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TRPV1 Channel: A Potential Drug Target for Treating Epilepsy

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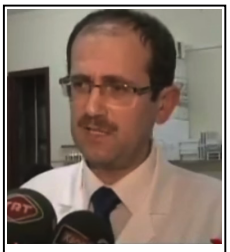

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Abstract: Epilepsy has 2-3% incidence worldwide. However, present antiepileptic drugs provide only partial control of seizures. Calcium ion accumulation in hippocampal neurons has long been known as a major contributor to the etiology of epilepsy. TRPV1 is a calcium-permeable channel and mediator of epilepsy in the hippocampus. TRPV1 is expressed in epileptic brain areas such as CA1 area and dentate gyrus of the hippocampus. Here the author reviews the patent literature on novel molecules targeting TRPV1 that are currently being investigated in the laboratory and are candidates for future clinical evaluation in the management of epilepsy.

A limited number of recent reports have implicated TRPV1 in the induction or treatment of epilepsy suggesting that this may be new area for potential drugs targeting this debilitating disease. Thus activation of TRPV1 by oxidative stress, resiniferatoxin, cannabinoid receptor (CB1) activators (i.e. anandamide) or capsaicin induced epileptic effects, and these effects could be reduced by appropriate inhibitors, including capsazepine (CPZ), 5'-iodoresiniferatoxin (IRTX), resolvins, and CB1 antagonists. It has been also reported that CPZ and IRTX reduced spontaneous excitatory synaptic transmission through modulation of glutaminergic systems and desensitization of TRPV1 channels in the hippocampus of rats. Immunocytochemical studies indicated that TRPV1 channel expression increased in the hippocampus of mice and patients with temporal lobe epilepsy.

Taken together, findings in the current literature support a role for calcium ion accumulation through TRPV1 channels in the etiology of epileptic seizures, indicating that inhibition of TRPV1 in the hippocampus may possibly be a novel target for prevention of epileptic seizures.

Keywords: Anadamide, Calcium ion, Epilepsy, Hippocampus, Seizures, TRPV1 channels.

INTRODUCTION

Epilepsy is a common neurological disorder with approximately 50 million individuals (>2-3% of the population) affected worldwide. Increased excitability of neurons in various brain regions plays an important role in the etiology of epilepsy. The disease is considered an acute transient complex neurobehavioral disease [1, 2]. Although numerous studies have been conducted on the etiology of epilepsy, clear cellular and molecular mechanisms involved in the etiology of epilepsy are still unclear [3-5]. Treatment of epilepsy is possible although currently available antiepileptic drugs provide only partial control of seizures [3, 6, 7]. Molecular targets of most of these antiepileptic drugs are ion channels such as glutamate receptor channels and transient receptor potential (TRP) channels that are thought to be partially responsible for epileptic seizures and peripheral pain [7-9]. For these reasons, the discovery of novel drugs to treat epilepsy would be highly desirable.

Calcium ion (Ca^{2+}) is an important second messenger and plays a role in numerous signal transduction pathways including neuronal excitability, neurotransmitter release, cell proliferation, and cell death [10,11]. It has long been known that Ca^{2+} is involved in the etiology of epilepsy. Different types of Ca^{2+} channels, such as voltage gated calcium channels (VGCC) and chemically gated calcium channels, likely play an important role in the etiology of epilepsy. Apart from the VGCC and chemically gated channels, one family of Ca^{2+} channels comprises transient receptor potential (TRP) cation channels. The TRP channels were firstly expressed in photoreceptors carrying *trp* gene induced a transient voltage changes to continuous light mutations of *Drosophila* flyers [12, 13]. One subfamily of TRP channels is the vanilloid group containing 8 members, including TRP vanilloid type 1 (TRPV1) cation channels. TRPV1 channels are non-selective cation channels. The polymodal transducer TRPV1 channel was first reported in sensory neurons such as dorsal root ganglion (DRG) and trigeminal ganglia neurons because the channels respond to various stimuli including oxidative stress, noxious heat (> 43 ^{o}C), protons and vanilloids (i.e. capsaicin) [14]. Na^{+} and Ca^{2+} entry result from activation of TRPV1 channels and neuronal excitability ensues [15-17]. In addition to expression of TRPV1 in the peripheral neurons [14], more recent studies have suggested that TRPV1 channels may also be a novel potential antiepileptic target [18, 19]. Indeed, the expression of TRPV1 protein was increased in epileptic brain areas such as the dentate gyrus of temporal lobe epilepsy-induced mice [20]. Recently, it was reported that epileptic activity was increased in hippocampal slices of rats by the TRPV1 channel agonist capsaicin, and this activity was blocked by a selective TRPV1 channel

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Table 1. Role of TRPV1 channels on molecular pathways in human and animals with epilepsy.

