathology of numerous neurological and psychiatric disorders has been increasingly documented as important pharmacological targets. Changes in TRP expression levels or channel sensitization or desensitization have been found to be associated with the pathophysiological process and progression in TRP-related diseases. TRP activities mediated by various endogenous and exogenous agents contribute to some opposite outcomes as they exhibit different channel electrophysiological properties and operate via downstream signaling pathways. In this regard, accumulating findings highlight TRP channels as promising pharmacological targets. Therefore, further studies are required to explore the physiological and pathological roles of TRPs in the brain and develop new therapeutic strategies for the treatment of neurological and psychiatric disorders.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| Aβ           | Amyloid-β   |
| AD           | Alzheimer disease |
| ADPR         | Adenosine diphosphoribose |
| APP          | Amyloid precursor protein |
| BD           | Bipolar disorders |
| BDNF         | Brain-derived neurotrophic factor |
| EFHC1        | EF-hand motif-containing protein |
| JME          | Juvenile myoclonic epilepsy |
| LTD          | Long-term depression |
| LTP          | Long-term potentiation |
| mGluR        | Metabotropic glutamate receptor |
| NMDA         | N-Methyl-D-aspartate |
| PD           | Parkinson’s disease |
| PS           | Presenilin |
| ROS          | Reactive oxygen species |
| SCI          | Spinal cord injury |
| SE           | Status epilepticus |
| TBI          | Traumatic brain injury |
| tMCAO        | Transient middle cerebral artery occlusion |
| TRP          | Transient receptor potential |
| TRPA         | Transient receptor potential ankyrin |
| TRPC         | Transient receptor potential canonical |
| TRPM         | Transient receptor potential melastatin |
| TRPML        | Transient receptor potential mucolipin |
| TRPN         | Transient receptor potential NOMPC-like |
| TRPP         | Transient receptor potential polycystin |

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

AWS conceptualized the research project; RW drafted the manuscript; ST, AWS and JMZ reviewed and modified the manuscript; AWS and JMZ supervised the research, led the discussion. All authors approved the final version of the manuscript.

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References

[1] D. J. Cosens and A. Manning, "Abnormal Electroretinogram from a Drosophila Mutant," Nature, vol. 224, no. 5216, pp. 285–287, 1969.

[2] B. Nilius and G. Owsianik, "The transient receptor potential family of ion channels," Genome Biology, vol. 12, no. 3, p. 218, 2011.

[3] T. Hofmann, M. Schaefer, G. Schultz, and T. Gudermann, "Subunit composition of mammalian transient receptor potential channels in living cells," Proceedings of the National Academy of Sciences, vol. 99, no. 11, pp. 7461–7466, 2002.

[4] W. B. Liedtke and S. J. C. P. Heller, "Coordination, α subunit increases Ca2+ selectivity and controls neurite length and growth cone morphology," Neuron, vol. 29, no. 6, pp. F1245–F1254, 2009.

[5] P. A. Zamudio-Bulcock and C. F. Valenzuela, "The TRPMLs: in sickness and in health.," Nature, vol. 30, no. 3, pp. 508–515, 2005.

[6] A. Liapi and J. N. Wood, "Extensive co-localization and heteromultimer formation of the vanilloid receptor-like protein TRPV2 and the capsaicin receptor TRPV1 in the adult rat cerebral cortex," European Journal of Neuroscience, vol. 22, no. 4, pp. 825–834, 2005.

[7] A. E. Chavez, V. M. Hernandez, A. Rodenas-Ruano, C. S. Chan, and P. E. Castillo, "Compartment-Specific Modulation of GABAergic Synaptic Transmission by TRPV1 Channels in the Dentate Gyrus," Journal of Neuroscience, vol. 34, no. 50, pp. 16621–16629, 2014.

[8] K. Shibasaki, N. Murayama, K. Ono, Y. Ishizaki, and M. Tominaga, "TRPV2 Enhances Axon Outgrowth through Its Activation by Membrane Stretch in Developing Sensory and Motor Neurons," Journal of Neuroscience, vol. 30, no. 13, pp. 4601–4612, 2010.

[9] B. A. Grueter, G. Brasnjo, and R. C. Malenka, "Postsynaptic TRPV1 triggers cell type-specific long-term depression in the nucleus accumbens," Nature Neuroscience, vol. 13, no. 12, pp. 1519–1525, 2010.

