REVIEW ARTICLE

TRP Channels as Emerging Therapeutic Targets in Neurological Disorders

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ABSTRACT

Neurological disorders like Parkinson disease (PD), Alzheimer's disease (AD), epilepsy, stroke, schizophrenia, depression, bipolar disorder, etc., are increasingly recognized as significant causes of death and disability globally. All these neurological disorders have several similar causes, such as disturbance in Ca^{2+} homeostasis and misfolded proteins deposition in the brain through impairing the function of a no. of ion channels, including TRP channels. TRP channels superfamily consists of a broad collection of non-selective Ca^{2+} permeable channels that plays a crucial role in regulating intracellular Ca^{2+} homeostasis. These channels function as cellular sensors and are stimulated by a variety of physio-chemical stimulus, and endogenous and exogenous ligands. Numerous neuronal diseases are caused by disturbances in the activity of TRP channels, which are abundantly expressed in neuronal cells. When the activity of TRP channels is disturbed under pathological conditions, there is disruption of the homeostasis of neurons via oxidative stress, Ca^{2+} dyshomeostasis, and mitochondrial dysfunction. Therefore, these channels act as promising therapeutic candidates for pharmacological interventions in several neurological disorders. Thus within this review, we emphasize the function of TRP channels in neurological disorders and highlight the pharmacological modulators that target TRP channels.

Keywords: Calcium dyshomeostasis, Mitochondrial dysfunction, Neurological disorders, Neuroprotection, Oxidative stress, Therapeutic interventions, TRP channels.

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INTRODUCTION

TRP channels superfamily comprises a broad collection of integral membrane proteins that serves as unique non-selective cation permeable channels. For a variety of physio-chemical stimuli, these channels function as cellular sensors. They have been noted in both humans and bacteria.[1-3] TRP channels discovery started in 1969 by Cosens and Manning's detection of Drosophila trp mutant, where the photoreceptor response declines under continual light. In 1989, the trp gene was cloned by Craig Montell and Gerald M Rubin, who recognized it as an integral membrane protein, but also come to the conclusion that it did not encodes the light-sensitive channels. Later, it was proven by Roger Hardie and Baruch Minke that TRP is a Ca^{2+} Channel that is activated by light in photoreceptor neuronal cells.[4] There are twenty-eight TRP channels that are members of seven families depending on the homology in their amino acid sequences. The various families of TRP channels includes TRPA(Ankyrin; one sub-member, TRPA1), TRPC(Canonical; seven sub-members, TRPC1-7), TRPM(Melastatin; eight sub-members, TRPM1-8), TRPP(Polycystein; three sub-members, TRPP1-3), TRPV(Vanilloid; six sub-members, TRPV1-6), TRPML(Mucolipin; three sub-members, TRPML1-3) and TRPN (NOMPC) – like; TRPN channel does not exist in mammals, it only exists in invertebrates and fish.[5] Notably, majority of TRP channels are non-selective cation permeable channels which are consistently permeable to Ca^{2+} ($P_{Ca}/P_{Na}<10$). Exceptionally, TRPM4 and TRPM5 channels are impermeable to Ca^{2+} but permeable to monovalent cations ($P_{Ca}/P_{Na}<0.05$), and TRPV5 and TRPV6 are extremely permeable to Ca^{2+} ($P_{Ca}/P_{Na}>100$). Also, TRPM6 and TRPM7 which are known as channel kinases are permeable to Mg^{2+}, Ca^{2+}, Na^{+}, Zn^{2+} and other trace metals.[6] Store-Operated Channels (SOCs) is another name for TRP channels that has been used to refer to the incompletely understood phenomena, however this terminology is very speculative. Phylogenetic, transmembrane segment prediction, and structural data indicate that voltage-gated cation channels and TRP channels are related superfamilies. All functional TRP channels has six transmembrane regions (S1 to S6), between S5 and S6 there is a pore-forming region that allows the passage of several monovalent and divalent ions, such as Na^{+}, K^{+}, Ca^{2+}, and Mg^{2+} as shown in Figure 1. Except for S4, which lacks voltage-sensing positively charged arginine residues, every transmembrane region (S1 to S6) is voltage sensitive. Both the amino (NH2-) and carboxy (COOH-) terminal are intracellular with variable length and different domains. Within the same or

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distinct subfamilies, TRP channels can aggregate into homo- or heterotetramers by functional association.[7,8] TRP channels are activated by various physiological, chemical and mechanical stimuli including osmolarity, temperature, pH, pressure, and tension as well as by a no. of endogenous or exogenous ligands (inflammatory molecules, irritant agents, pH changes and several natural compounds), secondary messengers and signaling molecules like Ca^{2+}, PIP_2, cyclic nucleotides, ADP-ribose etc. Upon activation, TRP channels changes the enzymatic activity, triggers exocytosis and endocytosis, modify the membrane potential, and translocate significant signaling ions into cytoplasm. TRP channels are therefore essential for several physiological activities, such as sensitivity to stimuli (including pheromone signalling, thermosensation, taste transduction, nociception, and mechanosensation), ions homeostasis (such as reabsorption of Ca^{2+} as well as Mg^{2+} and osmoregulation), motility (such as contraction of muscles and vasomotor control), intracellular protein interaction as well as cell survival, proliferation, and differentiation.[9,10]

The defect in TRP ion channels is known as TRP channelopathies. Therefore, TRP channel mutations or changes in protein function and/or expression causes TRP channel dysfunction that leads to several pathological states such as cardiomyopathy, cancer, dermatological conditions, asthma, chronic pain and diabetes. TRP channels are also responsible for pathogenesis of neurological disorders that are associated with disturbance in Ca^{2+} homeostasis including AD, PD, epilepsy, bipolar disorder, stroke, depression, migraine etc.[11,12]. TRP channels are broadly distributed in different brain regions.[13] The emphasis of this review is on TRP channels involvement in various neurological disorders.

