



Review

Pathophysiological Roles of Transient Receptor Potential (Trp) Channels and Zinc Toxicity in Brain Disease

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Abstract: Maintaining the correct ionic gradient from extracellular to intracellular space via several membrane-bound transporters is critical for maintaining overall cellular homeostasis. One of these transporters is the transient receptor potential (TRP) channel family that consists of six putative transmembrane segments systemically expressed in mammalian tissues. Upon the activation of TRP channels by brain disease, several cations are translocated through TRP channels. Brain disease, especially ischemic stroke, epilepsy, and traumatic brain injury, triggers the dysregulation of ionic gradients and promotes the excessive release of neuro-transmitters and zinc. The divalent metal cation zinc is highly distributed in the brain and is specifically located in the pre-synaptic vesicles as free ions, usually existing in cytoplasm bound with metallothionein. Although adequate zinc is essential for regulating diverse physiological functions, the brain-disease-induced excessive release and translocation of zinc causes cell damage, including oxidative stress, apoptotic cascades, and disturbances in energy metabolism. Therefore, the regulation of zinc homeostasis following brain disease is critical for the prevention of brain damage. In this review, we summarize recent experimental research findings regarding how TRP channels (mainly TRPC and TRPM) and zinc are regulated in animal brain-disease models of global cerebral ischemia, epilepsy, and traumatic brain injury. The blockade of zinc translocation via the inhibition of TRPC and TRPM channels using known channel antagonists, was shown to be neuroprotective in brain disease. The regulation of both zinc and TRP channels may serve as targets for treating and preventing neuronal death.

Keywords: transient receptor potential (TRP) channels; zinc; ischemic stroke; epilepsy; traumatic brain injury



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1. Introduction

1.1. Overview: Transient Receptor Potential Channels in the Brain

The transient receptor potential (TRP) channels consist of six subfamilies with a total of twenty-eight members. Subfamily includes the canonical (TRPC), melastatin (TRPM), vanilloid (TRPV), ankyrin (TRPA), mucolipin (TRPML), polycystic (TRPP) and NOMPC-like (TRPN, possess only invertebrate and fish, not in mammals) categories [1–3]. Activation of these TRP channels through external or internal stimuli depolarizes membrane action potential. Altered action potential induces an influx of calcium or zinc ions through voltage-gated ion channels [4,5]. These channels are all highly expressed in the brain and regulate

post-synaptically bound receptors and channels such as the N-methyl-D-aspartate receptor (NMDAR), voltage-gated calcium channel, and acid-sensing ion channel (ASIC) [5–7]. All TRP channels consist of six putative transmembrane spanning domains (S1–S6) that form a loop shape between the S5 and S6 domains [8,9]. Under physiological conditions, these channels regulate neuronal and glial functions, including signal transduction, action potential, development, and homeostasis [10].

The activation of TRP channels by various internal stimuli includes signal transductions and the chemical, biological, and (especially) intracellular storage of calcium concentrations [11]. The alteration of cytosolic calcium concentrations through TRP channels plays especially diverse fundamental roles in the synaptic-vesicle exocytosis-induced release of neurotransmitters, cell proliferation, and cell death [12,13]. Some TRP channels regulate the concentration of diverse cations such as sodium, calcium, magnesium, and zinc [4,14–18]. In this review, we provide current insights and experimental results related to the physiological and pathophysiological roles of zinc entry with other cations through the TRP channels, based on previous reports [19–21].

1.2. Transient Receptor Potential Canonical Channels (TRPC)

TRPCs. TRPCs, which consist of seven subunits (TRPC1–TRPC7), are expressed in most brain regions and calcium-permeable cation channels. Notably, TRPC2 is a pseudogene in humans and will not be discussed in this review [7]. The general roles of TRPCs include regulating progenitor cell proliferation and enhancing neural survival affected by neurotrophin-like brain-derived neurotrophic factor (BDNF) and neuronal growth by guiding neurite outgrowth [22,23].

1. **TRPC1.** The activation of TRPC1 is initiated by metabotropic glutamate receptors (mGluR1) in neurons, and the formation of excitatory post-synaptic potential is due to TRPC1 functions [11,24,25]. TRPC1 also impacts the developing brain by directing axonal growth [22,26]. In a previous study, short hairpin RNA (shRNA)-induced knockdown of the TRPC1 gene revealed that the adult neural progenitor cell cycle in the G1 phase was significantly decreased [27].
2. **TRPC3.** TRPC3 is also abundantly expressed in the brain, especially in the hippocampus. The main function of TRPC3 is slow excitatory post-synaptic potential (EPSP) and the progression of long-term depression (LTD) [28,29]. The function of TRPC3 is similar to that of TRPC1 which has different expression patterns (approximately ten times that of TRPC3). In addition, TRPC3 gene deletion was related to greater motor deficits compared with the wild type, but there were no differences in brain development [28]. TRPC3 is activated by BDNF, an essential neurotrophic factor for neuronal differentiation, maturation, and survival that possibly interacts with tropomyosin receptor kinase B [30–32].
3. **TRPC4 and TRPC5.** The similarity between TRPC4 and TRPC5 is due to these genes being homologs. Indeed, the TRPC4 and TRPC5 proteins share amino acid sequences with an approximately 65 percent overlap [33]. The structural N-terminal (S1 domain of the TRP channel) coil interacts with regulating microtubule dynamics and stathmin [26]. TRPC4 and TRPC5 are activated by G α i, a G-protein-coupled receptor, and implicated in neuronal neurite growth and branching problems [34]. These findings suggest that TRPC4 and TRPC5 are closely associated with the neuronal developmental pathways. Although the structures and functions of TRPC4 and TRPC5 are similar, TRPC5 is activated by oxidative damage, and the early induction of a calcium influx especially increases zinc [35].
4. **TRPC6.** TRPC6 is distributed in the molecular layer of the dentate gyrus and tyrosine-hydroxylase-positive neurons in the substantia nigra [36,37]. The molecular structure of TRPC6 shares approximately 75% of amino acids with TRPC3 and TRPC7 (homomultimers or heteromultimers) [6,38]. A previous study demonstrated that the overexpression of TRPC6 increases the numbers of branches and spines in hippocampal neurons, while TRPC6 knockdown using RNA interference decreases these

counts [39]. These results suggested that TRPC6 is related to functions of learning, memory, and brain plasticity and confirmed that TRPC6 promotes dendritic growth via the calcium/calmodulin-dependent kinase 4-cAMP response element-binding protein (CREB) signaling pathway [40].

1.3. Transient Receptor Potential Melastatin (TRPM)

TRPMs. TRPMs consist of eight subunits (TRPM1–TRPM8) and are ubiquitously expressed in tissues, including several brain regions. TRPMs are highly permeable to cations including calcium, magnesium, and zinc, which easily pass and are implicated in neuronal plasticity [4,16,41]. The N-terminal regions of TRPM (S1 domain) consist of four melastatin homology regions that have roles in sensing external stimuli and channel assembly [42,43]. The C-terminal regions of TRPM (S6 domain) are composed of the coiled-coil domain, which regulates the pore gating process [44].

5. *TRPM1* and *TRPM3*. The molecular structures of TRPM1 and TRPM3 are similar in that these channels share about 75 percent of their amino acid sequences [45]. TRPM1 is mainly expressed in the retinal region, and the corresponding knockout mouse presented impaired visual function [46]. TRPM3 is expressed in brain regions involving the hippocampus, cortex, cerebellum, and choroid plexus, especially the somatosensory neurons that regulate inflammation [47,48].
6. *TRPM2*. TRPM2 is highly expressed in the brain, especially in the hippocampus, stratum, and cortex, where TRPM2 is preferentially distributed in the microglia and macrophages [49–51]. As a non-selective cation channel, TRPM2 is permeable to diverse cations involving calcium and magnesium through the S5 to S6 domains [52,53]. The activation of TRPM2 is triggered by inflammatory cytokines, tumor necrotic factor alpha (TNF- α)-mediated calcium overload, and cell damage cascades [54]. This channel can also be activated by the intense stimulation of NMDAR and external stimuli that depend on reactive oxygen species (ROS) and hydrogen peroxide via intracellular poly ADP-ribose (ADPR) [55–58]. One pivotal role of TRPM2 is as an oxidative stress-induced redox signaling sensitive cation-permeable channel [59]. The antioxidant glutathione has an inhibitory effect on the current of TRPM2 in primary cultured neurons through a thiol-independent mechanism [60]. LTD impairment was shown in TRPM2 knockout mice, which significantly decreased expression of the major regulator protein of excitatory synapses, post-synaptic density protein and the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [41].
7. *TRPM4* and *TRPM5*. TRPM4 is ubiquitously expressed in the heart, prostate, and other tissues, while TRPM5 is primarily found in sensory receptor cells [61,62]. Both have molecular similarities in their sequence homology (about 50 percent) and share properties related to voltage-dependence, single-channel conductance, and channel regulation [62,63].
8. *TRPM7*. The N-terminal of TRPM7 contains a serine–threonine alpha-kinase domain [64,65]. The alpha-kinase domain on the S6 region of TRPM7 regulates cell growth and proliferation via eEF2-kinase/eEF2 or Akt/mTOR signaling [66,67]. TRPM7 is also a non-selective diverse cation channel that is permeable to zinc, magnesium, and calcium (order of permeability: zinc > magnesium > calcium) [68]. TRPM7 characteristics make it a target for brain injuries which activate oxidative stress [69] and also make it highly permeable to calcium and zinc. The physiological functions of TRPM7 are closely related in neurotransmitter release [70], proliferation, and cell survival [67,71]. TRPM knockdown using shRNA in animals showed significantly decreased synaptic density, memory function, and long-term potentiation under physiological conditions [72].

1.4. Transient Receptor Potential Vanilloid (TRPV)

TRPV1. The TRPV subfamily consists of six subunits (TRPV1–TRPV6) and these channels have high permeability to calcium ion. In the brain, especially, TRPV1 is activated by

diverse exo- and endogenous stimuli involving biotoxins and capsaicin [73,74]. Physiological roles of TRPV1 are related to neural development and neurogenesis in the hippocampal subgranular and subventricular zones which are active regions of neurogenesis [75]. Previous studies have reported that the TRPV1 agonist dihydrocapsaicin (DHC) attenuates ischemic stroke-induced cortical injury through hypothermic effect [76–78]. TRPV1 expression is also increased in the hippocampal dentate gyrus after temporal lobe epilepsy [79]. TRPV1 antagonists, capsazepine or 5'-Iodoresiniferatoxin, have potential therapeutic use in preventing excessive calcium entry and decreasing pain [80–82].

1.5. Physiological and Pathological Properties of Zinc in the Brain

Zinc is an essential cation abundantly distributed in all animal tissues, especially in the central nervous system (CNS) and hippocampus. Most zinc is tightly bound to metalloproteins and present in the metallothionein form or free ionic form (Zn^{2+}) within the synaptic vesicles along with several neurotransmitters such as glutamate [83,84]. Loosely bound zinc or Zn^{2+} is found in the synaptic vesicles and released by external or internal stimuli to the synaptic cleft. Re-uptake occurs in nearby synaptic terminals for signal transduction [85,86]. Synaptically located zinc is highly enriched in hippocampal mossy-fiber terminals. In contrast, other CNS regions including the cerebellum and spinal cord contain low concentrations of zinc [87]. Adequate concentrations of zinc are critical under physiological conditions, as zinc is essential for cell division and DNA synthesis, as well as to establish memory function [88,89]. However, in the case of brain diseases such as hypoglycemia, head trauma, epilepsy, and ischemic stroke, it was found that excessively released zinc from synaptic vesicles is translocated and accumulated in the post-synaptic neurons of the hippocampal pyramidal layer and dentate gyrus, as visualized by N-(6-methyl-8-quinolye)-para-tolurnesulfonamide [90]. Zinc has bilateral roles in both physiological and pathophysiological conditions, acting as a “double-edged sword”.