Material	Drugs	Effects	References
Mice	Anandamide Capsaicin Capsazepine	CPZ and low doses of anandamide anticonvulsant but capsaicin and high doses of anandamide pro-convulsant.	Manna and Umathe [21]
Mice	Anandamide Capsaicin CPZ	CPZ and low doses of anandamide inhibit marble-burying behavior effect but capsaicin and high doses of anandamide induce marble-burying behavior.	Umathe *et al*. [48]
Rat	Piperine	Anti-seizure property	Chen *et al*. [18]
Human	-	Increased TRPV1 expression in the hippocampus of patients with temporal lobe epilepsy	Sun *et al*. [73]
Mice	-	TRPV1 expression is unaltered in the hippocampus of mice with seizure history	von Rüden *et al*. [19]
Mice	CPZ	TRPV1 channel is expressed in the hippocampus of epileptic mice. CPZ suppressed ongoing ictal activity and propagation of seizure activity.	Gonzalez-Reyes *et al*. [5]
Rat	***OLDA*** and AMG-9810	OLDA (TRPV1 receptor agonist)- induced pro-convulsant effect were reversed by the pre-treatment of rat with AMG-9810 (TRPV1) antagonist.	Shirazi *et al*. [74]
Trpv1 deficient mice		Occurrence of febrile seizures temporally correlated with hyperthermia evoked TRPV1 activation	Kong *et al*. [75]
Rat	Capsaicin and CPZ	Capsaicin-induced TRPV1 channel activity is increased in hippocampus of rats by epilepsy.	Ghazizadeh and Nazıroğlu [22] Nazıroğlu *et al*. [23]
Rat	Capsaicin, CPZ and IRTX	Anti-seizure and anti-apoptotic properties	Nazıroğlu and Ovey [77]

CPZ, capsazepine; IRTX, 5'-iodoresiniferatoxin; OLDA, N-oleoyldopamine

antagonist iodoresiniferatoxin (IRTX) [2]. Other recent papers [18, 19, 21-23] have also reported antiepileptic actions of the TRPV1 channel antagonist, capsazepine (CPZ).

Current knowledge regarding the functional importance of TRPV1 channels in the hippocampus and epilepsy is still relatively sparse. Studies utilizing pharmacological manipulation of TRPV1 indicate that this channel is not only an important element of hippocampal functions but may also play a role in epilepsy. In the review, I have analyzed the most recent findings about the expression and function of TRPV1 in the hippocampus and epilepsy, and discussed the possibility of these channels as a potential target for the treatment of epilepsy.

EPILEPSY AND Ca^{2+}

About 50 million (2-3%) of the population worldwide are suffer from the chronic neurological disorder of epilepsy [24]. Epilepsy has been divided into three forms, specifically idiopathic, symptomatic, and cryptogenic forms. Some of the factors that are thought to contribute to the etiology of these epileptic forms include overload of Ca^{2+}, genetic defects and oxidative stress [4, 24-26].

Numerous functions of neurons such as action potentials, synaptic transmission, plasticity, and cell survival are affected by the cytosolic Ca^{2+} concentration [1,10,27]. Cation channels play a major role in regulating cytosolic Ca^{2+} concentrations in all cells, including neurons, because Ca^{2+} crosses the cell membranes to enter the cytosol by way of these channels.

It has long been known that Ca^{2+} entering through neuronal VGCC regulates activity-dependent processes such as neurotransmitter release, gene transcription, and cytosolic signaling processes. In healthy neurons, calcium channels regulate and activate homeostatic signaling processes [28]. In presynaptic neurons, VGCCs are opened by action potential-induced depolarization and neurotransmitter release is dependent upon calcium entry that creates local domains of high Ca^{2+} concentration. In post synaptic neurons, many signaling processes are regulated by changes in cytosolic Ca^{2+} concentration following Ca^{2+}entry through receptor operated channels and L-type VGDC. Neurons, synapses, and circuits in the nervous systems have very sensitive but powerful homeostatic set points of activity, and small changes in calcium channel activities can fine tune many synaptic outputs in a variety of ways [10, 28].