Critical Role of Ca^{2+} in the Pathogenesis of Neurological Disorders

Calcium serves as the most ubiquitous intracellular secondary messenger and calcium homeostasis in brain is crucial for controlling the physiological processes of neurons such as neural survival, neural proliferation, and neural maturation.[14] Thus, disturbance in Ca^{2+} homeostasis disrupts neuronal homeostasis via excessive ROS generation, mitochondrial dysfunction, neuroinflammation, and misfolded proteins deposition in the brain which are highly linked with the neuronal cell death and all these aspects are implicated in aetiology of a no. neurological disorders.[15] In healthy neurons, Ca^{2+} homeostasis is tightly regulated by Ca^{2+} handling proteins and by its intake and release by mitochondria. Large amounts of Ca^{2+} can be stored by mitochondria and accumulated there without endangerously increasing its osmotic concentration.[16] Additionally, the majority of cellular ROS are produced by mitochondria and their electron transport chain complexes. Healthy mitochondria produces only small amount of ROS. Under normal circumstances, ROS maintain an equilibrium with antioxidant system thus causes little damage. However, excessive ROS results in damage to proteins, lipids, and Mt DNA due to oxidative stress that disrupts the BBB and promotes neuroinflammation as well as neuronal cell death.[17] Oxidative stress is characterized by the disruption in equilibrium between ROS production and antioxidant defenses, with excessive ROS production. The high levels of ROS damaged ATP synthase, NADH dehydrogenase and cyt c oxidase which causes shuts down of mitochondrial energy generation. Also, overproduction of ROS can cause direct damage to Ca^{2+}-regulating proteins including voltage- and ligand-gated Ca^{2+} channels, ER Ca^{2+}-ATP synthases, and mitochondrial ETC proteins. This causes an elevation in calcium levels, which disrupts Ca^{2+} homeostasis. In addition, excessive ROS can lead to mitochondrial damage, such as Mt DNA mutations, impaired ETC, alterations in mitochondrial membrane integrity, and disturbances in Ca^{2+} homeostasis. Consequently, mitochondrial dysfunction is linked to the development of various neurological disorders.[18]

Under pathological conditions, as mentioned above mitochondrial damage includes reduced ATP production, impaired electron transport chain (that causes excessive ROS generation) and elevated Ca^{2+} levels inside the mitochondria. Elevation in mitochondrial Ca^{2+} level disrupts the activity of ETC which causes excessive ROS production. These mitochondrial generated ROS targets ER-based Ca^{2+} channels that causes the Ca^{2+} release from ER and further increased ROS to a toxic level, consequently forming a vicious cycle. Increased ROS and Ca^{2+} load in mitochondria opens the mitochondria permeability transition pore (mPTP), that leads to osmotic swelling of mitochondria until the outer mitochondrial membrane (OMM) finally ruptures. Cyt c is released into the cytoplasm upon OMM rupture and results in apoptotic cell death. Moreover, accumulation of misfolded proteins in the brain further leads to perturbation in neuronal homeostasis through oxidative stress, mitochondrial dysfunction, neuroinflammation and calcium dyshomeostasis via impairing the function of many ion channels, including TRP channels.[19] Therefore, disturbance in TRP channels activity leads to various neurological disorders.

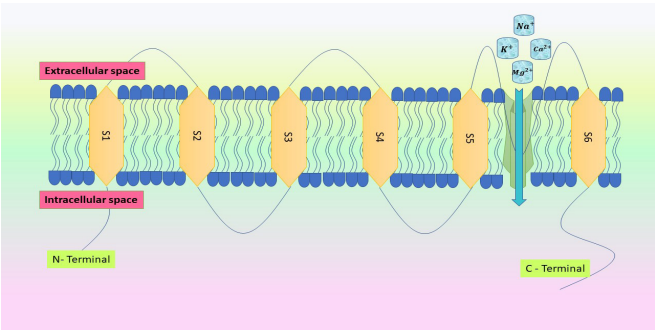

Figure 1: Schematic representation of TRP channels showing six transmembrane regions, with pores forming regions between S5 and S6 that allow passage of Na^+, K^+, Ca^{2+}, and Mg^{2+}.

Trp Channels in Neurological Disorders

Considering the broad distribution as well as different roles of TRP channels in neurons, it is possible that impairment in their function can have a significant impact on a wide range of pathological events of various neurological disorders and

Table 1 listed the pharmacological interventions that target TRP channels for corresponding disorders.