Zinc transporters (ZnTs), as well as Zrt- and Irt-like proteins (ZIPs), mediate Zn^{2+} transport from the cytosol to cell organelles or extracellular space. Most members of the ZnT subfamily are ubiquitously located and expressed in cellular organelles, including synaptic vesicles and the plasma membrane [91]. ZnT1 is expressed in the dendritic spine and synaptic membrane [92] and was implicated in Zn^{2+} overload-induced neuronal and glial damage, as well as brain disease [93,94]. The primary role of ZnT3 is regulating vesicular zinc. Vesicular zinc was reported to be implicated in hippocampal neurogenesis and cognitive function [95]. In a previous study, ZnT3 knockout-induced vesicular zinc depletion significantly reduced adult hippocampal neurogenesis, and supplementary zinc treatment remarkably enhanced progenitor cell proliferation and cognitive function [85]. An autistic phenotype was also observed in ZnT3 knockout mice and significantly decreased social interaction and novelty preference. The ZnT3 knockout brain was found to be larger than that of the wild type (megalencephaly) due to overexpressed BDNF-induced neurite outgrowth and increased neurogenesis [96].

Zinc plays an essential role in maintaining homeostasis, including the neurotransmitter and neuromodulator regulating cycle and synaptic plasticity [97,98]. Zinc homeostasis is destroyed by overloaded cellular zinc due to diverse brain diseases including ischemia, head trauma, and epilepsy. Brain-injury-induced excessive release of endogenous zinc at the glutamatergic postsynaptic neurons exacerbates pathogenesis. Zinc released by synaptic activity can cross the plasma membrane that is regulated by diverse membrane-bounded channels involving the NMDAR, the glutamate receptor 2 (GluR2)-lacking AMPA/kinase channel, the voltage-gated calcium channel, and the sodium–calcium exchanger [99,100]. The pathological properties of zinc in the brain are complex and complicated in that increased zinc can be deleterious to neurons [101] and induce apoptotic damage [102]. Increased intracellular zinc acts as an ionic regulator of excitotoxic neuronal damage [90,103], and brain-damage-mediated oxidative stress disassembles the loosely bound zinc from metalloproteins (zinc-binding proteins), which are an essential means of maintaining the zinc level in the brain; this leads to an increasing zinc concentration [104,105]. Intracellular

organelles involving mitochondria, lysosomes, and the endoplasmic reticulum excessively take up and store the increased intracellular zinc, which induces ROS production; consequently, the ROS-induced oxidative damage triggers cell death [106–108]. One of the possible aggravating cascades of zinc is overloaded zinc in the mitochondria. This causes caspase-dependent apoptotic cascades through depolarization, and the cytochrome C release via mitochondrial zinc contributes to the mitochondrial permeability transition pore [109,110]. In addition, the lysosomal zinc concentration rises rapidly after external or internal stimuli such as hydrogen peroxide exposure. Lysosomal zinc constructs a lysosomal membrane; consequently, proteolytic factors are secreted to the cytoplasm and lead to cell death [105].

However, pathological zinc-overloaded brain and spinal cord damage was attenuated by ZnT3 knockout: (1) The intra-hippocampal injection of colchicine induced extensive neuronal death, disturbance of axonal transport, destruction of the cytoskeletal structure, and zinc accumulation. However, in ZnT3 knockout mice, colchicine-injection-induced brain damage was strikingly attenuated [111]. (2) Myelin oligodendrocyte glycoprotein 35–55 peptide, *Mycobacterium tuberculosis*, and pertussis toxin-induced experimental autoimmune encephalomyelitis (EAE) caused neuronal demyelination, monocyte and neutrophil infiltration, immunoglobulin extravasation, and zinc accumulation. Vesicular zinc depletion via ZnT3 knockout reduced EAE-induced spinal cord damage [112]. On the other hand, from the perspective of clinical trials, chemotherapy can induce cognitive impairment. The anti-cancer agent, paclitaxel, decreases vesicular zinc concentration and hippocampal neurogenesis during the acute and chronic treatment period. Supplementing zinc can attenuate chemotherapy (paclitaxel)-induced cognitive dysfunction [113].

Several studies have explored targeting excessively released zinc from synaptic vesicles in neurological diseases to reduce brain damage. The zinc-chelating agent (1) extracellular zinc chelator, clioquinol (5-chloro-7-iodo-8-hydroxy-quinoline), has protective effects against EAE-induced neuronal demyelination and spinal cord damage [114]. (2) Targeting zinc and glutathione using N-acetyl-L-cysteine (NAC) attenuates hypoglycemia-induced neuronal damage cascades, including zinc overload [115]. (3) Targeting zinc and AMPK using the novel developed compounds 1H10 and 2G11s in EAE and ischemic stroke reduced spinal cord [116] and brain damage [117].

Following the above zinc-related published studies, this review considered the diverse modulatory roles of zinc and the TRP channels in pathophysiological conditions in the brain. Diverse divalent cations move into the intracellular space through most TRP channels, which are also zinc permeable (Table 1).

Table 1. Zinc-permeable and sensitivity of TRP channels.

Channels	Experimental Results	References
TRPM2	TRPM2-knockout microglial cells prevented high zinc exposure-induced zinc neurotoxicity. Hydrogen peroxide-induced intracellular zinc accumulation and ROS production were prevented in TRPM2-knockout hippocampal neurons.	[118,119]
TRPM7	TRPM7 is highly permeable to zinc and overexpression of TRPM7 exacerbates zinc toxicity.	[68,120]
TRPA1	Zinc entering through TRPA1 activates TRPA1 and causes pain and irritation via zinc toxicity.	[121]
TRPV6	TRPV6 transports zinc and overexpressed TRPV6 contributes to increasing zinc intoxication.	[122,123]
TRPC5	High zinc exposure-induced cellular toxicity through delayed calcium entry was prevented by TRPC5 blocker.	[35]

Previous studies have shown that brain injuries such as ischemia-, TBI-, epilepsy-, or hypoglycemia-induced vesicular zinc release, or liberation of free zinc from zinc-binding

metalloproteins, cause neuronal death cascades such as ROS production, glial activation and apoptosis. These cascades are closely related to additional TRP channel activation and leading to dysfunction of ionic homeostasis and aggravation of zinc accumulation [7,120,124]. Next, we provide that regulation of TRP channels especially TRPM and TRPC can contribute neuroprotection in diverse brain injuries such as cerebral ischemia, epilepsy, and traumatic brain injury through antagonists of TRPM and TRPC based on previous studies.

2. TRP Channels and Zinc in Brain Disease

2.1. Cerebral Ischemia

Ischemic stroke is caused by various injuries in which a sudden cardiac-arrest-induced decrease in the systemic blood flow or the blockage of brain vessels by blood clots causes a cessation of brain perfusion. There is an extreme risk of neurological impairment including cerebral infarction, neuronal loss, and behavioral dysfunction in global cerebral ischemia (GCI) survivors following the return of spontaneous circulation [125,126]. Post-resuscitation or in the thrombolytic phase after a GCI, additional ischemic injuries through blood reperfusion underlying pathophysiological cascades can cause brain damage through, e.g., free radical formation, neuroinflammation, and altered ionic homeostasis [127,128] (Figure 1A). The main ischemic problems are excessive neurotransmitter and neuromodulator release from the synaptic vesicles, including glutamate, calcium, and zinc, causing influxes to nearby postsynaptic neurons through a cation-selective channel. Overloaded calcium via NMDAR was inhibited by increasing the TRPC6 in transgenic mice [129]. Inhibited TRPC6 degradation by hyperforin following ischemia activated the neuroprotective pathway involving the CREB pathway to reduce brain damage [130]. One ischemic category, intracerebral hemorrhage (ICH), is an intracranial bleeding stroke. ICH leads to the formation of a glial scar that causes tissue damage, neuroinflammation, and toxic edema. The provoked neuroinflammatory cytokines, such as neutrophils, macrophages, and chemokines, lead to secondary injury following the primary ICH [131]. Thrombin in the hematoma treatment in cultured astrocytes activated TRPC3 expression [132], and the TRPC3 inhibitor, Pyr3, reduced astrocyte activation and behavior impairments following an ICH [133]. These reports suggest that diverse TRP channels are closely associated with cerebral ischemia, and targeting the TRP channels may be a therapeutic window for ischemic problems. In addition, Hong et al. developed a novel zinc chelator, 2G11, based on an AMPK inhibitor, compound C, through virtual screening [117]. AMPK is a well-known energy metabolism regulatory factor; however, the high phosphorylation of AMPK has deleterious effects on neurons, which activates neuronal nitrous oxide synthase (nNOS), and zinc excitotoxicity induces pre-apoptotic factors such as LKB1 and Bim [134,135].

Previous studies have confirmed high accumulations of extracellular zinc in the intraneuronal space in cerebral ischemic animal models [136]. There are possible deleterious cascades of overloaded zinc affecting the surrounding neurons or cellular organelles in an ischemic condition. Extra- and intraneuronal zinc chelation by N,N,N',N'-tetrakis(2-pyridylmethyl)ethylenediamine) OG significantly reduced brain infarction, behavior impairments, apoptotic cell damage including poly(ADP-ribose)polymerase-1 (PARP-1) cleavage, and PAR accumulation [137]. Overloaded zinc causes PARP activation, which is an essential modulator for cell damage cascades from diverse stimuli. In addition, zinc chelation in the ischemic condition contributed to decreasing ROS production, and the inhibition of NADPH oxidase-derived ROS production decreased zinc translocation [138]. These previous studies suggest that zinc is closely associated with neuronal-death-inducing cascades, and zinc translocation might be accelerated via zinc-related membrane-bounded channels from the initiated cell-death process (Figure 1B).

TRPM7 has been implicated in the transport of cations such as calcium, magnesium, and zinc. Aarts et al. demonstrated that oxygen–glucose deprivation-induced calcium overload and neuronal death were attenuated by using TRPM7 siRNA [69]. Sun et al. found that the recombinant adeno-associated virus-mediated suppression of hippocampal TRPM7 offered neuroprotection against global ischemia [139]. These results suggest that TRPM7

is closely related to brain injury, especially ischemic stroke. Several studies have investigated the relationship between TRPM7 and zinc. Inoue et al. showed that an overdose of extracellular zinc contributed to the activation of TRPM7 and increased intracellular zinc accumulation in cultured cells. Moreover, knockdown of TRPM7 using TRPM7 shRNA decreased zinc neurotoxicity [120]. Hong et al. applied known inhibitor of the TRPM7 channel, carvacrol (extracted from *Origanum vulgare*, a monoterpene phenol) [140,141], to a GCI animal disease model. It is known that carvacrol also activates TRPA1 and TRPV3 [142,143]. GCI was found to induce extensive neuronal death, zinc accumulation from excessively released pre-synaptic vesicles, oxidative-damage-mediated lipid peroxidation, and microglial and astroglial over-activation. Specifically, the authors observed the results after increasing TRPM7 activation three days after GCI. Carvacrol was found to offer neuroprotective effects against GCI by decreasing the expression of TRPM7 and zinc accumulation [144] (Figure 1C).