Epileptic seizure-induced brain injury involves many neuronal cell death inducing factors, including genetic changes, glutamate-mediated excitoxicity leading to changes in cytosolic Ca^{2+} metabolism, mitochondrial membrane abnormalities, induction of oxidative stress, and increased cytokine production [1]. At the cellular level, an enormous influx of Ca^{2+} *via* VGCC and N-methyl-D-aspartate (NMDA)-dependent calcium channels results in massive seizure activities [3, 7]. Following epilepsy, activation of

VGCC and NMDA receptors causes an elevation in cytosolic Ca^{2+} that in turn initiates biochemical cascades resulting in acute neuronal cell death [7]. In addition to VGCC and NMDA receptors, recent reports indicated the importance of massive Ca^{2+} entry through TRP channels, including TRPV1 channels, in the etiology of epilepsy [19-23]. This latter aspect with be the focus of the remaining sections of this review.

TRP CHANNELS

The transient receptor potential (TRP) family has transmembrane domains with hydrophobic 4 pores. The pores are located between the fifth and sixth transmembrane domains, and for most TRP channels Ca^{2+} passes the cell membrane through these pores non-selectively. There are 30 mammalian TRP channels and new members of the family continue to be discovered. Based on their structural homology, The TRP channels are divided into 7 subfamilies namely canonical (TRPC1-7), ankyrin (TRPA1-3), melastatin (TRPM1-8), mucolipin (TRPML1-3), vanilloid (TRPV1-6), polycystin (TRPP1-3), and no-mechano-potential (NOMCP or TRPN). The activation and inhibition mechanisms are very different within the subfamilies. For example, TRPM8 is activated by menthol and environmental noxious cold (<15 ^{o}C) while TRPV1 channels are activated by different stimulants, including environmental high temperature (≥43 ^{o}C), oxidative stress, capsaicin and products of inflammation. TRPA1 is activated by cinnamaldehyde of cinnamon oil, Wasabi, garlic and environmental vehicle exhaust gas. Expressions of the channels are also differing in different tissues of body. For example, TRPV1 and TRPM2 channels are mostly expressed in brain and neurons while TRPC1 channels are mostly expressed in the cardiovascular system. Hence, TRP channels have different cellular polymodal integrators that are sensitive to environment factors [8, 9, 11, 13, 16, 29].

An Overview of TRPV1

The TRPV1 channel was discovered in sensory neurons in 1997 [17]. Subsequently it was found that the channels are also expressed in non-neuronal cells [31, 32]. In the last decade, the first exogenous expression studies were performed and this led to screens for antagonists of TRPV1 channels for clinical studies. As it was mentioned above, TRPV1 is activated by painful physical stimuli such as high temperature (≥43 ^{o}C), voltage changes, N-arachidonoylethanolamide (anandamide) and protons (low pH). It can also be activated by capsaicin, the pungent ingredient of hot chili peppers, and by anandamide, oxidative stress, nitric oxide, hydrogen peroxide, and oxidized linoleic acid [29, 30, 33-35]. In primary DRG neurons, TRPV1 has an essential role in the induction of inflammatory hyperalgesia [17, 36]. TRPV1 channels are also activated in the central nervous system by fatty acid amide hydrolase (FAAH, the catabolic enzyme of anandamide) and anandamide [37]. In addition to these activators, TRPV1 levels in DRG neurons were increased by nerve growth factor and the activation of p38 mitogen-activated protein kinase in inflamed skin [38]. It has also been suggested that the TRPV1 channel is activated by phosphatidylinositol 3-kinase-induced heat hyperalgesia [39, 40]. In addition, the TRPV1 channel is activated by low pH [41, 42]. Thus, in addition to their role as thermo-receptors, the current reports indicated that TRPV1 channels are also modulated by various molecules and distinct molecular pathways.