TRP Channels in Alzheimer's Disease

AD is characterised by β-amyloid (Aβ) plaques accumulation, aberrant neurofibrillary tangles deposition and disturbed Ca^{2+} homeostasis in the neurons.[20] TRP channels involvement in the pathophysiology of AD is shown in figure 2. TRPC1 channels are linked to Store Operated Ca^{2+} Entry (SOCE) channels. It is interested to note that SOCE channels was significantly reduced in astrocytes of APP knockout mice suggesting that there is downregulated expression of TRPC1 within those astrocytes.[21] In the brain, TRPC3 channels are broadly dispersed and there is colocalization of TRPC3 channels with the tyrosine kinase B (TrkB) receptor.[22] TRPC3 channels are activated by BDNF-induced TrkB activation and are responsible for controlling Ca^{2+} entry across the cell through the involvement of PLC activity.[23] It has been reported that BDNF activity is altered in AD, which results in tau protein dysregulation and enhanced the susceptibility to memory deficits and neuronal apoptosis. Therefore, changes in BDNF activity results in disturbance in TRPC3 channel activity and Ca^{2+} homeostasis in the hippocampus, which in turn causes tau protein phosphorylation and increases AD development.[24] Among TRPC members, TRPC6 also play role in AD. Presenilin (PS) proteins are the transmembrane polypeptides which are found in the ER of neuronal cells. Presenilin genes mutation causes changes in the APP proteolytic processing which results in the development of young-onset AD. According to reports, PS-2 affects the Ca^{2+} influx into the HEK293 cells mediated by TRPC6 and causes the negative regulation of TRPC6 activity. In HEK293T cells, functional loss of the PS-2 mutant as well as TRPC6 increased the Ca^{2+} entry triggered by 1-oleoyl-2-acetyl-sn-glycerol (OAG) and angiotensin II (AngII).[25] Mutations of PS-2 promote Aβ generation by increasing the β-secretase activity and enhancing the β-site APP cleavage enzyme 1 expression. Hyperforin act as the TRPC6 activator which inhibit the TRPC6 induced brain damage.[26]

Upregulated expression of TRPM2 is associated with the memory related changes and neuronal apoptosis. A study has shown that TRPM2-/-/APP/PS1 Tg mice inhibits the ER stress, activation of microglia and age-related spatial memory deficits without affecting the formation of Aβ plaque.[27] TRPM2 channels therefore contribute to the progression of AD and genetic deletion or inhibition of TRPM2 may exerts neuroprotective effect in AD. Another TRPM family member, TRPM7, is essential for increasing the vulnerability to neurodegenerative processes as well as triggering anoxic neuronal apoptosis by disturbing the Ca^{2+} and Mg^{2+} homeostasis.[28]

According to a recent study, TRPV1 agonists (capsaicin and vanillin) has been shown to not only improving the memory impairment and brain damage but also reducing the nitrosative/oxidative stress and AChE activity in Alzheimer's disease.[29-31] Also, TRPV1 agonist has been found to reduce the tau protein phosphorylation in hippocampal neurons of NIDDM.[32] In contrast, upregulated expression of TRPV4 was reported in elderly rat's brains, that increased the neural apoptosis via increasing Ca^{2+} entry and ROS overproduction.[33]

The pathophysiology of AD is also influenced by TRPA1 channels. APP/PS1 Tg mice's astrocytes have been reported to have an upregulated TRPA1 expression. Functional loss of TRPA1 was found to enhance the spatial memory and reduced the formation of Aβ plaque in APP/PS1 Tg mice. APP/PS1 Tg mice's astrocytes have been reported to have an increased expression of TRPA1. TRPA1 are main ion channels that play role in metabolism of Aβ plaque and inflammatory responses that contribute to aetiology of AD. Transcriptional factors like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and nuclear factor of activated T cells (NFAT), that are activated by Aβ and cause the synthesis and secretion of pro-inflammatory cytokines like IL-1, IL-4, IL-6, and IL-10, have been shown to be inhibited by the TRPA1 antagonist HC030031.[34]

Lastly, In APP/PS1 Tg mice, TRPML1 expression has been reported to be reduced. Furthermore, increased TRPML1 expression decreases neuronal cell death through controlling autophagy via PPARγ/AMPK/Mtor signalling in APP/PS1 Tg mice.[35] Above findings imply that TRPs might be a treatment option in AD.

TRP Channels in Parkinson's Disease

Degeneration and death of DA neurons in substantia nigra are characteristic features of the complex, chronic, and progressive neurodegenerative condition known as Parkinson disease.[36] According to reports, TRP channels have a function in pathology of PD as shown in Figure 2. When monoamine oxidase B (MAO-B) is present, MPTP is transformed into MPP^+, which preferentially deposits and cause death of DA neurons in the SNpc and striatum. In addition, it impairs mitochondrial respiratory chain and reduces the mitochondrial membrane permeability, resulting in mitochondrial damage that causes death of neuronal cells.[37] After MPP^+ treatment, expression of TRPC1 was shown to decreased in SH-SY5Y neuroblastoma cells.[38] Furthermore, activation and overexpression of TRPC1 channels provides neuroprotection to the DA neurons from cellular toxicity induced by MPP^+ by inhibiting cyt

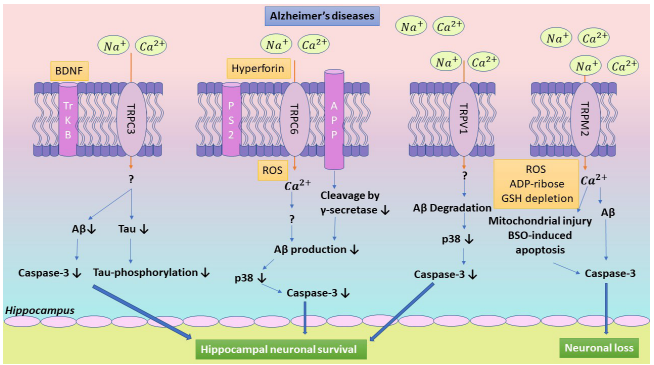

Figure 2: Schematic representation of TRP channels' involvement in the pathogenesis of Alzheimer's disease

c release and reducing levels of Bax and Apaf-1 protein whereas downregulation of TRPC1 channels was found to linked to an increase in SH-SY5Y cell death.[39] Apart from TRPC1, TRPC3 channels also provide neuroprotection in Parkinson disease. The mitochondria and plasma membrane of the GABAergic neurons of the SNr express these channels. Inhibitory neurotransmission, which has been shown to be disrupted in a number of neurodegenerative conditions, is maintained by TRPC3 channels. Thus, inhibition of TRPC3 channels results in the disturbance in the frequency at which GABAergic neurons fire in the SNr. However, TRPC3 channels also provide neuroprotection against mitochondrial damage mediated by α-synuclein in Parkinson disease.[40,41] However, further studies are needed to prove that these channels works alone or in synergism to provide neuroprotective action in Parkinson disease.