[10] A. E. Chavez, V. M. Hernandez, A. Rodenas-Ruano, C. S. Chan, and P. E. Castillo, "Compartment-Specific Modulation of GABAergic Synaptic Transmission by TRPV1 Channels in the Dentate Gyrus," Journal of Neuroscience, vol. 34, no. 50, pp. 16621–16629, 2014.
Oxidative Medicine and Cellular Longevity

Model of Mucolipidosis Type IV due to Defective Clearance of Apoptotic Cells,” Cell, vol. 135, no. 5, pp. 838–851, 2008.

[31] P. Pizzo, A. Burgo, T. Pozzan, and C. Fasolato, “Role of capacitative calcium entry on glutamate-induced calcium influx in type-I rat cortical astrocytes,” Journal of Neuroscience, vol. 79, no. 1, pp. 98–109, 2008.

[32] O. Beskina, A. Miller, A. Mazzocco-Spezia, M. V. Pulina, and V. A. Golovina, “Mechanisms of interleukin-1β-induced Ca2+-signals in mouse cortical astrocytes: roles of store- and receptor-operated Ca2+-entry,” American Journal of Physiology-Cell Physiology, vol. 293, no. 3, pp. C1103–C1111, 2007.

[33] T. Akita and Y. Okada, “Regulation of bradykinin-induced activation of volume-sensitive outwardly rectifying anion channels by Ca2+ nanodomains in mouse astrocytes,” The Journal of Physiology, vol. 589, no. 16, pp. 3909–3927, 2011.

[34] T. Mannari, S. Morita, E. Furube, M. Tominaga, and S. J. G. K. Shibasaki, Y. Ishizaki, and S. Mandadi, “Astrocytic TRPV1 ion channels detect blood-borne signals in the sensory circumventricular organs of adult mouse brains,” Glia, vol. 61, no. 6, pp. 957–971, 2013.

[35] K. Shibasaki, Y. Ishizaki, and S. Mandadi, “Astrocytes express functional TRPV2 ion channels,” Biochemical and Biophysical Research Communications, vol. 441, no. 2, pp. 327–332, 2013.

[36] V. Benfenati, M. Caprini, M. Dovizio et al., “An aquaporin-4 transient receptor potential vanilloid 4 (AQP4/TRPV4) complex is essential for cell-volume control in astrocytes,” Proceedings of the National Academy of Sciences, vol. 108, no. 6, pp. 2563–2568, 2011.

[37] K. M. Dunn, D. C. Hill-Eubanks, W. B. Liedtke, and M. T. Nelson, “TRPV4 channels stimulate Ca2+-induced Ca2+ release in astrocytic endfeet and amplify neurovascular coupling responses,” Proceedings of the National Academy of Sciences, vol. 110, no. 15, pp. 6157–6162, 2013.

[38] K. Shibasaki, K. Ikenaka, F. Tamalu, M. Tominaga, and Y. Ishizaki, “A Novel Subtype of Astrocytes Expressing TRPV4 (Transient Receptor Potential Vanilloid 4) Regulates Neuronal Excitability via Release of Gliotransmitters,” Journal of Biological Chemistry, vol. 289, no. 21, pp. 14470–14480, 2014.

[39] C. E. Bond and S. A. Greenfield, “Multiple cascade effects of oxidative stress on astroglia,” Glia, vol. 55, no. 13, pp. 1348–1361, 2007.

[40] Z. Zeng, T. Leng, X. Feng et al., “Silencing TRPM7 in Mouse Cortical Astrocytes Impairs Cell Proliferation and Migration via ERK and JNK Signaling Pathways,” PLOS ONE, vol. 10, no. 3, article e0119912, 2015.

[41] Y. Mizoguchi, A. Kato, Y. Seki et al., “Brain-derived Neurotrophic Factor (BDNF) Induces Sustained Intracellular Ca2+ Elevation through the Up-regulation of Surface Transient Receptor Potential 3 (TRPC3) Channels in Rodent Microglia,” Journal of Biological Chemistry, vol. 289, no. 26, pp. 18549–18555, 2014.