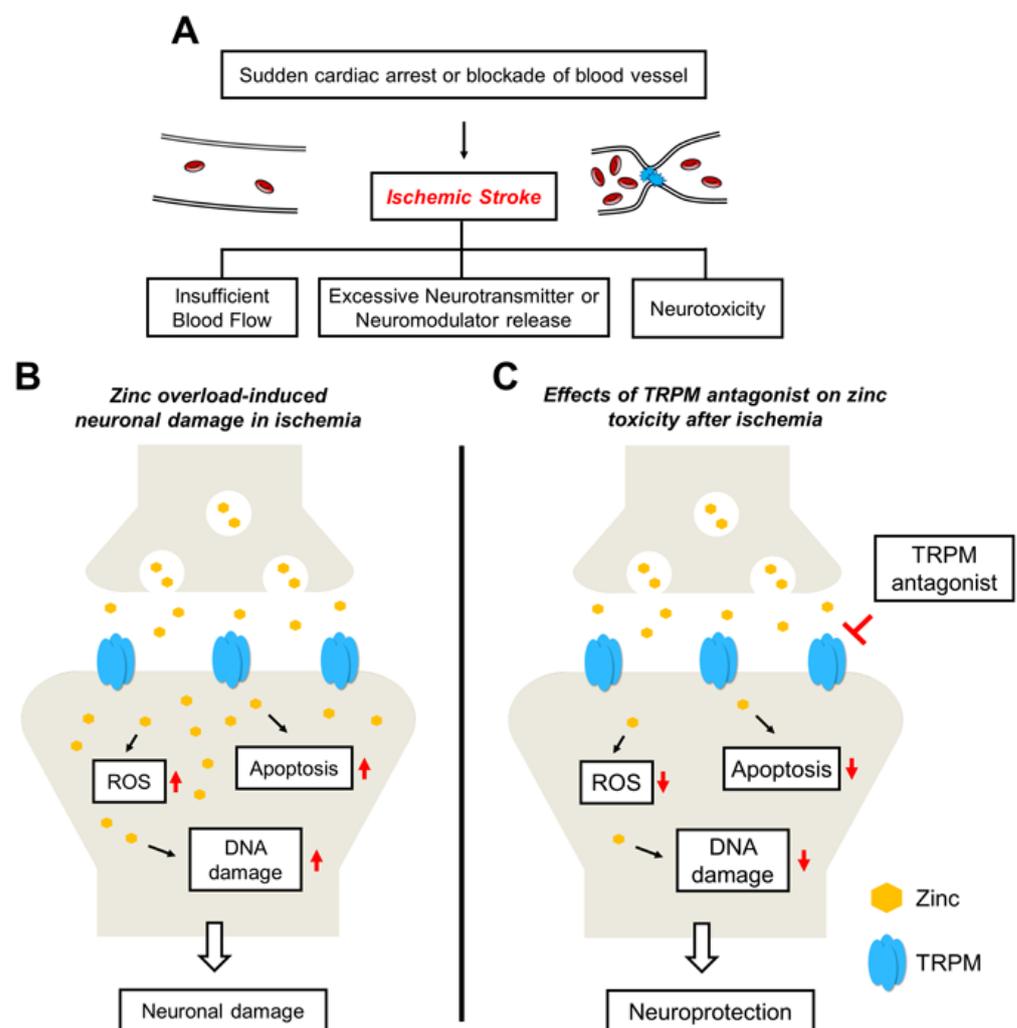


Figure 1. Proposed cascades for the neuroprotective effects of TRPM antagonists on global cerebral-ischemia-induced neuronal death. (A) The main cause of brain ischemia is drastically halted blood flow and the blockage of blood vessels. Deleterious mechanisms following brain ischemia are neurotoxicity, glutamate excitotoxicity, and zinc overload. (B) A schematic drawing illustrating the possible cascades via ischemia that can induce neuronal damage. Zinc that is excessively released from pre-synaptic vesicles and accumulated through the TRPM channel can trigger ROS production, thereby damaging the apoptotic pathway and DNA. Consequently, this accumulation can contribute to neuronal damage. (C) Possible neuroprotective properties of TRPM antagonists. Reduced post-synaptic zinc entering through the TRPM channel via antagonists can reduce neuronal damage.

2.2. Epilepsy

Epilepsy is characterized by a lasting predisposition to experiencing spontaneous epileptic seizures and suffering from unpredictable seizure behaviors [145,146]. The primary mechanism that initiates epileptic seizures is not understood, but diverse types of brain damage such as hypoxia, head trauma, and stroke contribute to promoting epileptic problems [147,148]. The signaling cascades in epilepsy are primarily caused by the disturbance of the ionic homeostasis, and the neural circuits show highly increased excitation [149] (Figure 2A). Although several risk factors can exacerbate epileptic brain damage, previous studies have focused on highly accumulated, zinc-mediated neurotoxicity [150–152] (Figure 2B). Epileptogenesis is closely related to greater depolarization in neurons and a high susceptibility to epileptic activity; the blockade of TRPC3 contributes to diminishing these hyper-excitable effects [153]. Epilepsy induces the downregulation of TRPC6, which increases seizure susceptibility and neuronal polarization. TRPC6 knockdown inhibited the programmed cell death in the hippocampus following status epilepticus (SE) [154].

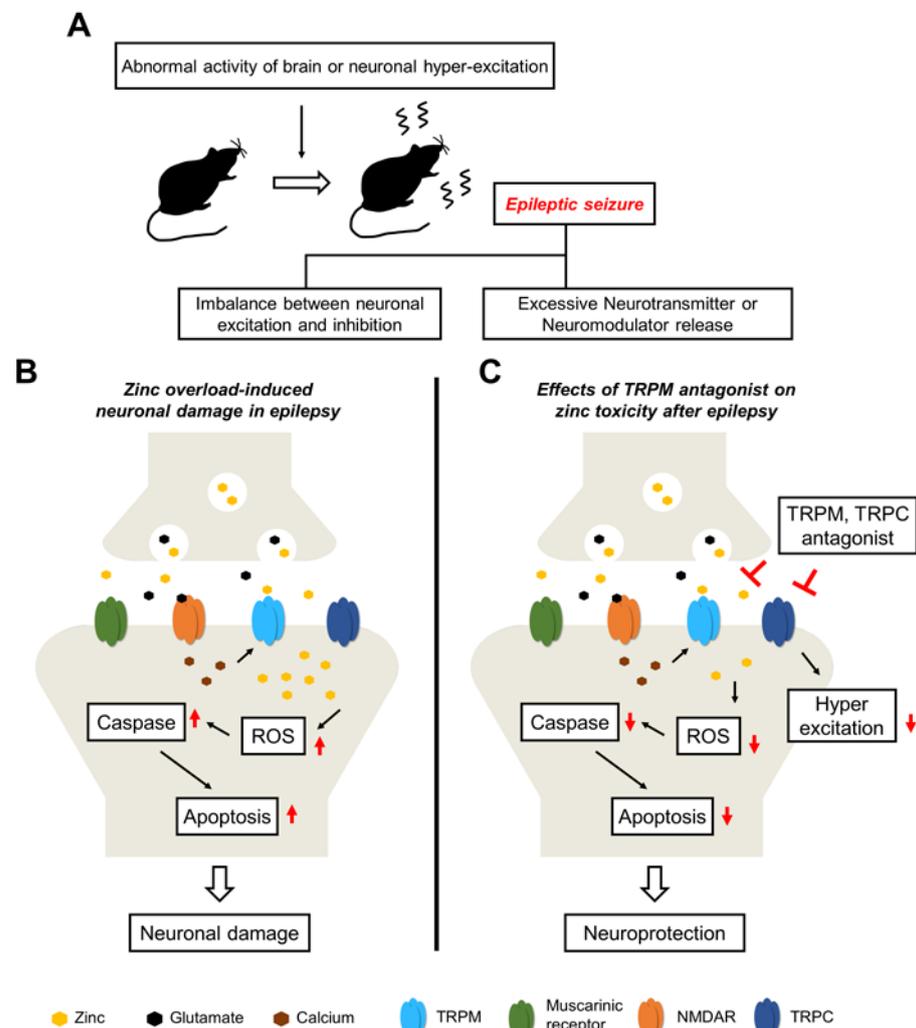


Figure 2. Proposed cascades for the neuroprotective effects of TRPM antagonists on epileptic seizure-induced neuronal death. (A) The main cause of epileptic seizures is excessively released excitatory-neurotransmitter-induced hyper-excitation and the dysfunction of neuronal action potential. (B) Schematic drawing showing how the possible cascades via epileptic seizures induce neuronal damage. Zinc that is excessively released from pre-synaptic vesicles and accumulated through the TRPM channel can trigger ROS production and lead to the apoptotic pathway, thereby contributing to neuronal damage. (C) Possible neuroprotective properties of TRPM antagonists. Reduced post-synaptic zinc entering through the TRPM channel via antagonists can reduce neuronal damage.

A cascade of epileptic-seizure-induced hippocampal neuron death is also associated with zinc concentration. ZnT3 null mice with kainate-induced epilepsy displayed decreased neuronal loss in the hippocampal CA1 region in the acute phase [155], and the ZnT3-reflected absence of vesicular zinc had more sensitivity following the epileptic seizure score [156]. However, a chronic zinc supplementation diet in an epileptic seizure animal model restored the cognitive and behavior outcomes, abnormal expression of GPR39, ZnT3, and myelin basic protein (MBP) when compared with a zinc-deficient diet [157]. These results suggest that consistent zinc supplementation induces positive outcomes after a seizure, but in the early-time phase of a seizure, modulating zinc concentration may be a therapeutic window for epileptic neuronal damage.

Khalil et al. demonstrated that carvacrol treatment after electrode-implantation-induced recurrent SE protected against cognitive decline, hippocampal neuronal damage, and early seizure frequency [158]. Jeong et al. applied the TRPM7 antagonist, carvacrol, to a pilocarpine-induced epileptic seizure animal model. Epilepsy causes the overexpression of TRPM7, excessive zinc accumulation, oxidative damage, immunoglobulin extravasation, and neuronal death. Carvacrol has overall neuroprotective effects on all aspects of epilepsy except for seizure-grade epilepsy (Racine stage). They also used 2-aminoethoxydiphenyl borate (2-APB), known nonspecific TRP-channel modulator, 2-APB inhibits TRPM7 [159] and TRPM2 [160] and also activates a number of TRPV channels [161,162]. Our previous study focused on the inhibitory effect of 2-aminoethoxydiphenyl borate (2-APB) on TRPM7 and found that it significantly reduced TRPM7 overexpression, zinc translocation, and neuronal damage [163] (Figure 2C).

2.3. Traumatic Brain Injury

Traumatic brain injury (TBI) is caused by external forces, such as accidents and violence, and causes disabilities in millions of people. TBI is a devastating brain injury that contributes to neuronal loss and the subsequent dysfunction of memory and cognition. When head-impact-induced primary injury occurs, the resulting immediate TBI can include brain edema and swelling that does not immediately cause neuronal damage. However, TBI evolves afterwards [164]. Secondary injury almost always follows the primary injury and can lead to severe brain damage, especially zinc translocation and microglial activation [165,166] (Figure 3A,B). There are several lines of evidence for suggesting a therapeutic approach following TBI-induced neuronal death using hypothermia, applying antioxidative compounds, and reducing the vesicular zinc [167–169]. Following TBI, there are increases in the TRPM2 mRNA levels in the hippocampal and cortical regions [170]. Vehbi et al. reported that TRPM2 reduction using melatonin decreased oxidative stress, apoptotic damage, and calcium influx after TBI [171].

Zinc is highly accumulated in postsynaptic neurons and causes neurotoxicity in the brain. Pretreatment of the extracellular zinc chelator, calcium ethylenediaminetetraacetic acid, increased the neuroprotection-related gene expression, including heme oxygenase-1 (HO-1), glutathione peroxidase 1 (GPX-1), and heat-shock protein 70 (HSP-70), and decreased apoptotic cell death following TBI [172]. However, a zinc-deficient diet contributes to the disturbance of hippocampal neurogenesis following TBI, where progenitor cell proliferation is immediately increased after a brain injury because of the repair process during the compensative mechanisms [173]. Choi et al. reported that the metal chelator, 5-chloro-7-iodo-8-hydroxy-quinoline (Clioquinol, CQ), reduced progenitor cell proliferation, neuroblast production, and vesicular zinc distribution, reducing TBI-induced neuronal damage [174].

Li et al. demonstrated the neuroprotective effects of carvacrol on cortical neurons with TBI. Increased intracellular calcium concentrations through TRPM7 were attenuated by carvacrol treatment. The results found that carvacrol treatment decreased calcium-overload-induced cellular damage, including neuronal nitric oxide synthase (nNOS) expression [175]. Xu et al. used a controlled cortical impact (CCI)-induced TBI animal disease model. TRPM suppression by shTRPM7 following TBI decreased TBI-induced neurological deficits, apop-

otic cell death cascades including terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining, and cleaved caspase-3 expression [176]. Park et al. demonstrated that the TRPC5 antagonist NU6027 has neuroprotective effects on a CCI-induced severe TBI animal model. The authors found that NU6027 treatment after TBI attenuated TBI-induced neuronal damage, oxidative stress, glial activation, and zinc translocation in the hippocampal CA3 region. TRPC5 was known and defined as a calcium channel, but these results suggest that zinc may also translocate through TRPC5 [177]. Lee et al. found that carvacrol decreases TRPM7 expression after TBI and that TBI-induced neuronal damage cascades including zinc accumulation were attenuated by carvacrol with the inhibition of TRPM7. Carvacrol recovered neurological deficits and delayed neuronal loss 7 days after TBI. The authors also demonstrated that the other TRPM7 antagonists 2-APB and NS8593 provide neuroprotective effects after TBI [166] (Figure 3C).