The pathology of PD is also influenced by the TRPM family. The ion MPP^+ has been shown to induce oxidative stress, which enhances intracellular Ca^{2+} entry by activating the TRPM2 channel and encourages death of DA neurons in SNpc.TRPM2 channels pharmacological blockage exhibits the neuroprotective effect by inhibiting the PD-related Ca^{2+} elevation and preventing apoptotic cell death.[42] Interestingly, TRPM7 channels plays a crucial role in regulating the homeostasis of Mg^{2+} in cells, and higher Mg^{2+} levels greatly prevent neurotoxicity caused by MPP^+ by decreasing the number of DA neurons and lengthening dopamine neurites.[43,44]

Several studies shows that TRPV1 activation increase Ca^{2+} load, mediate mitochondrial dysfunction and ultimately leads to the DA neuronal cell death.[45] It was demonstrated that TRPV1 channels have an important function in L-DOPA-mediated dyskinesias. TRPV1 channels was reported to play role in regulating L-DOPA-mediated hyperreactivity in Parkinson's disease induced by reserpine.[46] Oleoylethanolamide (OEA) and AMG9810 (TRPV1 antagonists) reduced the L-DOPA-mediated dyskinesia and PD-mediated hypokinetic behaviour respectively.[47]

TRPML1 channels also play role in PD. TRPML1 activation stimulate endoplasmic reticulum Ca^{2+} release and Ca^{2+} influx[48] which leads to increased lysosomal exocytosis, hence inhibiting the α-synuclein accumulation in DA

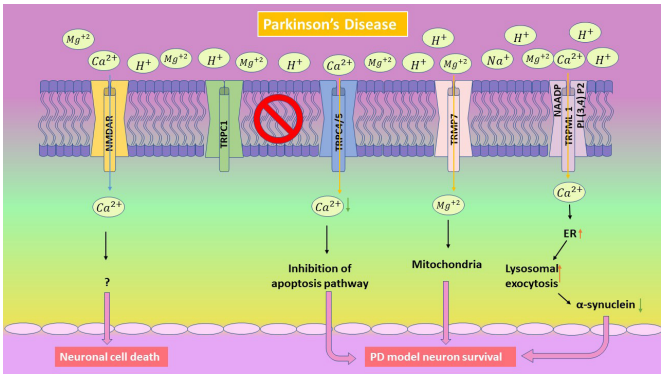

Figure 2: Schematic representation of TRP channels' involvement in the pathogenesis of Parkinson's disease

neurons[49]. So, above evidences suggesting that TRPs may be used as a potential target in Parkinson disease.

TRP Channels in Epilepsy

Epilepsy is characterised by the repeated epileptic seizures. Glutamate, Ca^{2+}, and GABA channels are molecular targets of currently available antiepileptic medications.[50] Recently, studies reported that TRPs are non-selective, Ca^{2+} permeable channels and these channels are believed to involved in seizure activity in the epilepsy. TRPC channels are crucial for growth and neurodevelopment of brain. These channels also important to play prominent function in epileptogenesis process. For example, increased TRPC1 expression is found in cortical lesions in epileptic patients.[51] In pilocarpine-induced status epilepticus model, it was reported that TRPC3 genetic elimination decreases the vulnerability of seizures to pilocarpine whereas increasing TRPC3 expression triggers hyperexcitability and increased sensitivity to epileptiform activity in the cortex region of brain.[52,53] In contrast, the genetic deletion of TRPC6 via SiTRPC6 enhanced the vulnerability to seizure and seizure-induced neuronal vulnerability in the dentate gyrus but not in CA1 and CA3 areas of hippocampus whereas TRPC6 expression was found to be decreased in chronically epileptic rats.[54] Hyperforin (TRPC6 agonist) administration reduced the neuroinflammatory response (activation of microglia, phosphorylation of p65-ser276-NFkB, and TNF-α) in rat's piriform cortex after status epilepticus.[55] Moreover, other TRPC family members including TRPC1/C4 and TRPC5 induces neuronal hyperexcitability and epileptiform bursting. Specifically, in the CA1 and CA3 areas of the hippocampus, TRPC1/C4 genetic deletion decreased seizure-induced neural apoptosis, whereas TRPC5 knockout mice decreased both seizure and seizure-induced neuronal apoptosis.[56] Additionally, it was shown that both the mRNA and protein expression of TRPC1 and TRPC5 were markedly elevated in the FCD linked to epileptic seizures in both children and adults. Consequently, the process of epileptogenesis is accelerated by the increased expression of TRPC1/C5 in FCD.[57] TRPC7 channels also play a vital function in spontaneous epileptiform bursting in the neurons of CA3 area whereas TRPC7 knockout (KO) mice reduced pilocarpine-induced status epilepticus.[58]

TRPM family also involves in epilepsy pathophysiology. It was shown that the TRPM2 channels are controlled in the hippocampus neurons and there is co-expression of TRPM2 channels with the EF-hand domain-containing protein 1 gene, that is associated with the enhanced vulnerability to juvenile myoclonic epilepsy.[59] Additionally, it has been discovered that TRPM7 is triggered during epilepsy. Interestingly, genetic deletion of TRPM7 inhibits cation current stimulation generated by OGD and cause the prevention of ROS-mediated OGD activation[60].