Studies indicate that TRPV1 is expressed in the brain area. For example, the CA1 area and dentate gyrus of the hippocampus have important roles in the induction of epilepsy and recent immunocytochemical studies indicated the presence of TRPV1 channels in the CA1 area and dentate gyrus of the hippocampus. Thus TRPV1 may play a role in the central nervous system in addition to its role as a polymodal sensory signal detector of peripheral pain [15, 31, 43-45].

AGONISTS AND ANTAGONISTS OF TRPV1 CHANNEL

Cannabinoids: Anandamide

An endogenous agonist of CB1 receptors is anandamide and TRPV1 channels are also activated by high concentrations of anandamide [33]. Glutamate release due to TRPV1 channel activation in the brain is well-known [46]. In addition, VGCC are blocked by CB1 activation. Hyperpolarization through potassium ion efflux and a decrease of neuro-transmitter release are also induced by CBI activation [47]. Low and high dose (biphasic) anandamide-induced effects on behavioral models correlate with CB1 receptors and TRPV1 activation, respectively [48]. In addition to the dose dependent effects of anandamide on TRPV1 channels, anandamide mediated TRPV1 responses are affected by many factors, including phosphorylation, voltage, temperature changes, pH, and CB1 receptor activation [33].

Activation of TRPV1 Channels Through Physical and Chemical Stimulus

The TRPV1 channel was first discovered and expressed as a receptor for capsaicin. Subsequently, the role of TRPV1 on different cellular processes was reported, for example the detection of noxious physical and chemical stimuli in peripheral neurons. The presence of TRPV1 channels in nociceptive Aδ and C-fibers of small and medium diameter sensory neurons (which are responsible for peripheral nociceptive pain) was also reported [49]. Recently we also observed a role for TRPV1 channels in the etiology of an inflammatory disease [50]. It seems that TRPV1 functions as a multi-detector against physical and chemical stimuli. The hippocampus is a main area in the etiology of epilepsy and recent evidence suggests functional TRPV1 channels are expressed in the hippocampus.

Activation of TRPV1 Channels Through Capsaicin and Resiniferatoxin

Capsaicin is a pungent ingredient in red hot peppers of the *Capsicum plants* [51] and TRPV1 was originally discovered as a receptor of capsaicin. Although capsaicin induces pain it has been used as a treatment of pain due to its ability to desensitize TRPV1 channels in neurons [52]. In addition to the agonist effect of capsaicin, resiniferatoxin is also a potent TRPV1 channel agonist at low concentrations [32, 53].

Activation of TRPV1 Channels *via* Oxidative Stress

Oxidative stress occurs due to over production of reactive oxygen species (ROS). ROS are produced through electron transport mechanisms during physiological functions such as mitochondrial substrate oxidation and phagocytic activity. They are also produced in response to different environmental factors and metabolic diseases including, traumatic brain injury, diabetes, and electromagnetic radiation [54, 55]. If the production of ROS is controlled by antioxidants their ability to cause damage DNA, lipids, proteins and carbohydrates is lessened [8, 9, 11, 55]. There is considerable interest in the relationship between these reactive species and the etiology of a variety of diseases, including epilepsy [1]. There are two major types of free radical species: ROS and reactive nitrogen species (RNS). The ROS and RNS involve changes in specific amino acid residues, especially cysteine sulfhydryls, which may be located on signaling proteins [56]. TRPV1 is activated directly by RNS and oxidants through modification of cysteine free sulfhydryl groups [57] although cysteine redox system antioxidants, such as selenium, glutathione and N-acetyl cysteine, inhibited capsaicin and oxidative stress-induced activation of TRPV1 channels [15, 30, 34, 50]. It has been shown that Cys553 and Cys558 are present between the fifth and sixth transmembrane of TRPV1 channels and these amino acids have an essential role for the TRPV1 activation in response to nitric oxide stimulation [29, 57, 58]. TRPV1 channels are also activated by nitric oxide directly, while a TRPV1 mutant with substitutions at these conserved cysteines gives significantly suppressed responses to nitric oxide.