[42] S. R. Kim, S. U. Kim, U. Oh, and B. K. Jin, “Transient Receptor Potential Vanilloid Subtype 1 Mediates Microglial Cell Death In Vivo and In Vitro via Ca2+-Mediated Mitochondrial Damage and Cytochrome c Release,” The Journal of Immunology, vol. 177, no. 7, pp. 4322–4329, 2006.

[43] T. Miyake, H. Shirakawa, T. Nakagawa, and S. Kaneko, “Activation of mitochondrial transient receptor potential vanilloid 1 channel contributes to microglial migration,” Glia, vol. 63, no. 10, pp. 1870–1882, 2015.

[44] S. Hassan, K. Eldeeb, P. J. Mills, A. J. Bennett, S. P. H. Alexander, and D. A. Kendall, “Cannabidiol enhances microglial phagocytosis via transient receptor potential (TRP) channel activation,” British Journal of Pharmacology, vol. 171, no. 9, pp. 2426–2439, 2014.

[45] M. Konno, H. Shirakawa, S. Iida et al., “Stimulation of transient receptor potential vanilloid 4 channel suppresses abnormal activation of microglia induced by lipopolysaccharide,” Glia, vol. 60, no. 5, pp. 761–770, 2012.

[46] T. Miyake, H. Shirakawa, A. Kusano et al., “TRPM2 contributes to LPS/IFNγ-induced production of nitric oxide via the p38/JNK pathway in microglia,” Biochemical and Biophysical Research Communications, vol. 444, no. 2, pp. 212–217, 2014.

[47] T. Siddiqui, S. Lively, R. Ferreira, R. Wong, and L. C. Schlichter, “Expression and Contributions of TRPM7 and KCa2.3/ SK3 Channels to the Increased Migration and Inhibition of Microglia in Anti-Inflammatory Activation States,” PLoS ONE, vol. 9, no. 8, 2014.

[48] S. Marques, A. Zeisel, S. Codeluppi et al., “Oligodendrocyte heterogeneity in the mouse juvenile and adult central nervous system,” Science, vol. 352, no. 6291, pp. 1326–1329, 2016.

[49] P. M. Paez, D. Fulton, V. Spreuer, V. Handley, and A. T. Campagnoni, “Modulation of Canonical Transient Receptor Potential Channel 1 in the Proliferation of Oligodendrocyte Precursor Cells by the Golli Products of the Myelin Basic Protein Gene,” Journal of Neuroscience, vol. 31, no. 10, pp. 3625–3637, 2011.

[50] K. D. Jo, K.-S. Lee, W. T. Lee, M.-S. Hur, and H.-J. Kim, “Expression of transient receptor potential channels in the ependymal cells of the developing rat brain,” Anatomy & Cell Biology, vol. 46, no. 1, pp. 68–78, 2013.

[51] S. Earley, A. L. Gonzales, and Z. I. Garcia, “A Dietary Agonist of Transient Receptor Potential Cation Channel V3 Elicits Endothelium-Dependent Vasodilation,” Molecular Pharmacology, vol. 77, no. 4, pp. 612–620, 2010.

[52] S. Earley, A. L. Gonzales, and R. Crnich, “Endothelium-Dependent Cerebral Artery Dilatation Mediated by TRPA1 and Ca2+-Activated K+ Channels,” Circulation Research, vol. 104, no. 8, pp. 987–994, 2009.

[53] S. Earley, B. J. Waldron, and J. E. Brayden, “Critical Role for Transient Receptor Potential Channel TRPM4 in Myogenic Constriction of Cerebral Arteries,” Circulation Research, vol. 95, no. 9, pp. 922–929, 2004.

[54] S. P. Marrelli, R. G. O’Neil, R. C. Brown, and R. M. Bryan Jr., “PLA2 and TRPV4 channels regulate endothelial calcium in cerebral arteries,” American Journal of Physiology-Heart and Circulatory Physiology, vol. 292, no. 3, pp. H1390–H1397, 2007.

[55] Y. Lin, J.-C. Zhang, J. Fu et al., “Inhibition of TRPC6 degradation suppresses ischemic brain damage in rats,” Journal of Clinical Investigation, vol. 120, no. 10, pp. 3480–3492, 2010.
[58] J. Zhang, X. Mao, T. Zhou, X. Cheng, and Y. J. N. Lin, "IL-17A contributes to brain ischemia reperfusion injury through calpain-TRPC6 pathway in mice," *Neuroscience*, vol. 274, pp. 419–428, 2014.