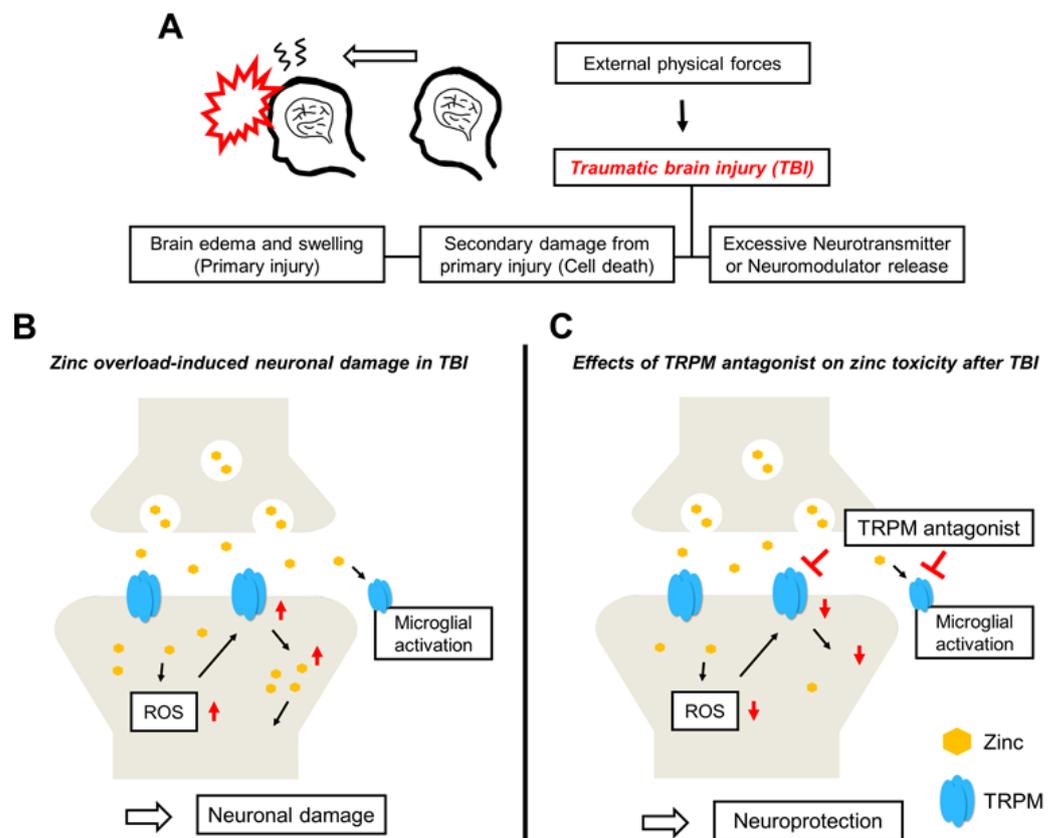


Figure 3. Proposed cascades for the neuroprotective effects of TRPM antagonists on traumatic brain-injury-induced neuronal death: (A) The main causes of TBI are external physical forces and stimuli. TBI-induced primary damage produces brain edema, and swelling is caused instantly. Secondary damage from primary insult leads to deleterious cellular cascades. (B) Schematic drawing showing how the possible cascades via TBI induce neuronal damage. Excessively released zinc from pre-synaptic vesicles and zinc accumulated through the TRPM channel can trigger ROS production and, thereby, trigger further activation of TRPM, leading to an increase in the intracellular zinc concentration. This concentration of zinc contributes to neuronal damage. (C) Possible neuroprotective properties of TRPM antagonists. Reduced post-synaptic zinc entering through the TRPM channel via antagonists can reduce neuronal damage.

3. Conclusions

The process of neurons being damaged after several brain injury types involves diverse extra- and intracellular detrimental cascades, mainly the homeostasis disturbance-induced dysregulation of cellular functions. Recent preclinical studies have found that the physiological and pathological properties of TRP channels and zinc have deleterious effects

in brain diseases. This review focused on both alterations in the ionic gradient between extra and intracellular spaces through TRP channels and the translocation of zinc with ionic influxes. Blocking these channels was found to have neuroprotective properties in multiple brain disease conditions and represents a promising therapeutic avenue. Additionally, the regulation of zinc concentration is essential for the prevention of brain injury because zinc overload can contribute to, or exacerbate, brain damage following different types of such injuries. Several reports explain that using zinc as a neurotoxic component in brain disease and regulating zinc concentration levels unveils a therapeutic approach. On the other hand, consistent zinc supplementation recovers behavior outcomes in animal disease models and clinical trials. Therefore, in this review we suggest that modulation of the zinc concentration in each brain disease or time-dependent phase is an effective approach to solving brain injury-induced neuronal damage; moreover, targeting risk factors for these devastating brain disorders could represent an effective option for treating or preventing ischemic, epileptic, and traumatic brain-injury-induced neuronal death.

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References

1. Samanta, A.; Hughes, T.E.T.; Moiseenkova-Bell, V.Y. Transient Receptor Potential (TRP) Channels. *Subcell. Biochem.* **2018**, *87*, 141–165. [[CrossRef](#)]
2. Wang, R.; Tu, S.; Zhang, J.; Shao, A. Roles of TRP Channels in Neurological Diseases. *Oxid. Med. Cell. Longev.* **2020**, *2020*, 7289194. [[CrossRef](#)] [[PubMed](#)]
3. Yang, F.; Sivils, A.; Cegielski, V.; Singh, S.; Chu, X.P. Transient Receptor Potential (TRP) Channels in Pain, Neuropsychiatric Disorders, and Epilepsy. *Int. J. Mol. Sci.* **2023**, *24*, 4714. [[CrossRef](#)]
4. Leng, T.; Shi, Y.; Xiong, Z.G.; Sun, D. Proton-sensitive cation channels and ion exchangers in ischemic brain injury: New therapeutic targets for stroke? *Prog. Neurobiol.* **2014**, *115*, 189–209. [[CrossRef](#)]
5. Wu, L.J.; Sweet, T.B.; Clapham, D.E. International Union of Basic and Clinical Pharmacology. LXXVI. Current progress in the mammalian TRP ion channel family. *Pharmacol. Rev.* **2010**, *62*, 381–404. [[CrossRef](#)] [[PubMed](#)]
6. Nilius, B.; Szallasi, A. Transient receptor potential channels as drug targets: From the science of basic research to the art of medicine. *Pharmacol. Rev.* **2014**, *66*, 676–814. [[CrossRef](#)]
7. Vennekens, R.; Menigoz, A.; Nilius, B. TRPs in the Brain. *Rev. Physiol. Biochem. Pharmacol.* **2012**, *163*, 27–64. [[CrossRef](#)] [[PubMed](#)]
8. Gaudet, R. TRP channels entering the structural era. *J. Physiol.* **2008**, *586*, 3565–3575. [[CrossRef](#)]
9. Gaudet, R. Divide and conquer: High resolution structural information on TRP channel fragments. *J. Gen. Physiol.* **2009**, *133*, 231–237. [[CrossRef](#)]
10. Sawamura, S.; Shirakawa, H.; Nakagawa, T.; Mori, Y.; Kaneko, S. TRP Channels in the Brain: What Are They There for? In *Neurobiology of TRP Channels*; Emir, T.L.R., Ed.; Frontiers in Neuroscience; CRC Press: Boca Raton, FL, USA, 2017; pp. 295–322.
11. Clapham, D.E. TRP channels as cellular sensors. *Nature* **2003**, *426*, 517–524. [[CrossRef](#)]
12. Katz, B.; Miledi, R. Ionic requirements of synaptic transmitter release. *Nature* **1967**, *215*, 651. [[CrossRef](#)] [[PubMed](#)]
13. Berridge, M.J.; Lipp, P.; Bootman, M.D. The versatility and universality of calcium signalling. *Nat. Rev. Mol. Cell Biol.* **2000**, *1*, 11–21. [[CrossRef](#)] [[PubMed](#)]