TRPV1 Blockers and Potential Therapeutic Use

There are two main TRPV1 channel blockers, namely CPZ and resiniferatoxin. CPZ is the first reported blocker of TRPV1 channels and it has been used in pharmacological studies [60]. CPZ binds in the channel pore of TRPV1 and blocks all four monomers of the tetrameric channel through interacting with residues of the monomers [45]. 5'-Iodoresiniferatoxin (IRTX) is also potential blocker for TRPV1 channel although some TRPV1 agonist effects were reported for this drub. IRTX has been also proposed as a potentially useful analgesic agent through modulation of TRPV1 channels [32,53]. It appears that TRPV1 receptor antagonists cannot treat the pain totally but in fact provide complementary approaches to management of pain.

The TRPV1 channel is of great interest in the pharmaceutical industry because the TRPV1 channel, as the molecular target for capsaicin, was first discovered in peripheral neurons [36]. Other TRP channels such as TRPM8 and TRPA1 are found in DRG and also have important roles in the etiology of peripheral pain [59, 61]. In patients with acute and chronic pain, the threshold of pain sensitivity increases due to cation channel-mediated cytosolic Ca^{2+} accumulation. As a result, searches for potential pain alleviating drugs have focused on this Ca^{2+} modulating cation channels. Specifically, drug companies have sought to develop TRPV1 antagonists for the management of acute and chronic pain [52]. In addition to the TRPV1 channel agonist effects of capsaicin, this agent has also been used as an analgesic given as a low-dose cream or as a single application of a high-dose patch [52,62]. However, its ability to alleviate analgesia is temporary due to adaptation and desensitization of neurons (graphical abstract). At the beginning of the treatment, application of capsaicin induces pain until down regulation of TRPV1 channels through desensitization occurs. Hence, a local anesthetic may be useful during the first treatment phase with capsaicin [59]. Several studies have reported that neuropathic and peripheral pain was reduced by TRPV1 antagonists. It was reported that TRPV1 channel inhibition by antagonists reduced neuropathic pain [36]. Recently, a number of TRPV1 antagonists, including ABT-102, SB-705498, AMG-517, MK2295 and GRC-6211 have been used as analgesic agents for treatment of patients with chronic pain. However, some TRPV1 antagonists (e.g. AMG517) have adverse health effects by disrupting the effect of TRPV1 in body-temperature regulation (hyperthermia). Nonetheless, TRPV1 antagonists and agonists remain promising pharmacological targets [63-65].

EPILEPSY AND THE TRPV1 CHANNEL

The discovery of activators of TRP channels provided useful tools for unraveling the molecular pathways of epilepsy in experimental animal and human studies. A understanding of the molecular pathways developed, this fueled interest in developing drug therapies for the treatment of patients with epilepsy.

Glutamate neurotransmitters are known to play an important role in the etiology of epilepsy. It was reported that glutamate release and glutamate-induced signaling in humans and experimental animals are enhanced by TRPV1 channel activity [46, 66, 67]. Thus, the duration of postsynaptic stimulation is increased through activation of TRPV1 channels at glutamatergic synapses [68]. Therefore, targeting the TRPV1 channel activity may provide a promising strategy for the regulation of neuronal activity in epilepsy [2].

It's well known that influxes of Na^+ and Ca^{2+} cations induce neurons to depolarize and fire action potentials, which in turn can further increase the influx of Na^+ and Ca^{2+} cations [69]. In addition to interaction between glutamate release and TRPV1 channel activation, the activation of TRPV1 channels caused a decrease in the release of GABA and catecholamines [19, 68, 69], neurotransmitters that have been shown to modulate activity-dependent synaptic efficacy and epilepsy [70, 71].

Studies have demonstrated that CB1 receptor activation by endocannabinoids like anandamide or 2-arachidonylglycerol induced neuroprotection in the hippocampus. Endocannabinoids were found effective in inhibiting epileptic seizures in epileptic models [70, 71]. In contrast, other studies indicated that seizure threshold was reduced thus facilitating epileptogenesis [72]. Sun *et al*. [73] reported increased TRPV1 expression in the hippocampus of patients with temporal lobe epilepsy. Following on this observation, von Rüden *et al*. [19] investigated the role of the endocannabinoid and endovanilloid systems through TRPV1 channel activation on the etiology of epilepsy in temporal lobe epilepsy-induced mice. They observed an increase in

hippocampal CB1 receptor expression and seizure rate in the mice although TRPV1 channel expression did not correlate with the repetitive seizures. They suggested that TRPV1 does not play a role in etiology of epilepsy induction although the endovanilloid system may be strongly involved in ictogenesis or seizure induction. The endocannabinoid signaling pathways are blocked in severe chronic epilepsy and induction of absence epilepsy is reduced by down regulation of CB1 receptors in the endocannabinoid system although there are also conflicting views on the role of TRPV1 channels in the induction of epilepsy [71].