[59] Y.-Q. Gao, H. Gao, Z.-Y. Zhou, S.-D. Lu, and F.-Y. Sun, "Expression of transient receptor potential channel 4 in striatum and hippocampus of rats is increased after focal cerebral ischemia," *Acta Physiologica Sinica*, vol. 56, pp. 153–157, 2004.

[60] Y. Hara, M. Wakamori, M. Ishii et al., "LTRPC2 Ca2+-Permeable Channel Activated by Changes in Redox Status Contributes Susceptibility to Cell Death," *Molecular Cell*, vol. 9, no. 1, pp. 163–173, 2002.

[61] I. Alim, L. Teves, R. Li, Y. Mori, and M. Tymianski, "Modulation of NMDAR Subunit Expression by TRPM2 Channels Regulates Neuronal Vulnerability to Ischemic Cell Death," *Journal of Neuroscience*, vol. 33, no. 44, pp. 17264–17277, 2013.

[62] T. Shimizu, R. M. Dietz, I. Cruz-Torres et al., "Extended therapeutic window of a novel peptide inhibitor of TRPM2 channels following focal cerebral ischemia," *Experimental Neurology*, vol. 283 Part A, pp. 151–156, 2016.

[63] E. Fonfria, C. Mattei, K. Hill et al., "TRPM2 is Elevated in the tMCAO Stroke Model, Transcriptionally Regulated, and Functionally Expressed in C13 Microglia," *Journal of Receptors and Signal Transduction*, vol. 26, no. 3, pp. 179–198, 2008.

[64] S. Yamamoto, S. Shimizu, S. Kiyonaka et al., "TRPM2-mediated Ca2+ influx induces chemokine production in monocytes that aggravates inflammatory neutrophil infiltration," *Nature Medicine*, vol. 14, no. 7, pp. 738–747, 2008.

[65] M. Gelderblom, N. Melzer, B. Schattling et al., "Transient Receptor Potential Melastatin Subfamily Member 2 Cation Channel Regulates Detrimental Immune Cell Invasion in Ischemic Stroke," *Stroke*, vol. 45, no. 11, pp. 3395–3402, 2014.

[66] M. Aarts, K. Ihara, W.-L. Wei et al., "A Key Role for TRPM7 Channels in Anoxic Neuronal Death," *Cell*, vol. 115, no. 7, pp. 863–877, 2003.

[67] J. Jiang, M. Li, and L. Yue, "Potentiation of TRPM7 Inward Currents by Protons," *Journal of General Physiology*, vol. 126, no. 2, pp. 137–150, 2005.

[68] W. Chen, B. Xu, A. Xiao et al., "TRPM7 inhibitor carvacrol protects brain from neonatal hypoxic-ischemic injury," *Molecular Brain*, vol. 8, no. 1, pp. 11–15, 2015.

[69] K. P. Loh, G. Ng, C. Y. Yu et al., "TRPM4 inhibition promotes angiogenesis after ischemic stroke," *Pflügers Archiv - European Journal of Physiology*, vol. 466, no. 3, pp. 563–576, 2014.

[70] J. Miyahara, H. Shirakawa, K. Sanpei, T. Nakagawa, and S. Kaneko, "A pathophysiological role of TRPV1 in ischemic injury after transient focal cerebral ischemia in mice," *Biochemical and Biophysical Research Communications*, vol. 467, no. 3, pp. 478–483, 2015.

[71] Z. Cao, A. Balasubramanian, and S. P. Marrelli, "Pharmacologically induced hypothermia via TRPV1 channel agonism provides neuroprotection following ischemic stroke when initiated 90 min after reperfusion," *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, vol. 306, no. 2, pp. R149–R156, 2014.

[72] O. Butenko, D. Dzamba, J. Benesova et al., "The Increased Activity of TRPV4 Channel in the Astrocytes of the Adult Rat Hippocampus after Cerebral Hypoxia/Ischemia," *PLoS ONE*, vol. 7, no. 6, article e99959, 2012.