Recent research revealed that the TRPV1 channels activation is crucial for the development of epilepsy. The dentate gyrus of mice with temporal lobe epilepsy, the hippocampus of the rat and the cortex of people with mesial temporal lobe epilepsy

have all shown elevated expression of TRPV1,[61-63] These clinical and experimental results have been confirmed by the observations that the TRPV1 channel inhibitors including capsazepine (CPZ), 5-iodoresiniferatoxin as well as resolvins has been found to induce neuroprotective effect against epileptic seizures.[64] In addition, it was found that capsaicin co-administration with cannabinoid agonist (F212-2 and WIN 55) decreased the epileptic magnitude using an acute rat model of temporal epilepsy.[65] Furthermore, TRPV1 antagonists (AMG-9810 and α-spinasterol) demonstrated considerable antiepileptic action in a variety of epilepsy models, such as PTZ & MES models of epilepsy.[66] Apart from TRPV1, TRPV4 also involved in pathology of epilepsy. Another research using the pilocarpine-induced status epilepticus model reported that TRPV4 inhibition by HC-067047, a TRPV4 blocker, substantially enhanced neuronal cells survival after status epilepticus while TRPV4 activation by GSK1016790A, a TRPV4 activator, caused an increased in pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α.[67] Above findings showed that TRPV1 and TRPV4 channels are implicated in aetiology of epileptic seizures and could be targeted for epileptic treatment.

In contrast to previous research on the TRPV4 channel, TRPV4 expression was found to be unchanged whereas TRPA1 expression was shown to be increased in an epileptic model in which epilepsy is induced by kainic acid.[68] Differential TRP channels distribution across different regions of brain could be a possible reason for this. Also, in the same study, increased PKCα and ERK1/2 expression and reduced PKCε expression was observed in the hippocampal neurons of epileptic seizure group animals in which epilepsy is induced by kainic acid suggesting the presence of PKC isoforms and ERK1/2 in the downstream cascade of cellular and molecular reactions to TRP channels in epilepsy pathophysiology.[69] Aforementioned findings recommended that TRP channels could be a great therapeutic target in epilepsy.

TRP Channels in Stroke

Ischaemic stroke: Cerebral blood artery obstruction is the characteristic feature of ischaemic stroke. Excitotoxicity is regarded as the main factor of cell death in ischemic stroke, which is caused by an increase in Ca^{2+} load[70]. Previous studies showed that TRPC6 overexpression in neurons suppressed the overload of Ca^{2+} caused by NMDA and induce protective action against ischaemia. It has been reported that during ischaemic insult, TRPC6 inhibition or downregulation cause brain damage and TRPC6 activators (hyperforin and resveratrol) inhibits TRPC6 induced brain damage by their activation or upregulation.[71,72] Thus, TRPC6 channel expression in neuronal cells is necessary for their survival.

Increased Ca^{2+} load results in overproduction of ROS, H_2O_2, RNS and arachidonic acid, that altogether leads to the TRPM2 and TRPM7 activation. In agreement with the same, several studies linked the TRPM channels with neuronal apoptosis following ischaemia. Recent findings showed that TRPM2 and TRPM7 inhibition induced neuroprotective effect against ischaemic neuronal damage.[73,74] Interestingly, tat-M2NX, a TRPM2 inhibitor provides neuroprotection against ischaemic stroke. Though, TRPM2 channel knockdown by shRNA or TRPM2 channel inhibition by clotrimazole in male mice results in a substantial decrease in infarct volume, no impact was seen in female mice. Furthermore, carvacrol, a TRPM7 inhibitor exerts neuroprotective effect against neonatal-hypoxic-ischaemic injury by inhibiting neuronal cell death, decreasing infarct volume as well as improved overall behavioural responses.[75] In addition, after an ischemic stroke, the vascular endothelium in the penumbra area was found to have upregulated expression of TRPM4 channels. Thus, blocking TRPM4 channels by 9-phenanthrol exerts cardioprotective effect against Ischaemic stroke injury.[76]

TRPV1 family is also involved in cerebral ischaemia. Knockout mice have been observed to decreased neurological and motor impairments as well as a reduced infarct volume than wild-type mice in the tMCAO paradigm. Capsazepine, a TRPV1 antagonist, was also injected intracerebroventricularly to reduced infarct size and behavioural abnormalities.[77] Another study, however, showed the TRPV1's contradicted function in stroke. After focal cerebral Ischaemia, a TRPV1 agonist dihydrocapsaicin (DHC) induces hypothermia and offers neuroprotection.[78] Apart from these studies, TRPV4 expression was found to be elevated in ipsilateral cortex after cerebral ischaemia which that results in damage to neurons by downregulating AKT signalling pathway. TRPV4 antagonists like HC-067047 and Ruthenium red significantly antagonizes the above-mentioned results as well as exerts protective effect via reduction in infarct size in ischaemia.[79]

Haemorrhagic Stroke (Intracerebral Haemorrhage and Subarachnoid Haemorrhage)