In contrary to results of von Rüden *et al*. [19], results of recent studies have reported that TRPV1 may be a novel anti-epileptogenic drug target [21-23, 38]. This hypothesis is supported by results of several experimental studies. For example, induction of temporal lobe epilepsy is associated with an increase in the expression of TRPV1 channels [20]. In addition, temporal lobe epilepsy is associated with increased excitatory circuit activity and TRPV1 channel activation in the dentate gyrus of mice, implicating TRPV1 channels in the etiology of epilepsy [20, 38].

The biphasic effects of anandamide and TRPV1 (CPZ) or CB1 (AM251) receptor antagonists on marble-burying behavior (MBB) as a behavioral model was investigated in mice [48]. MBB is reduced by a low dose (10 μg/mouse) of CPZ but not by high doses (20 and 40 μg/mouse) of CPZ. In addition, blockade of the CB1 receptor induced an anti-compulsive effect in the mice. Similarly, Shirazi *et al*. [74] investigated the role of TRPV1 receptors on the development of pentylenetetrazole (PTZ) and amygdala-induced kindling in rats. They observed that the pro-convulsant effects of OLDA (a TRPV1 receptor agonist) were reversed by pre-treatment of rats with AMG-9810, a (TRPV1 antagonist).

TRPV1 channels are activated by high environmental temperature. Recently, Kong *et al*. [75] investigated the role of TRPV1 on the threshold to PTZ-induced epileptic seizures in wild type and TRPV1 gene knock-out C57/BL6 mice. Their results indicated that the threshold to PTZ-induced seizures temporally correlated with hyperthermia-induced TRPV1 channel activation in the mice. According to these results, hyperthermia-induced TRPV1 might be an important candidate therapeutic target in neurological disorders with heat-induced hyper-excitation.

Piperine is important active principal of black pepper. Black pepper has been used as a traditional medicine analgesic in the treatment of epilepsy [76]. A recent study reported an anti-epileptic effect of piperine through TRPV1 channels in the PTZ and maximal electroshock seizure mouse models [18].

It's well known that 4-aminopyridine (4-AP) induces epileptiform electrical depolarization by blocking voltage gated K^+ channels in rat hippocampus. An antiepileptic activity of CPZ was tested using 4-AP as a convulsant agent by Gonzalez-Reyes *et al*. [5]. CPZ administration suppressed ongoing ictal activity in the rat hippocampus. In addition, they concluded that peripherally injected CPZ passed the blood-brain barrier easily to reach anti-convulsant concentrations in the brain.

Overload of cytosolic Ca^{2+} induces the generation of ROS, through uncoupling of mitochondria and activation of many cytosolic catabolic enzymes [30, 34]. Exposure of mitochondria to an overload of cytosolic free Ca^{2+} has been shown to increase formation of ROS [23, 34]. Production of NADPH and ATP are also impaired by increased mitochondrial membrane depolarization and enhanced ROS formation [11]. Currently, ROS are known to be both a contributor to the cause, as well as a consequence of epileptic seizures [1].