[73] P. Jie, Z. Lu, Z. Hong et al., "Activation of Transient Receptor Potential Vaniloid 4 is Involved in Neuronal Injury in Mid-dle Cerebral Artery Occlusion in Mice," *Molecular Neurobiology*, vol. 53, no. 1, pp. 8–17, 2016.

[74] D. J. Rossi, J. D. Brady, and C. Mohr, "Astrocyte metabolism and signaling during brain ischemia," *Nature Neuroscience*, vol. 10, no. 11, pp. 1377–1386, 2007.

[75] C. Rakers, M. Schmid, and G. C. Petzold, "TRPV4 channels contribute to calcium transients in astrocytes and neurons during peri-infarct depolarizations in a stroke model," *Glia*, vol. 65, no. 9, pp. 1550–1561, 2017.

[76] H. Shirakawa, S. Sakimoto, K. Nakao et al., "Transient Receptor Potential Canonical 3 (TRPC3) Mediates Thrombin-Induced Astrocyte Activation and Upregulates Its Own Expression in Cortical Astrocytes," *Journal of Neuroscience*, vol. 30, no. 39, pp. 13116–13129, 2010.

[77] M. Munakata, H. Shirakawa, K. Nagayasu et al., "Transient Receptor Potential Canonical 3 Inhibitor Pyr3 Improves Outcomes and Attenuates Astrogliaosis After Intracerebral Hemorrhage in Mice," *Stroke*, vol. 44, no. 7, pp. 1981–1987, 2013.

[78] H. Zhao, K. Zhang, R. Tang et al., "TRPV4 Blockade Preserves the Blood–Brain Barrier by Inhibiting Stress Fiber Formation in a Rat Model of Intracerebral Hemorrhage," *Frontiers in Molecular Neuroscience*, vol. 11, 2018.

[79] F. Thiło, O. Suess, Y. Liu, and M. Tepel, "Decreased Expression of Transient Receptor Potential Channels in Cerebral Vascular Tissue from Patients After Hypertensive Intracerebral Hemorrhage," *Clinical and Experimental Hypertension*, vol. 33, no. 8, pp. 533–537, 2011.

[80] A. Xie, Y. Aiha, V. A. Bouriy et al., "Novel mechanism of endothelin-1-induced vasospasm after subarachnoid hemorrhage," *Journal of Cerebral Blood Flow & Metabolism*, vol. 27, no. 10, pp. 1692–1701, 2007.

[81] N. L. Cook, R. Vink, S. C. Helps, J. Manavis, and C. van den Heuvel, "Transient Receptor Potential Melastatin 2 Expression is Increased Following Experimental Traumatic Brain Injury in Rats," *Journal of Molecular Neuroscience*, vol. 42, no. 2, pp. 192–199, 2010.

[82] V. Yüürker, M. Nazuroğlu, and N. Şenol, "Reduction in traumatic brain injury-induced oxidative stress, apoptosis, and calcium entry in rat hippocampus by melatonin: Possible involvement of TRPM2 channels," *Metabolic Brain Disease*, vol. 30, no. 1, pp. 223–231, 2015.

[83] V. Gerzanich, S. K. Woo, R. Vennekens et al., "De novo expression of Trpm4 initiates secondary hemorrhage in spinal cord injury," *Nature Medicine*, vol. 15, no. 2, pp. 185–191, 2009.

[84] N. L. Cook, C. Van Den Heuvel, and R. Vink, "Are the transient receptor potential melastatin (TRPM) channels important in magnesium homeostasis following traumatic brain injury?" *Magnesium Research*, vol. 22, no. 4, pp. 225–234, 2009.

[85] V. C. Bomben and H. W. Sontheimer, "Inhibition of transient receptor potential canonical channels impairs cytokinesis in human malignant gliomas," *Cell Proliferation*, vol. 41, no. 1, pp. 98–121, 2008.

[86] V. A. Cuddapah, K. L. Turner, and H. Sontheimer, "Calcium entry via TRPC1 channels activates chloride currents in human glioma cells," *Cell Calcium*, vol. 53, no. 3, pp. 187–194, 2013.