14. Zierler, S.; Sumoza-Toledo, A.; Suzuki, S.; Duill, F.O.; Ryazanova, L.V.; Penner, R.; Ryazanov, A.G.; Fleig, A. TRPM7 kinase activity regulates murine mast cell degranulation. *J. Physiol.* **2016**, *594*, 2957–2970. [[CrossRef](#)]
15. Maroto, R.; Raso, A.; Wood, T.G.; Kurosky, A.; Martinac, B.; Hamill, O.P. TRPC1 forms the stretch-activated cation channel in vertebrate cells. *Nat. Cell Biol.* **2005**, *7*, 179–185. [[CrossRef](#)] [[PubMed](#)]
16. Pedersen, S.F.; Owsianik, G.; Nilius, B. TRP channels: An overview. *Cell Calcium* **2005**, *38*, 233–252. [[CrossRef](#)]
17. Krall, R.F.; Tzounopoulos, T.; Aizenman, E. The Function and Regulation of Zinc in the Brain. *Neuroscience* **2021**, *457*, 235–258. [[CrossRef](#)]
18. Hou, S.; Vigeland, L.E.; Zhang, G.; Xu, R.; Li, M.; Heinemann, S.H.; Hoshi, T. Zn²⁺ activates large conductance Ca²⁺-activated K⁺ channel via an intracellular domain. *J. Biol. Chem.* **2010**, *285*, 6434–6442. [[CrossRef](#)]
19. Bouron, A.; Kiselyov, K.; Oberwinkler, J. Permeation, regulation and control of expression of TRP channels by trace metal ions. *Pflugers Arch.* **2015**, *467*, 1143–1164. [[CrossRef](#)]
20. Uchida, K.; Tominaga, M. Extracellular zinc ion regulates transient receptor potential melastatin 5 (TRPM5) channel activation through its interaction with a pore loop domain. *J. Biol. Chem.* **2013**, *288*, 25950–25955. [[CrossRef](#)]
21. Inoue, K.; O'Bryant, Z.; Xiong, Z.G. Zinc-permeable ion channels: Effects on intracellular zinc dynamics and potential physiological/pathophysiological significance. *Curr. Med. Chem.* **2015**, *22*, 1248–1257. [[CrossRef](#)]
22. Tai, Y.; Feng, S.; Du, W.; Wang, Y. Functional roles of TRPC channels in the developing brain. *Pflugers Arch.* **2009**, *458*, 283–289. [[CrossRef](#)] [[PubMed](#)]
23. Heo, D.K.; Chung, W.Y.; Park, H.W.; Yuan, J.P.; Lee, M.G.; Kim, J.Y. Opposite regulatory effects of TRPC1 and TRPC5 on neurite outgrowth in PC12 cells. *Cell. Signal.* **2012**, *24*, 899–906. [[CrossRef](#)]
24. Beech, D.J.; Muraki, K.; Flemming, R. Non-selective cationic channels of smooth muscle and the mammalian homologues of Drosophila TRP. *J. Physiol.* **2004**, *559*, 685–706. [[CrossRef](#)] [[PubMed](#)]
25. Kim, S.J.; Kim, Y.S.; Yuan, J.P.; Petralia, R.S.; Worley, P.F.; Linden, D.J. Activation of the TRPC1 cation channel by metabotropic glutamate receptor mGluR1. *Nature* **2003**, *426*, 285–291. [[CrossRef](#)] [[PubMed](#)]
26. Greka, A.; Navarro, B.; Oancea, E.; Duggan, A.; Clapham, D.E. TRPC5 is a regulator of hippocampal neurite length and growth cone morphology. *Nat. Neurosci.* **2003**, *6*, 837–845. [[CrossRef](#)] [[PubMed](#)]
27. Li, M.; Chen, C.; Zhou, Z.; Xu, S.; Yu, Z. A TRPC1-mediated increase in store-operated Ca²⁺ entry is required for the proliferation of adult hippocampal neural progenitor cells. *Cell Calcium* **2012**, *51*, 486–496. [[CrossRef](#)]
28. Hartmann, J.; Dragicevic, E.; Adelsberger, H.; Henning, H.A.; Sumser, M.; Abramowitz, J.; Blum, R.; Dietrich, A.; Freichel, M.; Flockerzi, V.; et al. TRPC3 channels are required for synaptic transmission and motor coordination. *Neuron* **2008**, *59*, 392–398. [[CrossRef](#)]
29. Kim, D.S.; Ryu, H.J.; Kim, J.E.; Kang, T.C. The reverse roles of transient receptor potential canonical channel-3 and -6 in neuronal death following pilocarpine-induced status epilepticus. *Cell. Mol. Neurobiol.* **2013**, *33*, 99–109. [[CrossRef](#)]
30. Li, H.S.; Xu, X.Z.; Montell, C. Activation of a TRPC3-dependent cation current through the neurotrophin BDNF. *Neuron* **1999**, *24*, 261–273. [[CrossRef](#)]
31. Acheson, A.; Conover, J.C.; Fandl, J.P.; DeChiara, T.M.; Russell, M.; Thadani, A.; Squinto, S.P.; Yancopoulos, G.D.; Lindsay, R.M. A BDNF autocrine loop in adult sensory neurons prevents cell death. *Nature* **1995**, *374*, 450–453. [[CrossRef](#)]
32. Huang, E.J.; Reichardt, L.F. Neurotrophins: Roles in neuronal development and function. *Annu. Rev. Neurosci.* **2001**, *24*, 677–736. [[CrossRef](#)] [[PubMed](#)]
33. Beck, A.; Speicher, T.; Stoerger, C.; Sell, T.; Dettmer, V.; Jusoh, S.A.; Abdulmughni, A.; Cavalie, A.; Philipp, S.E.; Zhu, M.X.; et al. Conserved gating elements in TRPC4 and TRPC5 channels. *J. Biol. Chem.* **2013**, *288*, 19471–19483. [[CrossRef](#)] [[PubMed](#)]
34. Jeon, J.P.; Roh, S.E.; Wie, J.; Kim, J.; Kim, H.; Lee, K.P.; Yang, D.; Jeon, J.H.; Cho, N.H.; Kim, I.G.; et al. Activation of TRPC4beta by Galphai subunit increases Ca²⁺ selectivity and controls neurite morphogenesis in cultured hippocampal neuron. *Cell Calcium* **2013**, *54*, 307–319. [[CrossRef](#)]
35. Park, S.E.; Song, J.H.; Hong, C.; Kim, D.E.; Sul, J.W.; Kim, T.Y.; Seo, B.R.; So, I.; Kim, S.Y.; Bae, D.J.; et al. Contribution of Zinc-Dependent Delayed Calcium Influx via TRPC5 in Oxidative Neuronal Death and its Prevention by Novel TRPC Antagonist. *Mol. Neurobiol.* **2019**, *56*, 2822–2835. [[CrossRef](#)]
36. Chung, Y.H.; Sun Ahn, H.; Kim, D.; Hoon Shin, D.; Su Kim, S.; Yong Kim, K.; Bok Lee, W.; Ik Cha, C. Immunohistochemical study on the distribution of TRPC channels in the rat hippocampus. *Brain Res.* **2006**, *1085*, 132–137. [[CrossRef](#)] [[PubMed](#)]
37. Giampa, C.; DeMarch, Z.; Patassini, S.; Bernardi, G.; Fusco, F.R. Immunohistochemical localization of TRPC6 in the rat substantia nigra. *Neurosci. Lett.* **2007**, *424*, 170–174. [[CrossRef](#)]
38. Dietrich, A.; Gudermann, T. Trpc6. In *Handbook of Experimental Pharmacology*; Springer: Berlin/Heidelberg, Germany, 2007; pp. 125–141. [[CrossRef](#)]
39. Zhou, J.; Du, W.; Zhou, K.; Tai, Y.; Yao, H.; Jia, Y.; Ding, Y.; Wang, Y. Critical role of TRPC6 channels in the formation of excitatory synapses. *Nat. Neurosci.* **2008**, *11*, 741–743. [[CrossRef](#)]
40. Tai, Y.; Feng, S.; Ge, R.; Du, W.; Zhang, X.; He, Z.; Wang, Y. TRPC6 channels promote dendritic growth via the CaMKIV-CREB pathway. *J. Cell. Sci.* **2008**, *121*, 2301–2307. [[CrossRef](#)]
41. Xie, Y.F.; Belrose, J.C.; Lei, G.; Tymianski, M.; Mori, Y.; Macdonald, J.F.; Jackson, M.F. Dependence of NMDA/GSK-3beta mediated metaplasticity on TRPM2 channels at hippocampal CA3-CA1 synapses. *Mol. Brain* **2011**, *4*, 44. [[CrossRef](#)]

42. Winkler, P.A.; Huang, Y.; Sun, W.; Du, J.; Lu, W. Electron cryo-microscopy structure of a human TRPM4 channel. *Nature* **2017**, *552*, 200–204. [[CrossRef](#)]
43. Jimenez, I.; Prado, Y.; Marchant, F.; Otero, C.; Eltit, F.; Cabello-Verrugio, C.; Cerda, O.; Simon, F. TRPM Channels in Human Diseases. *Cells* **2020**, *9*, 2604. [[CrossRef](#)] [[PubMed](#)]
44. Jiang, L.H. Subunit interaction in channel assembly and functional regulation of transient receptor potential melastatin (TRPM) channels. *Biochem. Soc. Trans.* **2007**, *35*, 86–88. [[CrossRef](#)]
45. Lee, N.; Chen, J.; Sun, L.; Wu, S.; Gray, K.R.; Rich, A.; Huang, M.; Lin, J.H.; Feder, J.N.; Janovitz, E.B.; et al. Expression and characterization of human transient receptor potential melastatin 3 (hTRPM3). *J. Biol. Chem.* **2003**, *278*, 20890–20897. [[CrossRef](#)]
46. Morgans, C.W.; Zhang, J.; Jeffrey, B.G.; Nelson, S.M.; Burke, N.S.; Duvoisin, R.M.; Brown, R.L. TRPM1 is required for the depolarizing light response in retinal ON-bipolar cells. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 19174–19178. [[CrossRef](#)] [[PubMed](#)]
47. Vangeel, L.; Benoit, M.; Miron, Y.; Miller, P.E.; De Clercq, K.; Chaltin, P.; Verfaillie, C.; Vriens, J.; Voets, T. Functional expression and pharmacological modulation of TRPM3 in human sensory neurons. *Br. J. Pharmacol.* **2020**, *177*, 2683–2695. [[CrossRef](#)] [[PubMed](#)]
48. Grimm, C.; Kraft, R.; Sauerbruch, S.; Schultz, G.; Harteneck, C. Molecular and functional characterization of the melastatin-related cation channel TRPM3. *J. Biol. Chem.* **2003**, *278*, 21493–21501. [[CrossRef](#)]
49. Kraft, R.; Harteneck, C. The mammalian melastatin-related transient receptor potential cation channels: An overview. *Pflugers Arch.* **2005**, *451*, 204–211. [[CrossRef](#)]
50. Kraft, R.; Grimm, C.; Grosse, K.; Hoffmann, A.; Sauerbruch, S.; Kettenmann, H.; Schultz, G.; Harteneck, C. Hydrogen peroxide and ADP-ribose induce TRPM2-mediated calcium influx and cation currents in microglia. *Am. J. Physiol. Cell Physiol.* **2004**, *286*, C129–C137. [[CrossRef](#)]
51. Turlova, E.; Feng, Z.P.; Sun, H.S. The role of TRPM2 channels in neurons, glial cells and the blood-brain barrier in cerebral ischemia and hypoxia. *Acta Pharmacol. Sin.* **2018**, *39*, 713–721. [[CrossRef](#)]
52. Xia, R.; Mei, Z.Z.; Mao, H.J.; Yang, W.; Dong, L.; Bradley, H.; Beech, D.J.; Jiang, L.H. Identification of pore residues engaged in determining divalent cationic permeation in transient receptor potential melastatin subtype channel 2. *J. Biol. Chem.* **2008**, *283*, 27426–27432. [[CrossRef](#)]
53. Belrose, J.C.; Jackson, M.F. TRPM2: A candidate therapeutic target for treating neurological diseases. *Acta Pharmacol. Sin.* **2018**, *39*, 722–732. [[CrossRef](#)]
54. Hara, Y.; Wakamori, M.; Ishii, M.; Maeno, E.; Nishida, M.; Yoshida, T.; Yamada, H.; Shimizu, S.; Mori, E.; Kudoh, J.; et al. LTRPC2 Ca²⁺-permeable channel activated by changes in redox status confers susceptibility to cell death. *Mol. Cell* **2002**, *9*, 163–173. [[CrossRef](#)]
55. Olah, M.E.; Jackson, M.F.; Li, H.; Perez, Y.; Sun, H.S.; Kiyonaka, S.; Mori, Y.; Tymianski, M.; MacDonald, J.F. Ca²⁺-dependent induction of TRPM2 currents in hippocampal neurons. *J. Physiol.* **2009**, *587*, 965–979. [[CrossRef](#)]
56. Wehage, E.; Eisfeld, J.; Heiner, I.; Jungling, E.; Zitt, C.; Luckhoff, A. Activation of the cation channel long transient receptor potential channel 2 (LTRPC2) by hydrogen peroxide. A splice variant reveals a mode of activation independent of ADP-ribose. *J. Biol. Chem.* **2002**, *277*, 23150–23156. [[CrossRef](#)] [[PubMed](#)]
57. McHugh, D.; Flemming, R.; Xu, S.Z.; Perraud, A.L.; Beech, D.J. Critical intracellular Ca²⁺ dependence of transient receptor potential melastatin 2 (TRPM2) cation channel activation. *J. Biol. Chem.* **2003**, *278*, 11002–11006. [[CrossRef](#)] [[PubMed](#)]
58. Harteneck, C. Function and pharmacology of TRPM cation channels. *Naunyn Schmiedebergs Arch. Pharmacol.* **2005**, *371*, 307–314. [[CrossRef](#)]
59. Kaneko, S.; Kawakami, S.; Hara, Y.; Wakamori, M.; Itoh, E.; Minami, T.; Takada, Y.; Kume, T.; Katsuki, H.; Mori, Y.; et al. A critical role of TRPM2 in neuronal cell death by hydrogen peroxide. *J. Pharmacol. Sci.* **2006**, *101*, 66–76. [[CrossRef](#)]
60. Belrose, J.C.; Xie, Y.F.; Gierszewski, L.J.; MacDonald, J.F.; Jackson, M.F. Loss of glutathione homeostasis associated with neuronal senescence facilitates TRPM2 channel activation in cultured hippocampal pyramidal neurons. *Mol. Brain* **2012**, *5*, 11. [[CrossRef](#)]
61. Perez, C.A.; Huang, L.; Rong, M.; Kozak, J.A.; Preuss, A.K.; Zhang, H.; Max, M.; Margolskee, R.F. A transient receptor potential channel expressed in taste receptor cells. *Nat. Neurosci.* **2002**, *5*, 1169–1176. [[CrossRef](#)] [[PubMed](#)]
62. Guo, J.; She, J.; Zeng, W.; Chen, Q.; Bai, X.C.; Jiang, Y. Structures of the calcium-activated, non-selective cation channel TRPM4. *Nature* **2017**, *552*, 205–209. [[CrossRef](#)]
63. Guinamard, R.; Demion, M.; Launay, P. Physiological roles of the TRPM4 channel extracted from background currents. *Physiology* **2010**, *25*, 155–164. [[CrossRef](#)] [[PubMed](#)]
64. Nadler, M.J.; Hermosura, M.C.; Inabe, K.; Perraud, A.L.; Zhu, Q.; Stokes, A.J.; Kurotsaki, T.; Kinet, J.P.; Penner, R.; Scharenberg, A.M.; et al. LTRPC7 is a Mg.ATP-regulated divalent cation channel required for cell viability. *Nature* **2001**, *411*, 590–595. [[CrossRef](#)]
65. Runnels, L.W.; Yue, L.; Clapham, D.E. TRP-PLIK, a bifunctional protein with kinase and ion channel activities. *Science* **2001**, *291*, 1043–1047. [[CrossRef](#)]
66. Perraud, A.L.; Zhao, X.; Ryazanov, A.G.; Schmitz, C. The channel-kinase TRPM7 regulates phosphorylation of the translational factor eEF2 via eEF2-k. *Cell. Signal.* **2011**, *23*, 586–593. [[CrossRef](#)] [[PubMed](#)]
67. Sahni, J.; Scharenberg, A.M. TRPM7 ion channels are required for sustained phosphoinositide 3-kinase signaling in lymphocytes. *Cell Metab.* **2008**, *8*, 84–93. [[CrossRef](#)]
68. Monteilh-Zoller, M.K.; Hermosura, M.C.; Nadler, M.J.; Scharenberg, A.M.; Penner, R.; Fleig, A. TRPM7 provides an ion channel mechanism for cellular entry of trace metal ions. *J. Gen. Physiol.* **2003**, *121*, 49–60. [[CrossRef](#)]