Cerebral blood vessels rupturing is a hallmark of haemorrhagic stroke. Blood-derived substances may extravasate into the parenchyma of brain in haemorrhagic stroke and contribute to the pathogenesis of brain damage. According to reports, thrombin significantly induced upregulation of TRPC3 in rat's primary cortical astrocytes. In addition, it was demonstrated that this mechanism causes astrocytes to become pathologically active by upregulating their own expression in a feedforward manner.[80] Pyr 3 (TRPC3 inhibitor) is reported to decrease astrocyte perihematomal deposition and reduce brain damage.[81] HC-067047 (a TRPV4 inhibitor) reduces neurological symptoms, brain oedema, neuronal cell injury and protects the BBB following an intracranial haemorrhage whereas activation of TRPV4 results in disruption of Ca^{2+} balance.[82] In contradiction, TRPC3, TRPC5, and TRPM6 expression was found to be downregulated in cerebral vascular tissue from individuals following hypertensive intracerebral haemorrhage. Amongst these, hypoxia inducible factor-1a and TRPC3 mRNA have a good correlation, indicating its relation with hypertension and hypoxia.[83] Furthermore, TRPC1 and TRPC4 proteins was found to be increased in canine smooth muscle after subarachnoid haemorrhage, and the endothelin-

1-induced vasospasm is mediated by the elevated Ca^{2+} entry through TRPC channels.[84] Hence, TRPs could be utilized as a possible target in the treatment of stroke.

TRP Channels in Schizophrenia

Schizophrenia is complex, long-lasting, and devastating psychotic illness. It represents one of the major psychiatric disorders characterized by hallucinations, delusions, and impairment in thought and behaviour. genetic and environmental factors are the greatest risk factors of schizophrenia.[85] To date, numerous studies has reported that a no. of genes including NRG1, DISC1, dysbindin (DTNBP1), COMT, PRODH and RGS4 act as susceptibility genes for schizophrenia.[86] Although there is no direct data to prove the link of TRP channels to the pathogenesis of schizophrenia, various features of its aetiology have revealed that TRP channels may have a direct or indirect role in schizophrenia.[87] DISC1 protein is best known as a genetic risk factor of schizophrenia. In prefrontal cortex, DISC1 protein modified the ionic current generated via small conductance K^+ and TRPC channels. There is an increased Ca^{2+} through mGluR receptor activation when DISC1 protein is disrupted by short hairpin RNA (shRNA).[88]

In addition, TRPV1 channels also involved in the physiopathology of schizophrenia. TRPV1 receptors act as the target of capsaicin (TRPV1 agonist). Spontaneously hypertensive rats (SHR) that were used in animal model of schizophrenia are found to increase social interaction by capsaicin treatment.[89] So, it shows that disturbance in TRPC and TRPV1 channel activity are involved in physiopathology of schizophrenia and thus these channels can be a potential target in schizophrenia.

TRP Channels in Bipolar Disorder

BD is a prolonged mental disorder that causes change in state of mood and energy. It is characterised by the presence of hypomanic or manic and depressive episodes. Worldwide, it is one of the major cause of death by suicide. Bipolar disorder includes type-I and type-II BD. Patients with type-I BD experience manic and depressive episodes whereas those with type-II BD experience hypomanic episodes.[90] There are various mechanisms related with the pathogenesis of bipolar disorder but disturbance in Ca^{2+} homeostasis is one of the major cause of bipolar disorder progression. Although the proper mechanism associated with altered Ca^{2+} homeostasis in bipolar disorder is not clearly understood. However, recent studies shows that TRP channels contribute to development and pathogenesis of bipolar disorder.[91] Genetic linkage analysis revealed the involvement of TRPM2 in bipolar disorder. D543E, a mutant of TRPM2 gene is commonly expressed by patients with bipolar disorder, induces loss of TRPM2 channel activity. TRPM2 gene knockout mice exhibited bipolar disorder like-behaviour such as fluctuation in mood, aggressiveness, and cognitive impairment, along with impaired electroencephalogram activity. The brains of TRPM2-deficient mice shows an increased in phosphorylated glycogen synthase kinase-3 (Ser9-GSK-3β) levels, an important polypeptide in bipolar disorder-like behaviour and a target of mood stabilizer lithium. However, TRPM2 activation induces the dephosphorylation of GSK-3β via calcineurin, a Ca^{2+}-dependent phosphatase (thus confirming that maintenance of Ca^{2+} homeostasis is crucial for BD prevention). Therefore, D543E mutant overexpression results in failure of dephosphorylation of GSK-3β. Consequently, genetic abnormalities in TRPM2 genes causes uncontrollable phosphorylation of GSK-3β, leading to the pathogenesis of bipolar disorder.[92]

In addition, TRPC7 channels has been implicated in disturbance in Ca^{2+} homeostasis in bipolar disorder type-I. BLCLs of bipolar disorder type-I patients showed substantially decreased TRPC7 mRNA expression.[93] Although studies done on involvement of TRP channels in bipolar disorder are limited but above evidences indicate that TRPM2 as well as TRPC7 channels could be a target for bipolar disorder.