Prior to 2014, publications on epilepsy and TRPV1 channels dealt with channel expression and seizure activity but not with Ca^{2+} influx (by patch-clamp or optical techniques). More recently, we have performed three molecular level studies on TRPV1 channels with Ca^{2+} influx analyses in PTZ-induced epileptic rats. In two studies, hippocampal and DRG neurons from epileptic rats were isolated and they were pre-incubated with CPZ before capsaicin stimulation. We found that hippocampal apoptosis, caspase-3, caspase-9, ROS, mitochondrial depolarization and $[Ca^{2+}]_i$ concentration were increased by epilepsy induction. Hence, PTZ administration to the rats is characterized by increased oxidative stress, Ca^{2+} influx and apoptosis. Administration of the TRPV1 channel blocker, CPZ, caused a decrease in $[Ca^{2+}]_i$ concentration. To the best of our knowledge, these two studies were the first to investigate epilepsy with particular reference to its effects on oxidative stress, Ca^{2+} signaling and the apoptosis-redox system in PTZ-induced hippocampal injury in rats [22, 23]. In a third study [77], we demonstrated that cytosolic calcium elevation through activation of TRPV1 channels by the agonist capsaicin, causes apoptosis in DRG and hippocampus of rats. These results indicate that calcium accumulation through TRPV1 channels plays a physiologically relevant role in the regulation of epileptic seizures. In addition, the TRPV1 channel blockers, IRTX and CPZ, induced protective effects against epilepsy, capsaicin-induced Ca^{2+} entry through TRPV1 and apoptosis in the neurons. Hence, the results of the three studies taken together indicate that a decrease in calcium accumulation, through inhibition of TRPV1 channels, can play a neuronal protective role against epilepsy-induced Ca^{2+} entry in hippocampal and DRG neurons. This interaction may play an important role in epilepsy and peripheral pain diseases associated with activation of TRPV1 channels.

CONCLUSIONS AND FUTURE DIRECTIONS

TRPV1 is a non-selective channel with high Ca^{2+} permeability [8], and its activation typically promotes glutamate release by increasing the excitability of neurons and synaptic terminals [37]. The hippocampus is highly sensitive to environmental stimuli including Ca^{2+} entry, especially given its inability to regenerate. Also, it has been known for some time that glutamate receptors and their agonists such as NMDA and kainic acid, are thought to play an important role in the etiology of epilepsy. Glutamate-induced spontaneous excitatory synaptic transmission is increased in the hippocampus by the TRPV1 channel agonist capsaicin [20, 66] while it was reduced in the hippocampus slices of rats by both CPZ and IRTX, presumably acting

through through modulation of glutaminergic systems [37]. Moreover, pretreatment with CPZ in hippocampal neurons exerts a protective effect on the capsaicin-induced increase in caspase activity and apoptosis [22]. Current findings in the literature suggest that the antiepileptic effects of TRPV1 channel antagonists may be result from modulation of glutamate release. Therefore, in this review, on the basis of recent findings in the literature, we may conclude that Ca^{2+} accumulation through TRPV1 channels has a regulatory role in the diseases of hippocampal and sensory neurons.

Anandamide is an endogenous agonist at CB1 and also activates TRPV1. Results of recent reports indicate that activation of CB1 receptors and TRPV1 channels are affected in epileptic animals by anandamide and CPZ in a dose dependent manner [48]. Although the role of anandamide in induction and treatment of epilepsy is clear, the role of TRPV1 channels in the etiology of epilepsy is less clear. In addition, there are few reports on anandamide-dependent activation of TRPV1 channels and induction of epilepsy in the literature. Hence, additional studies on this subject are needed.

Oxidative stress plays an important role in the induction of epilepsy, and TRPV1 channels are activated by oxidative stress. The results of recent studies indicate that critical