69. Aarts, M.; Iihara, K.; Wei, W.L.; Xiong, Z.G.; Arundine, M.; Cerwinski, W.; MacDonald, J.F.; Tymianski, M. A key role for TRPM7 channels in anoxic neuronal death. *Cell* **2003**, *115*, 863–877. [[CrossRef](#)] [[PubMed](#)]
70. Krapivinsky, G.; Mochida, S.; Krapivinsky, L.; Cibulsky, S.M.; Clapham, D.E. The TRPM7 ion channel functions in cholinergic synaptic vesicles and affects transmitter release. *Neuron* **2006**, *52*, 485–496. [[CrossRef](#)]
71. Schmitz, C.; Perraud, A.L.; Johnson, C.O.; Inabe, K.; Smith, M.K.; Penner, R.; Kurosaki, T.; Fleig, A.; Scharenberg, A.M. Regulation of vertebrate cellular Mg^{2+} homeostasis by TRPM7. *Cell* **2003**, *114*, 191–200. [[CrossRef](#)] [[PubMed](#)]
72. Liu, Y.; Chen, C.; Liu, Y.; Li, W.; Wang, Z.; Sun, Q.; Zhou, H.; Chen, X.; Yu, Y.; Wang, Y.; et al. TRPM7 Is Required for Normal Synapse Density, Learning, and Memory at Different Developmental Stages. *Cell Rep.* **2018**, *23*, 3480–3491. [[CrossRef](#)]
73. Hui, K.; Liu, B.; Qin, F. Capsaicin activation of the pain receptor, VR1: Multiple open states from both partial and full binding. *Biophys. J.* **2003**, *84*, 2957–2968. [[CrossRef](#)] [[PubMed](#)]
74. Bohlen, C.J.; Priel, A.; Zhou, S.; King, D.; Siemens, J.; Julius, D. A bivalent tarantula toxin activates the capsaicin receptor, TRPV1, by targeting the outer pore domain. *Cell* **2010**, *141*, 834–845. [[CrossRef](#)] [[PubMed](#)]
75. Ramirez-Barrantes, R.; Cordova, C.; Poblete, H.; Munoz, P.; Marchant, I.; Wianny, F.; Olivero, P. Perspectives of TRPV1 Function on the Neurogenesis and Neural Plasticity. *Neural Plast.* **2016**, *2016*, 1568145. [[CrossRef](#)]
76. Cao, Z.; Balasubramanian, A.; Marrelli, S.P. Pharmacologically induced hypothermia via TRPV1 channel agonism provides neuroprotection following ischemic stroke when initiated 90 min after reperfusion. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2014**, *306*, R149–R156. [[CrossRef](#)] [[PubMed](#)]
77. Muzzi, M.; Felici, R.; Cavone, L.; Gerace, E.; Minassi, A.; Appendino, G.; Moroni, F.; Chiarugi, A. Ischemic neuroprotection by TRPV1 receptor-induced hypothermia. *J. Cereb. Blood Flow Metab.* **2012**, *32*, 978–982. [[CrossRef](#)] [[PubMed](#)]
78. Cao, Z.; Balasubramanian, A.; Pedersen, S.E.; Romero, J.; Pautler, R.G.; Marrelli, S.P. TRPV1-mediated Pharmacological Hypothermia Promotes Improved Functional Recovery Following Ischemic Stroke. *Sci. Rep.* **2017**, *7*, 17685. [[CrossRef](#)] [[PubMed](#)]
79. Bhaskaran, M.D.; Smith, B.N. Effects of TRPV1 activation on synaptic excitation in the dentate gyrus of a mouse model of temporal lobe epilepsy. *Exp. Neurol.* **2010**, *223*, 529–536. [[CrossRef](#)]
80. Smith, H.; Brooks, J.R. Capsaicin-based therapies for pain control. In *Progress in Drug Research*; Springer: Basel, Switzerland, 2014; Volume 68, pp. 129–146. [[CrossRef](#)]
81. Iannotti, F.A.; Hill, C.L.; Leo, A.; Alhusaini, A.; Soubrane, C.; Mazzarella, E.; Russo, E.; Whalley, B.J.; Di Marzo, V.; Stephens, G.J. 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 Chem. Neurosci.* **2014**, *5*, 1131–1141. [[CrossRef](#)]
82. Gonzalez-Reyes, L.E.; Ladas, T.P.; Chiang, C.C.; Durand, D.M. TRPV1 antagonist capsazepine suppresses 4-AP-induced epileptiform activity in vitro and electrographic seizures in vivo. *Exp. Neurol.* **2013**, *250*, 321–332. [[CrossRef](#)]
83. Frederickson, C.J.; Suh, S.W.; Silva, D.; Frederickson, C.J.; Thompson, R.B. Importance of zinc in the central nervous system: The zinc-containing neuron. *J. Nutr.* **2000**, *130*, 1471S–1483S. [[CrossRef](#)]
84. Sensi, S.L.; Paoletti, P.; Koh, J.Y.; Aizenman, E.; Bush, A.I.; Hershfinkel, M. The neurophysiology and pathology of brain zinc. *J. Neurosci.* **2011**, *31*, 16076–16085. [[CrossRef](#)] [[PubMed](#)]
85. Choi, B.Y.; Hong, D.K.; Jeong, J.H.; Lee, B.E.; Koh, J.Y.; Suh, S.W. Zinc transporter 3 modulates cell proliferation and neuronal differentiation in the adult hippocampus. *Stem Cells* **2020**, *38*, 994–1006. [[CrossRef](#)] [[PubMed](#)]
86. Mott, D.D.; Dingledine, R. Unraveling the role of zinc in memory. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 3103–3104. [[CrossRef](#)] [[PubMed](#)]
87. Frederickson, C.J. Neurobiology of zinc and zinc-containing neurons. *Int. Rev. Neurobiol.* **1989**, *31*, 145–238. [[CrossRef](#)] [[PubMed](#)]
88. Golub, M.S.; Takeuchi, P.T.; Keen, C.L.; Gershwin, M.E.; Hendrickx, A.G.; Lonnerdal, B. Modulation of behavioral performance of prepubertal monkeys by moderate dietary zinc deprivation. *Am. J. Clin. Nutr.* **1994**, *60*, 238–243. [[CrossRef](#)] [[PubMed](#)]
89. MacDonald, R.S. The role of zinc in growth and cell proliferation. *J. Nutr.* **2000**, *130*, 1500S–1508S. [[CrossRef](#)]
90. Koh, J.Y.; Suh, S.W.; Gwag, B.J.; He, Y.Y.; Hsu, C.Y.; Choi, D.W. The role of zinc in selective neuronal death after transient global cerebral ischemia. *Science* **1996**, *272*, 1013–1016. [[CrossRef](#)]
91. Sensi, S.L.; Paoletti, P.; Bush, A.I.; Sekler, I. Zinc in the physiology and pathology of the CNS. *Nat. Rev. Neurosci.* **2009**, *10*, 780–791. [[CrossRef](#)]
92. Sindreu, C.; Bayes, A.; Altafaj, X.; Perez-Clausell, J. Zinc transporter-1 concentrates at the postsynaptic density of hippocampal synapses. *Mol. Brain* **2014**, *7*, 16. [[CrossRef](#)]
93. Palmiter, R.D.; Findley, S.D. Cloning and functional characterization of a mammalian zinc transporter that confers resistance to zinc. *EMBO J.* **1995**, *14*, 639–649. [[CrossRef](#)]
94. Nolte, C.; Gore, A.; Sekler, I.; Kresse, W.; Hershfinkel, M.; Hoffmann, A.; Kettenmann, H.; Moran, A. ZnT-1 expression in astroglial cells protects against zinc toxicity and slows the accumulation of intracellular zinc. *Glia* **2004**, *48*, 145–155. [[CrossRef](#)] [[PubMed](#)]
95. Sindreu, C.; Palmiter, R.D.; Storm, D.R. Zinc transporter ZnT-3 regulates presynaptic Erk1/2 signaling and hippocampus-dependent memory. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 3366–3370. [[CrossRef](#)] [[PubMed](#)]
96. Yoo, M.H.; Kim, T.Y.; Yoon, Y.H.; Koh, J.Y. Autism phenotypes in ZnT3 null mice: Involvement of zinc dyshomeostasis, MMP-9 activation and BDNF upregulation. *Sci. Rep.* **2016**, *6*, 28548. [[CrossRef](#)] [[PubMed](#)]
97. Smart, T.G.; Xie, X.; Krishek, B.J. Modulation of inhibitory and excitatory amino acid receptor ion channels by zinc. *Prog. Neurobiol.* **1994**, *42*, 393–441. [[CrossRef](#)] [[PubMed](#)]