TRP Channels in Depression

Depression is a serious mood disorder. It is characterised by sadness, loss of interest, lack of energy, depressed mood, feeling guilty, poor concentration, and suicidal thoughts.[94] Different regions of the brain are involved in the depression including amygdala, thalamus, hippocampus, anterior cingulate cortex, hypothalamus and cerebellum.[95] It has been found that TRP channels contribute to the aetiology of depression. According to a study using a chronic unpredictable stress model, the hippocampal region of the brain had decreased levels of TRPC6 protein expression.[96] Further studies shows that TRPC4/C5 also play role in depression. M084, an inhibitor of TRPC4/C5 channels showed anti-anxiety and anti-depressive actions in mice. In the forced swimming and tail suspension tests, it reported a substantial decrease in the immobility time, however the elevated plus maze and light/dark transition test revealed a significantly increase in duration spent in open arm. At the molecular basis, treatment of M084 significantly elevates the p-AKT as well as p-ERK levels in prefrontal cortex of M084 treated mice compared to depressive mice's. By blocking the TRPC4/C5 channels, M084 treatment also enhanced BDNF signalling in the depressed state.[97] A latest report shows that HC-070, which is a strong antagonist of TRPC4/C5 channels in anxiety and depressive condition has further validate the involvement of these channels in depression. In the brain's amygdala and cortical regions, that are well known to involve in anxiogenic activity, TRPC4 as well as TRPC5 channels are abundantly expressed. According to studies, CCK-4 treatment increases the EPSC frequency in the basolateral amygdala neuronal cells by causing induction of fear and anxiety like-behaviour in rodents. In comparison to CCK-4-treated neurons, the administration of HC-070 decreased the EPSC frequency in neuronal cells of basolateral amygdala. Furthermore, in-vivo experiment using an elevated plus-maze also confirmed that HC-070 treatment reduced the anxiogenic CCK-4 induced anxiogenic effect in mice.[98] Additionally, TRPV1 channels also involved in anxiety disorder. Elevated plus maze and light-dark test confirmed that TRPV1 -deficient mice showed anti-

anxiety action and shows a significant decreased in anxiety-like behaviour. A competitive TRPV1 antagonist, capsazepine, also decreased anxiety-like behaviour in mice, suggesting the TRPV1 channel's role in anxiety disorders.[99] Further study revealed that TRPV1 blockage by capsazepine shows anti-anxiety effect whereas capsaicin, a TRPV1 agonist, increases anxiety-like behaviour.[100] A recent study also reported the involvement of TRPV family in depression. Capsaicin and olvanil, two TRPV1 agonists, have been reported to have antidepressant effects in nicotine-induced depression-like behaviour.[101] Also, TRPM2 channels play role in depression. deletion of TRPM2 decreased the chronic unpredictable stress (CUS)-mediated ROS as well as calpain stimulation and inhibited the hyperactivation of cdk5. Therefore, the genetic deletion of TRPM2 produced antidepressant effect in mice model of CUS.[102] This suggest that TRPM2 could be a prominent target for depression.

TRP Channels in Migraine

Migraine is a neurovascular headache disorder related to the recurrence of headache. Worldwide, there are fifteen percent of people who are suffering from migraines. It is linked to the trigeminovascular system's activation, which is made up of sensory neurons originating from the trigeminal ganglia.[103] TRPs play an important function in sensory neurons as well as control neural excitation. Genome-wide association study revealed that TRPM8 channels involved in migraine. TRPM8 channels are cold temperature sensors. However, the association between TRPM8 channel and migraine pathogenesis is not clearly understood. Though menthol (TRPM8 activator) administration has been found to be useful for alleviating symptoms of migraine. Another research showed that TRPM8 channel activation through icilin at dura mater play role in migraine. Systemic pre-treatment with the TRPM8 antagonist AMG1161 was found to attenuate this effect.[104]

TRPV and TRPA channels control the release of CGRP (a crucial neuropeptide in pathophysiology of migraines) in sensory neurons.[105] Numerous studies reported the co-expression of TRPV1 channels with CGRP and Substance-P with CGRP initiate the meningeal neuronal inflammation. Trigeminal nucleus caudalis sensitization was found to be prevented in preclinical trials with the TRPV1 antagonist SB-705498, which leads to blockage of central sensitization.[106] Another investigation using TRPV1 antagonist A-993610 also revealed that capsaicin-mediated vasodilation was increased without inhibition of neurogenic vasodilation or neuronal activity.[107] Therefore, TRPV1 blockers shows an intriguing action on migraine attacks. Several other investigations showed that TRPA1 channels are implicated in the pathophysiology of migraine attacks and TRPA1 activators was shown to trigger migraine episodes. Cinnamaldehyde, a TRPA1 activator causes the CGRP release from trigeminal nerve which results in elevation of cerebral blood flow and cause the triggering of migraine attacks. In addition, meningeal blood flow is increased by TRPA1 activators and is inhibited by HC- 030031 (a TRPA1 antagonist).[108] Inflammation causes the sensitization of trigeminal nerve due to TRP channels activation and enhance the CGRP as well as substance-P release. It causes TRPA1 channel gating properties alterations and increased CGRF release by sensitising the dural, meningeal trigeminovascular afferent and TRPA1 channels. At dural afferents, TRPA1 channel and TRPV1 channel are substantially co-localized. Though, TRPA1 expression in the trigeminal nerve is moderately decreased, it increases the neurovascular activities by sensitizing ion channel instead of changing ion channel expression.[109,110] Above evidences indicate that TRPM8, TRPA1 as well as TRPV1 channels are pathologically involve in migraine and could be targeted for prophylaxis of migraine.