[87] M. Nabiissi, M. B. Morelli, M. Santoni, and G. J. C. Santoni, "Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents," *Carcinogenesis*, vol. 34, no. 1, pp. 48–57, 2013.
[88] M. B. Morelli, M. Nabissi, C. Amantini et al., “Overexpression of transient receptor potential mucolipin-2 ion channels in gliomas: role in tumor growth and progression,” *Oncotarget*, vol. 7, no. 28, pp. 43654–43668, 2016.

[89] C. B. Lessard, M. P. Lussier, S. Cayouette, G. Bourque, and G. Boulay, “The overexpression of presenilin2 and Alzheimer’s-disease-linked presenilin2 variants influences TRPC6-enhanced Ca2+ entry into HEK293 cells,” *Cellular Signalling*, vol. 17, no. 4, pp. 437–445, 2005.

[90] E. Fonfria, I. C. B. Marshall, I. Boyeldieu et al., “Amyloid beta-peptide(1-42) and hydrogen peroxide-induced toxicity are mediated by TRPM2 in rat primary striatal cultures,” *Journal of Neurochemistry*, vol. 95, no. 3, pp. 715–723, 2005.

[91] L. Park, G. Wang, J. Moore et al., “The key role of transient receptor potential melastatin-2 channels in amyloid-β-induced neurovascular dysfunction,” *Nature Communications*, vol. 5, no. 1, 2014.

[92] V. G. Ostapchenko, M. Chen, M. S. Guzman et al., “The Transient Receptor Potential Melastatin 2 (TRPM2) Channel Contributes to -Amyloid Oligomer-Related Neurotoxicity and Memory Impairment,” *Journal of Neuroscience*, vol. 35, no. 45, pp. 15157–15169, 2015.

[93] A. Bosson, A. Paumier, S. Boisseau, M. Jacquier-Sarlin, and M. Albrieux, “Overexpression of 6-OHDA on motor and cognitive functions in a rat model of Parkinson’s disease via cannabinoid Arachidonoyl-2 Chloroethanolamine,” *Oleoylethanolamide* TRPV1 antagonist capsazepine suppresses 4-AP-induced epileptiform activity in vitro and electrographic seizures in vivo,” *Experimental Neurology*, vol. 250, pp. 321–332, 2013.

[94] A. B. Clement, E. G. Hawkins, A. H. Lichtman, and B. F. Cravatt, “Increased Seizure Susceptibility and Proconvulsant Activity of Anandamide in Mice Lacking Fatty Acid Amide Hydrolase,” *The Journal of Neuroscience*, vol. 23, no. 9, pp. 3916–3923, 2003.

[95] N. A. Jones, A. J. Hill, I. Smith et al., “Cannabinoid Displays Antiepileptiform and Antiseizure Properties In Vitro and In Vivo,” *Journal of Pharmacology and Experimental Therapeutics*, vol. 332, no. 2, pp. 569–577, 2010.

[96] Y. Jang, S. H. Lee, B. Lee et al., “Innate sensory deprivation induced by neonatal capsaicin treatment induces changes in rat brain and behaviour of possible relevance to schizophrenia,” *British Journal of Pharmacology*, vol. 146, no. 3, pp. 408–418, 2005.

[97] A. McQuillin, N. J. Bass, G. Kalsi et al., “Fine mapping of a susceptibility locus for bipolar and genetically related unipolar affective disorders, to a region containing the C21ORF29 and TRPM2 genes on chromosome 21q22.3,” *Molecular Psychiatry*, vol. 11, no. 2, pp. 134–142, 2006.

[98] Y. Sun, P. Sukumaran, S. Selvaraj et al., “TRPM2 Promotes Neurotoxicity MPP+/MPTP-Induced Cell Death,” *Molecular Neurobiology*, vol. 55, no. 1, pp. 409–420, 2018.

[99] J. H. Nam, E. S. Park, S.-Y. Won et al., “TRPV1 on astrocytes rescues nigral dopamine neurons in Parkinson’s disease via CNTF,” *Brain*, vol. 138, no. 12, pp. 3610–3622, 2015.

[100] J. Lee, V. Di Marzo, and J. M. Brotchie, “A role for vanillin receptor 1 (TRPV1) and endocannabinoid signalling in the regulation of spontaneous and L-DOPA induced locomotion in normal and reserpine-treated rats,” *Neuropharmacology*, vol. 51, no. 3, pp. 557–565, 2006.