98. Frederickson, C.J.; Koh, J.Y.; Bush, A.I. The neurobiology of zinc in health and disease. *Nat. Rev. Neurosci.* **2005**, *6*, 449–462. [[CrossRef](#)]
99. Sensi, S.L.; Jeng, J.M. Rethinking the excitotoxic ionic milieu: The emerging role of Zn²⁺ in ischemic neuronal injury. *Curr. Mol. Med.* **2004**, *4*, 87–111. [[CrossRef](#)] [[PubMed](#)]
100. Choi, D.W.; Koh, J.Y. Zinc and brain injury. *Annu. Rev. Neurosci.* **1998**, *21*, 347–375. [[CrossRef](#)]
101. Bozym, R.A.; Chimienti, F.; Giblin, L.J.; Gross, G.W.; Korichneva, I.; Li, Y.; Libert, S.; Maret, W.; Parviz, M.; Frederickson, C.J.; et al. Free zinc ions outside a narrow concentration range are toxic to a variety of cells in vitro. *Exp. Biol. Med.* **2010**, *235*, 741–750. [[CrossRef](#)]
102. Manev, H.; Kharlamov, E.; Uz, T.; Mason, R.P.; Cagnoli, C.M. Characterization of zinc-induced neuronal death in primary cultures of rat cerebellar granule cells. *Exp. Neurol.* **1997**, *146*, 171–178. [[CrossRef](#)]
103. Weiss, J.H.; Hartley, D.M.; Koh, J.Y.; Choi, D.W. AMPA receptor activation potentiates zinc neurotoxicity. *Neuron* **1993**, *10*, 43–49. [[CrossRef](#)]
104. Chung, R.S.; Fung, S.J.; Leung, Y.K.; Walker, A.K.; McCormack, G.H.; Chuah, M.I.; Vickers, J.C.; West, A.K. Metallothionein expression by NG2 glial cells following CNS injury. *Cell. Mol. Life Sci.* **2007**, *64*, 2716–2722. [[CrossRef](#)] [[PubMed](#)]
105. Hwang, J.J.; Lee, S.J.; Kim, T.Y.; Cho, J.H.; Koh, J.Y. Zinc and 4-hydroxy-2-nonenal mediate lysosomal membrane permeabilization induced by H₂O₂ in cultured hippocampal neurons. *J. Neurosci.* **2008**, *28*, 3114–3122. [[CrossRef](#)] [[PubMed](#)]
106. Trushina, E.; McMurray, C.T. Oxidative stress and mitochondrial dysfunction in neurodegenerative diseases. *Neuroscience* **2007**, *145*, 1233–1248. [[CrossRef](#)]
107. Zhang, Y.; Wang, H.; Li, J.; Jimenez, D.A.; Levitan, E.S.; Aizenman, E.; Rosenberg, P.A. Peroxynitrite-induced neuronal apoptosis is mediated by intracellular zinc release and 12-lipoxygenase activation. *J. Neurosci.* **2004**, *24*, 10616–10627. [[CrossRef](#)] [[PubMed](#)]
108. Aizenman, E.; Stout, A.K.; Hartnett, K.A.; Dineley, K.E.; McLaughlin, B.; Reynolds, I.J. Induction of neuronal apoptosis by thiol oxidation: Putative role of intracellular zinc release. *J. Neurochem.* **2000**, *75*, 1878–1888. [[CrossRef](#)]
109. Jiang, D.; Sullivan, P.G.; Sensi, S.L.; Steward, O.; Weiss, J.H. Zn²⁺ induces permeability transition pore opening and release of pro-apoptotic peptides from neuronal mitochondria. *J. Biol. Chem.* **2001**, *276*, 47524–47529. [[CrossRef](#)]
110. Malaiyandi, L.M.; Vergun, O.; Dineley, K.E.; Reynolds, I.J. Direct visualization of mitochondrial zinc accumulation reveals uniporter-dependent and -independent transport mechanisms. *J. Neurochem.* **2005**, *93*, 1242–1250. [[CrossRef](#)]
111. Choi, B.Y.; Hong, D.K.; Suh, S.W. ZnT3 Gene Deletion Reduces Colchicine-Induced Dentate Granule Cell Degeneration. *Int. J. Mol. Sci.* **2017**, *18*, 2189. [[CrossRef](#)]
112. Choi, B.Y.; Kim, I.Y.; Kim, J.H.; Kho, A.R.; Lee, S.H.; Lee, B.E.; Sohn, M.; Koh, J.Y.; Suh, S.W. Zinc transporter 3 (ZnT3) gene deletion reduces spinal cord white matter damage and motor deficits in a murine MOG-induced multiple sclerosis model. *Neurobiol. Dis.* **2016**, *94*, 205–212. [[CrossRef](#)]
113. Lee, B.E.; Choi, B.Y.; Hong, D.K.; Kim, J.H.; Lee, S.H.; Kho, A.R.; Kim, H.; Choi, H.C.; Suh, S.W. The cancer chemotherapeutic agent paclitaxel (Taxol) reduces hippocampal neurogenesis via down-regulation of vesicular zinc. *Sci. Rep.* **2017**, *7*, 11667. [[CrossRef](#)]
114. Choi, B.Y.; Jang, B.G.; Kim, J.H.; Seo, J.N.; Wu, G.; Sohn, M.; Chung, T.N.; Suh, S.W. Copper/zinc chelation by clioquinol reduces spinal cord white matter damage and behavioral deficits in a murine MOG-induced multiple sclerosis model. *Neurobiol. Dis.* **2013**, *54*, 382–391. [[CrossRef](#)] [[PubMed](#)]
115. Kho, A.R.; Choi, B.Y.; Kim, J.H.; Lee, S.H.; Hong, D.K.; Lee, S.H.; Jeong, J.H.; Sohn, M.; Suh, S.W. Prevention of hypoglycemia-induced hippocampal neuronal death by N-acetyl-L-cysteine (NAC). *Amino Acids* **2017**, *49*, 367–378. [[CrossRef](#)] [[PubMed](#)]
116. Choi, B.Y.; Jeong, J.H.; Eom, J.W.; Koh, J.Y.; Kim, Y.H.; Suh, S.W. A Novel Zinc Chelator, 1H10, Ameliorates Experimental Autoimmune Encephalomyelitis by Modulating Zinc Toxicity and AMPK Activation. *Int. J. Mol. Sci.* **2020**, *21*, 3375. [[CrossRef](#)] [[PubMed](#)]
117. Hong, D.K.; Eom, J.W.; Kho, A.R.; Lee, S.H.; Kang, B.S.; Lee, S.H.; Koh, J.Y.; Kim, Y.H.; Choi, B.Y.; Suh, S.W. The Inhibition of Zinc Excitotoxicity and AMPK Phosphorylation by a Novel Zinc Chelator, 2G11, Ameliorates Neuronal Death Induced by Global Cerebral Ischemia. *Antioxidants* **2022**, *11*, 2192. [[CrossRef](#)] [[PubMed](#)]
118. Mortadza, S.S.; Sim, J.A.; Stacey, M.; Jiang, L.H. Signalling mechanisms mediating Zn²⁺-induced TRPM2 channel activation and cell death in microglial cells. *Sci. Rep.* **2017**, *7*, 45032. [[CrossRef](#)]
119. Li, X.; Yang, W.; Jiang, L.H. Alteration in Intracellular Zn²⁺ Homeostasis as a Result of TRPM2 Channel Activation Contributes to ROS-Induced Hippocampal Neuronal Death. *Front. Mol. Neurosci.* **2017**, *10*, 414. [[CrossRef](#)]
120. Inoue, K.; Branigan, D.; Xiong, Z.G. Zinc-induced neurotoxicity mediated by transient receptor potential melastatin 7 channels. *J. Biol. Chem.* **2010**, *285*, 7430–7439. [[CrossRef](#)]
121. Hu, H.; Bandell, M.; Petrus, M.J.; Zhu, M.X.; Patapoutian, A. Zinc activates damage-sensing TRPA1 ion channels. *Nat. Chem. Biol.* **2009**, *5*, 183–190. [[CrossRef](#)]
122. Kovacs, G.; Danko, T.; Bergeron, M.J.; Balazs, B.; Suzuki, Y.; Zsembery, A.; Hediger, M.A. Heavy metal cations permeate the TRPV6 epithelial cation channel. *Cell Calcium* **2011**, *49*, 43–55. [[CrossRef](#)]
123. Kovacs, G.; Montalbetti, N.; Franz, M.C.; Graeter, S.; Simonin, A.; Hediger, M.A. Human TRPV5 and TRPV6: Key players in cadmium and zinc toxicity. *Cell Calcium* **2013**, *54*, 276–286. [[CrossRef](#)]
124. Takahashi, N.; Mori, Y. TRP Channels as Sensors and Signal Integrators of Redox Status Changes. *Front. Pharmacol.* **2011**, *2*, 58. [[CrossRef](#)] [[PubMed](#)]

125. Girotra, S.; Chan, P.S.; Bradley, S.M. Post-resuscitation care following out-of-hospital and in-hospital cardiac arrest. *Heart* **2015**, *101*, 1943–1949. [[CrossRef](#)] [[PubMed](#)]
126. Lipton, P. Ischemic cell death in brain neurons. *Physiol. Rev.* **1999**, *79*, 1431–1568. [[CrossRef](#)] [[PubMed](#)]
127. Kang, Y. Management of post-cardiac arrest syndrome. *Acute Crit. Care* **2019**, *34*, 173–178. [[CrossRef](#)]
128. Neumar, R.W. Molecular mechanisms of ischemic neuronal injury. *Ann. Emerg. Med.* **2000**, *36*, 483–506. [[CrossRef](#)]
129. Li, H.; Huang, J.; Du, W.; Jia, C.; Yao, H.; Wang, Y. TRPC6 inhibited NMDA receptor activities and protected neurons from ischemic excitotoxicity. *J. Neurochem.* **2012**, *123*, 1010–1018. [[CrossRef](#)]
130. Lin, Y.; Zhang, J.C.; Fu, J.; Chen, F.; Wang, J.; Wu, Z.L.; Yuan, S.Y. Hyperforin attenuates brain damage induced by transient middle cerebral artery occlusion (MCAO) in rats via inhibition of TRPC6 channels degradation. *J. Cereb. Blood Flow Metab.* **2013**, *33*, 253–262. [[CrossRef](#)]
131. Zhou, Y.; Wang, Y.; Wang, J.; Anne Stetler, R.; Yang, Q.W. Inflammation in intracerebral hemorrhage: From mechanisms to clinical translation. *Prog. Neurobiol.* **2014**, *115*, 25–44. [[CrossRef](#)]
132. Shirakawa, H.; Sakimoto, S.; Nakao, K.; Sugishita, A.; Konno, M.; Iida, S.; Kusano, A.; Hashimoto, E.; Nakagawa, T.; Kaneko, S. Transient receptor potential canonical 3 (TRPC3) mediates thrombin-induced astrocyte activation and upregulates its own expression in cortical astrocytes. *J. Neurosci.* **2010**, *30*, 13116–13129. [[CrossRef](#)]
133. Munakata, M.; Shirakawa, H.; Nagayasu, K.; Miyahara, J.; Miyake, T.; Nakagawa, T.; Katsuki, H.; Kaneko, S. Transient receptor potential canonical 3 inhibitor Pyr3 improves outcomes and attenuates astrogliosis after intracerebral hemorrhage in mice. *Stroke* **2013**, *44*, 1981–1987. [[CrossRef](#)]
134. Kim, Y.H.; Eom, J.W.; Koh, J.Y. Mechanism of Zinc Excitotoxicity: A Focus on AMPK. *Front. Neurosci.* **2020**, *14*, 577958. [[CrossRef](#)] [[PubMed](#)]
135. Ronnett, G.V.; Ramamurthy, S.; Kleman, A.M.; Landree, L.E.; Aja, S. AMPK in the brain: Its roles in energy balance and neuroprotection. *J. Neurochem.* **2009**, *109* (Suppl. 1), 17–23. [[CrossRef](#)]
136. Frederickson, C.J.; Giblin, L.J.; Krezel, A.; McAdoo, D.J.; Mueller, R.N.; Zeng, Y.; Balaji, R.V.; Masalha, R.; Thompson, R.B.; Fierke, C.A.; et al. Concentrations of extracellular free zinc (pZn) in the central nervous system during simple anesthetization, ischemia and reperfusion. *Exp. Neurol.* **2006**, *198*, 285–293. [[CrossRef](#)] [[PubMed](#)]
137. Zhao, Y.; Pan, R.; Li, S.; Luo, Y.; Yan, F.; Yin, J.; Qi, Z.; Yan, Y.; Ji, X.; Liu, K.J. Chelating intracellularly accumulated zinc decreased ischemic brain injury through reducing neuronal apoptotic death. *Stroke* **2014**, *45*, 1139–1147. [[CrossRef](#)]
138. Zhao, Y.; Yan, F.; Yin, J.; Pan, R.; Shi, W.; Qi, Z.; Fang, Y.; Huang, Y.; Li, S.; Luo, Y.; et al. Synergistic Interaction Between Zinc and Reactive Oxygen Species Amplifies Ischemic Brain Injury in Rats. *Stroke* **2018**, *49*, 2200–2210. [[CrossRef](#)] [[PubMed](#)]
139. Sun, H.S.; Jackson, M.F.; Martin, L.J.; Jansen, K.; Teves, L.; Cui, H.; Kiyonaka, S.; Mori, Y.; Jones, M.; Forster, J.P.; et al. Suppression of hippocampal TRPM7 protein prevents delayed neuronal death in brain ischemia. *Nat. Neurosci.* **2009**, *12*, 1300–1307. [[CrossRef](#)]
140. Parnas, M.; Peters, M.; Dadon, D.; Lev, S.; Vertkin, I.; Slutsky, I.; Minke, B. Carvacrol is a novel inhibitor of Drosophila TRPL and mammalian TRPM7 channels. *Cell Calcium* **2009**, *45*, 300–309. [[CrossRef](#)]
141. Chen, W.L.; Barszczyk, A.; Turlova, E.; Deurloo, M.; Liu, B.; Yang, B.B.; Rutka, J.T.; Feng, Z.P.; Sun, H.S. Inhibition of TRPM7 by carvacrol suppresses glioblastoma cell proliferation, migration and invasion. *Oncotarget* **2015**, *6*, 16321–16340. [[CrossRef](#)]
142. Cui, T.T.; Wang, G.X.; Wei, N.N.; Wang, K. A pivotal role for the activation of TRPV3 channel in itch sensations induced by the natural skin sensitizer carvacrol. *Acta Pharmacol. Sin.* **2018**, *39*, 331–335. [[CrossRef](#)]
143. Niu, C.; Sun, X.; Hu, F.; Tang, X.; Wang, K. Molecular determinants for the chemical activation of the warmth-sensitive TRPV3 channel by the natural monoterpenoid carvacrol. *J. Biol. Chem.* **2022**, *298*, 101706. [[CrossRef](#)]
144. Hong, D.K.; Choi, B.Y.; Kho, A.R.; Lee, S.H.; Jeong, J.H.; Kang, B.S.; Kang, D.H.; Park, K.H.; Suh, S.W. Carvacrol Attenuates Hippocampal Neuronal Death after Global Cerebral Ischemia via Inhibition of Transient Receptor Potential Melastatin 7. *Cells* **2018**, *7*, 231. [[CrossRef](#)]
145. Thijs, R.D.; Surges, R.; O'Brien, T.J.; Sander, J.W. Epilepsy in adults. *Lancet* **2019**, *393*, 689–701. [[CrossRef](#)] [[PubMed](#)]
146. Thurman, D.J.; Beghi, E.; Begley, C.E.; Berg, A.T.; Buchhalter, J.R.; Ding, D.; Hesdorffer, D.C.; Hauser, W.A.; Kazis, L.; Kobau, R.; et al. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia* **2011**, *52* (Suppl. 7), 2–26. [[CrossRef](#)]
147. Quinlan, S.M.M.; Rodriguez-Alvarez, N.; Molloy, E.J.; Madden, S.F.; Boylan, G.B.; Henshall, D.C.; Jimenez-Mateos, E.M. Complex spectrum of phenobarbital effects in a mouse model of neonatal hypoxia-induced seizures. *Sci. Rep.* **2018**, *8*, 9986. [[CrossRef](#)]
148. Yang, H.; Rajah, G.; Guo, A.; Wang, Y.; Wang, Q. Pathogenesis of epileptic seizures and epilepsy after stroke. *Neurol. Res.* **2018**, *40*, 426–432. [[CrossRef](#)] [[PubMed](#)]
149. Bozzi, Y.; Provenzano, G.; Casarosa, S. Neurobiological bases of autism-epilepsy comorbidity: A focus on excitation/inhibition imbalance. *Eur. J. Neurosci.* **2018**, *47*, 534–548. [[CrossRef](#)] [[PubMed](#)]
150. Frederickson, C.J.; Hernandez, M.D.; McGinty, J.F. Translocation of zinc may contribute to seizure-induced death of neurons. *Brain Res.* **1989**, *480*, 317–321. [[CrossRef](#)] [[PubMed](#)]
151. Suh, S.W.; Jo, S.M.; Vajda, Z.; Danscher, G. Adrenalectomy causes loss of zinc ions in zinc-enriched (ZEN) terminals and decreases seizure-induced neuronal death. *Brain Res.* **2001**, *895*, 25–32. [[CrossRef](#)]
152. Cote, A.; Chiasson, M.; Peralta, M.R., 3rd; Lafortune, K.; Pellegrini, L.; Toth, K. Cell type-specific action of seizure-induced intracellular zinc accumulation in the rat hippocampus. *J. Physiol.* **2005**, *566*, 821–837. [[CrossRef](#)]
153. Zhou, F.W.; Roper, S.N. TRPC3 mediates hyperexcitability and epileptiform activity in immature cortex and experimental cortical dysplasia. *J. Neurophysiol.* **2014**, *111*, 1227–1237. [[CrossRef](#)]