TRP Channels in Brain Tumours

Malignant glioma including glioblastoma accounts for majority of primary brain tumours which have poor prognosis. It has been reported that TRPs have been implicated in brain tumours pathology. Recent studies showed that TRPCs and TRPVs regulate the development and progression of malignant cells. Glioma cell lines and acute patient-derived tissues have been found to consistently express the TRPC1, TRPC3, TRPC5, and TRPC6 channels. These channels contribute to glioma cells resting conductance by generating moderate, non-voltage-dependent cation currents. SKF96365 (a non-specific TRPC channels inhibitor) suppress cytokinesis and causes multinucleated and enlarger cells. The pathological characteristics of glioblastoma multiforme include these multinucleated and enlarged cells, which suggests that a dysfunction of TRPC channels may be responsible for the cellular defects in this tumour type.[111] Similar morphological alterations, which are caused through Ca^{2+} influx by TRPC1 and stimulated Cl^- currents, have been related to higher invasiveness in glioma cells of humans.[112] Additionally, glioma cell growth is prevented via cannabidiol (CBD)-mediated TRPV2 expression and activation, caused by TRPV2-dependent Ca^{2+} influx and cannabidiol (CBD) by inducing TRPV2-dependent Ca^{2+} influx increased the chemotherapeutic medication uptake, that simultaneously increases the cytotoxic activity in human glioma cells.[113]

Normal astrocytes, brain stem/progenitor cells and glioma tissues have human TRPML-2 channel expression. Glioma cells with high TRPML-2 channel expression results in enhanced survival and growth signalling, indicating that TRPML-2 play a pro-tumorigenic function in the development of glioma cells. However, TRPML-2 knockdown prevents glioma cell line's viability, proliferation, and induction of apoptosis.[114] So, TRP channels act as a potential target which causes interference in glioma proliferation.

TRP Channels in Traumatic Brain Injury and Spinal Cord Injury

TBI and SCI are consequences of primary and secondary injuries. Primary injury causes initial mechanical trauma to tissues and indirectly delayed the secondary injury damage which can last for days or even weeks after injury that leads to progressive tissue damage.[115] TRP channels have been found

Table 1: Pharmacological interventions that target TRP channels in various neurological disorders

Channel name	Pharmacological interventions	Diseases	References
TRPV1	Capsaicin	AD, epilepsy, schizophrenia, depression	30,64,88,99
	Capsazepine	epilepsy, ischaemic stroke	63,76
	AMG-9810	epilepsy, PD	65,46
	Vanillin	AD	29
	Oleoylethanolamide	PD	46
	5-iodoresiniferatoxin	epilepsy	63
	Resolvins	epilepsy	63
	α-spinasterol	epilepsy	63
	Dihydrocapsaicin	ischaemic stroke	77
	Olvanil	depression	100
	SB-705498	migraine	105
	A-993610	migraine	106
TRPV4	HC-067047	epilepsy, ischaemic stroke, hemorrhagic stroke	66,78,81
	Ruthenium red	ischaemic stroke	78
TRPM2	Tat-M2NX	ischaemic stroke	74
TRPM4	9-phenanthrol	ischaemic stroke	75
TRPM7	Carvacrol	ischaemic stroke	72
TRPM8	Menthol	migraine	103
	AMG-1161	migraine	103
TRPC3	Pyr-3	hemorrhagic stroke	80
TRPC4/C5	M084	anxiety, depression	96
	HC-070	anxiety, depression	97
TRPC6	Hyperforin	AD, epilepsy, ischaemic stroke	70,54,70
	1-oleoyl-2-acetyl-sn-glycerol	AD	24
	Resveratrol	ischaemic stroke	71
TRPA1	HC-030031	AD, migraine	33,107

to be implicated in traumatic brain injury as well as spinal cord injury. Recent studies revealed involvement of TRPM2 channels in TBI, TRPM2 mRNA and protein expression are considerably enhance in hippocampus and cerebral cortex (areas especially vulnerable to injury during TBI) in an impact-acceleration model of diffuse traumatic brain injury in sprague dawley mature male rats indicating that TRPM2 involve in the pathology of TBI.[116] Another study showed the involvement of TRPM2 channels in Ca^{2+} influx mediated neural apoptosis and the negative regulation of TRPM2 channel activity by melatonin treatment may account for neuroprotective effect of TRPM2 channels against oxidative stress, Ca^{2+} influx, as well as neuronal apoptosis in neuronal cells of hippocampus of TBI-induced rats.[117] After traumatic brain injury, intracellular Mg^{2+} becomes depleted which causes poor neurological prognosis. Particularly, TRPM6 and TRPM7 are crucial for maintaining Mg^{2+} homeostasis after TBI.[118] Moreover, literature reviews also revealed that TRPM4 mRNA and protein significantly increased in capillaries after SCI, which caused the capillaries to break down and develop petechial haemorrhages.[119] Thus, above findings suggest that TRPs can be targeted for the treatment of TBI and SCI.

CONCLUSION

In the present era, neurological disorders are becoming more common globally. Although advancements have been made in the field of diagnosis and treatment. Neurological disorders can presently only be treated with symptomatic alleviation. Disrupted Ca^{2+} homeostasis is the common etiology among these neurological disorders that results in neural damage. Neuronal cells regulate the Ca^{2+} levels by several ways, TRP channels being one of them. TRPs are crucial for maintaining Ca^{2+} homeostasis, and disturbance in TRP channel activity results in various neurological disorders. In pathological conditions, there is an alteration in the expression of the TRP channels, which causes oxidative stress, neuroinflammation, and mitochondrial damage, contributing to the death of neuronal cells. So far, a no. of pharmacological modulators targeting TRP channels in neurological disorders has been investigated, as shown in Table 1. However, developing therapeutics by targeting the TRP channels is difficult due to the shortage of their specific activator(s) and blocker(s), blood-brain barrier permeability, diverse expression, and incomplete knowledge of the mechanism of mechanism activation and unwanted effects of their modulators. Furthermore, TRP channels are the key player in regulating ionic homeostasis. Thus, specific pharmacological treatments targeting TRP channels may open the door to developing neuroprotective treatments for neurological disorders.

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