[101] M. Razaviniasab, A. Shamsizadeh, M. Shabani et al., “Pharmacological blockade of TRPV1 receptors modulates the effects of 6-OHDA on motor and cognitive functions in a rat model of Parkinson’s disease,” *Fundamental & Clinical Pharmacology*, vol. 27, no. 6, pp. 632–640, 2013.

[102] R. González-Aparicio and R. Moratalla, “Oleylethanolamide reduces L-DOPA-induced dyskinesia via TRPV1 receptor in a mouse model of Parkinson’s disease,” *Neurobiology of Disease*, vol. 62, pp. 416–425, 2014.

[103] L. E. Gonzalez-Reyes, T. P. Ladas, C.-C. Chiang, and D. M. Durand, “TRPV1 antagonist capsazepine suppresses 4-AP-induced epileptiform activity in vitro and electrographic seizures in vivo,” *Experimental Neurology*, vol. 250, pp. 321–332, 2013.

[104] F. A. Iannotti, C. L. Hill, A. Leo et al., “Nonpsychotropic Plant Cannabinoids, Cannabidivarin (CBDV) and Cannabidiol (CBD), Activate and Desensitize Transient Receptor Potential Vanilloid 1 (TRPV1) Channels in Vitro: Potential for the Treatment of Neuronal Hyperexcitability,” *ACS Chemical Neuroscience*, vol. 5, no. 11, pp. 1131–1141, 2014.

[105] K. Y. Kwan, A. J. Allchorne, M. A. Vollrath et al., “TRPA1 Contributes to Cold, Mechanical, and Chemical Nociception but Is Not Essential for Hair-Cell Transduction,” *Neuron*, vol. 50, no. 2, pp. 277–289, 2006.

[106] A. Calignano, G. La Rana, A. Giuffrida, and D. Piomelli, “Control of pain initiation by endogenous cannabinoids,” *Nature*, vol. 394, no. 6690, pp. 277–281, 1998.

[107] N. A. Jeske, A. M. Patwardhan, N. Gamper, T. J. Price, A. N. Akopian, and K. M. Hargreaves, “Fundamental & Clinical Pharmacology of Biological Chemistry,” *Journal of Neuroscience*, vol. 35, no. 34, pp. 11811–11823, 2015.

[108] A. B. Clement, E. G. Hawkins, A. H. Lichtman, and B. F. Cravatt, “Increased Seizure Susceptibility and Proconvulsant Activity of Anandamide in Mice Lacking Fatty Acid Amide Hydrolase,” *The Journal of Neuroscience*, vol. 23, no. 9, pp. 3916–3923, 2003.

[109] Y. Jang, S. H. Lee, B. Lee et al., “TRPM2, a Susceptibility Gene for Bipolar Disorder, Regulates Glycogen Synthase Kinase-3 Activity in the Brain,” *Journal of Neuroscience*, vol. 35, no. 34, pp. 11811–11823, 2015.

[110] F. A. Iannotti, C. L. Hill, A. Leo et al., “Nonpsychotropic Plant Cannabinoids, Cannabidivarin (CBDV) and Cannabidiol (CBD), Activate and Desensitize Transient Receptor Potential Vanilloid 1 (TRPV1) Channels in Vitro: Potential for the Treatment of Neuronal Hyperexcitability,” *ACS Chemical Neuroscience*, vol. 5, no. 11, pp. 1131–1141, 2014.

[111] N. A. Jeske, A. M. Patwardhan, N. Gamper, T. J. Price, A. N. Akopian, and K. M. Hargreaves, “Fundamental & Clinical Pharmacology of Biological Chemistry,” *Journal of Neuroscience*, vol. 35, no. 34, pp. 11811–11823, 2015.

[112] A. Calignano, G. La Rana, A. Giuffrida, and D. Piomelli, “Control of pain initiation by endogenous cannabinoids,” *Nature*, vol. 394, no. 6690, pp. 277–281, 1998.

[113] N. A. Jeske, A. M. Patwardhan, N. Gamper, T. J. Price, A. N. Akopian, and K. M. Hargreaves, “Fundamental & Clinical Pharmacology of Biological Chemistry,” *Journal of Neuroscience*, vol. 35, no. 34, pp. 11811–11823, 2015.