154. Kim, Y.J.; Kang, T.C. The role of TRPC6 in seizure susceptibility and seizure-related neuronal damage in the rat dentate gyrus. *Neuroscience* **2015**, *307*, 215–230. [[CrossRef](#)]
155. Lee, J.Y.; Cole, T.B.; Palmiter, R.D.; Koh, J.Y. Accumulation of zinc in degenerating hippocampal neurons of ZnT3-null mice after seizures: Evidence against synaptic vesicle origin. *J. Neurosci.* **2000**, *20*, RC79. [[CrossRef](#)]
156. Cole, T.B.; Robbins, C.A.; Wenzel, H.J.; Schwartzkroin, P.A.; Palmiter, R.D. Seizures and neuronal damage in mice lacking vesicular zinc. *Epilepsy Res.* **2000**, *39*, 153–169. [[CrossRef](#)] [[PubMed](#)]
157. Chen, N.N.; Zhao, D.J.; Sun, Y.X.; Wang, D.D.; Ni, H. Long-Term Effects of Zinc Deficiency and Zinc Supplementation on Developmental Seizure-Induced Brain Damage and the Underlying GPR39/ZnT-3 and MBP Expression in the Hippocampus. *Front. Neurosci.* **2019**, *13*, 920. [[CrossRef](#)] [[PubMed](#)]
158. Khalil, A.; Kovac, S.; Morris, G.; Walker, M.C. Carvacrol after status epilepticus (SE) prevents recurrent SE, early seizures, cell death, and cognitive decline. *Epilepsia* **2017**, *58*, 263–273. [[CrossRef](#)] [[PubMed](#)]
159. Chokshi, R.; Fruasaha, P.; Kozak, J.A. 2-aminoethyl diphenyl borinate (2-APB) inhibits TRPM7 channels through an intracellular acidification mechanism. *Channels* **2012**, *6*, 362–369. [[CrossRef](#)]
160. Togashi, K.; Inada, H.; Tominaga, M. Inhibition of the transient receptor potential cation channel TRPM2 by 2-aminoethoxydiphenyl borate (2-APB). *Br. J. Pharmacol.* **2008**, *153*, 1324–1330. [[CrossRef](#)]
161. Hu, H.Z.; Gu, Q.; Wang, C.; Colton, C.K.; Tang, J.; Kinoshita-Kawada, M.; Lee, L.Y.; Wood, J.D.; Zhu, M.X. 2-aminoethoxydiphenyl borate is a common activator of TRPV1, TRPV2, and TRPV3. *J. Biol. Chem.* **2004**, *279*, 35741–35748. [[CrossRef](#)]
162. Chung, M.K.; Lee, H.; Mizuno, A.; Suzuki, M.; Caterina, M.J. 2-aminoethoxydiphenyl borate activates and sensitizes the heat-gated ion channel TRPV3. *J. Neurosci.* **2004**, *24*, 5177–5182. [[CrossRef](#)]
163. Jeong, J.H.; Lee, S.H.; Kho, A.R.; Hong, D.K.; Kang, D.H.; Kang, B.S.; Park, M.K.; Choi, B.Y.; Choi, H.C.; Lim, M.S.; et al. The Transient Receptor Potential Melastatin 7 (TRPM7) Inhibitors Suppress Seizure-Induced Neuron Death by Inhibiting Zinc Neurotoxicity. *Int. J. Mol. Sci.* **2020**, *21*, 7897. [[CrossRef](#)]
164. Ghajar, J. Traumatic brain injury. *Lancet* **2000**, *356*, 923–929. [[CrossRef](#)]
165. DeWitt, D.S.; Jenkins, L.W.; Prough, D.S. Enhanced vulnerability to secondary ischemic insults after experimental traumatic brain injury. *New Horiz.* **1995**, *3*, 376–383.
166. Lee, M.; Lee, S.H.; Choi, S.; Choi, B.Y.; Suh, S.W. Carvacrol Inhibits Expression of Transient Receptor Potential Melastatin 7 Channels and Alleviates Zinc Neurotoxicity Induced by Traumatic Brain Injury. *Int. J. Mol. Sci.* **2022**, *23*, 13840. [[CrossRef](#)]
167. Marion, D.W.; Penrod, L.E.; Kelsey, S.F.; Obrist, W.D.; Kochanek, P.M.; Palmer, A.M.; Wisniewski, S.R.; DeKosky, S.T. Treatment of traumatic brain injury with moderate hypothermia. *N. Engl. J. Med.* **1997**, *336*, 540–546. [[CrossRef](#)] [[PubMed](#)]
168. Eakin, K.; Baratz-Goldstein, R.; Pick, C.G.; Zindel, O.; Balaban, C.D.; Hoffer, M.E.; Lockwood, M.; Miller, J.; Hoffer, B.J. Efficacy of N-acetyl cysteine in traumatic brain injury. *PLoS ONE* **2014**, *9*, e90617. [[CrossRef](#)] [[PubMed](#)]
169. Choi, B.Y.; Lee, S.H.; Choi, H.C.; Lee, S.K.; Yoon, H.S.; Park, J.B.; Chung, W.S.; Suh, S.W. Alcohol dependence treating agent, acamprosate, prevents traumatic brain injury-induced neuron death through vesicular zinc depletion. *Transl. Res.* **2019**, *207*, 1–18. [[CrossRef](#)] [[PubMed](#)]
170. Cook, N.L.; Vink, R.; Helps, S.C.; Manavis, J.; van den Heuvel, C. Transient receptor potential melastatin 2 expression is increased following experimental traumatic brain injury in rats. *J. Mol. Neurosci.* **2010**, *42*, 192–199. [[CrossRef](#)]
171. Yuruker, V.; Naziroglu, M.; Senol, N. Reduction in traumatic brain injury-induced oxidative stress, apoptosis, and calcium entry in rat hippocampus by melatonin: Possible involvement of TRPM2 channels. *Metab. Brain Dis.* **2015**, *30*, 223–231. [[CrossRef](#)]
172. Hellmich, H.L.; Frederickson, C.J.; DeWitt, D.S.; Saban, R.; Parsley, M.O.; Stephenson, R.; Velasco, M.; Uchida, T.; Shimamura, M.; Prough, D.S. Protective effects of zinc chelation in traumatic brain injury correlate with upregulation of neuroprotective genes in rat brain. *Neurosci. Lett.* **2004**, *355*, 221–225. [[CrossRef](#)] [[PubMed](#)]
173. Zheng, W.; ZhuGe, Q.; Zhong, M.; Chen, G.; Shao, B.; Wang, H.; Mao, X.; Xie, L.; Jin, K. Neurogenesis in adult human brain after traumatic brain injury. *J. Neurotrauma* **2013**, *30*, 1872–1880. [[CrossRef](#)] [[PubMed](#)]
174. Choi, B.Y.; Kim, J.H.; Kim, H.J.; Lee, B.E.; Kim, I.Y.; Sohn, M.; Suh, S.W. Zinc chelation reduces traumatic brain injury-induced neurogenesis in the subgranular zone of the hippocampal dentate gyrus. *J. Trace Elem. Med. Biol.* **2014**, *28*, 474–481. [[CrossRef](#)] [[PubMed](#)]
175. Li, W.T.; Zhang, S.Y.; Zhou, Y.F.; Zhang, B.F.; Liang, Z.Q.; Liu, Y.H.; Wei, Y.; Li, C.K.; Meng, X.J.; Xia, M.; et al. Carvacrol attenuates traumatic neuronal injury through store-operated Ca²⁺ entry-independent regulation of intracellular Ca²⁺ homeostasis. *Neurochem. Int.* **2015**, *90*, 107–113. [[CrossRef](#)] [[PubMed](#)]
176. Xu, H.L.; Liu, M.D.; Yuan, X.H.; Liu, C.X. Suppression of cortical TRPM7 protein attenuates oxidative damage after traumatic brain injury via Akt/endothelial nitric oxide synthase pathway. *Neurochem. Int.* **2018**, *112*, 197–205. [[CrossRef](#)]
177. Park, M.K.; Choi, B.Y.; Kho, A.R.; Lee, S.H.; Hong, D.K.; Jeong, J.H.; Kang, D.H.; Kang, B.S.; Suh, S.W. Effects of Transient Receptor Potential Cation 5 (TRPC5) Inhibitor, NU6027, on Hippocampal Neuronal Death after Traumatic Brain Injury. *Int. J. Mol. Sci.* **2020**, *21*, 8256. [[CrossRef](#)] [[PubMed](#)]

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