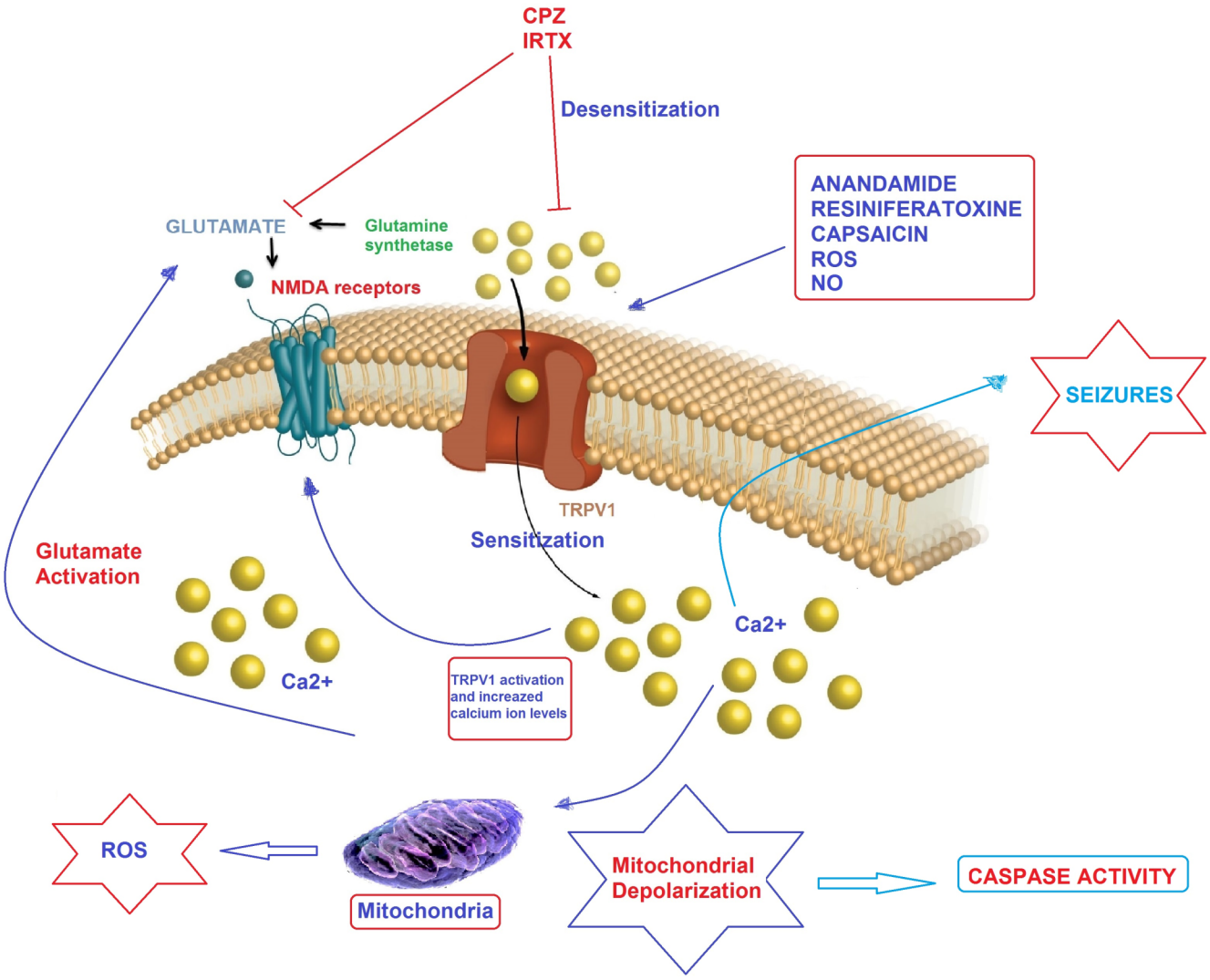

Fig. (1). Possible molecular pathways of TRPV1 channel activation on epilepsy in hippocampal neurons. Convulsions in epilepsy can results in augmented glutamate release, leading to Ca^{2+} uptake through NMDA receptor and TRP channels. Mitochondria were reported to accumulate Ca^{2+} provided cytosolic Ca^{2+} rises, thereby leading to depolarization of mitochondrial membranes. At the extreme, Ca^{2+} entry causes severe ***mitochondrial*** permeability transition or even the rupture of the mitochondrial membrane, substantial swelling of the mitochondria with rupture of the outer membrane and release of apoptosis-inducing factors such as caspase 3 and 9. Anandamide, capsaicin, resiniferatoxin, nitric oxide (NO) and reactive oxygen species (ROS) induce Ca^{2+} accumulation through desensitization of TRPV1 channels although pharmacological desensitization of TRPV1 channels through antagonists such as capsazepine (CPZ) and 5'-iodoresiniferatoxin (IRTX) contributes to an immediate reduction on neuronal excitability [78]. ROS enhance also spontaneous release of glutamate from presynaptic terminals onto neurons through TRPV1 channel activation. The molecular pathway may be a cause of epileptic seizures and the subject should urgently investigate.

cysteine groups are present in the structure of TRPV1 channels [57]. Glutathione, selenium and N-acetyl cysteine have potent effects on the cysteine redox system. Recently we observed a modulatory role of glutathione and N-acetyl cysteine on inhibition of TRPV1 channels in DRG and hippocampus of rats [15, 30]. To my knowledge, there is no study on the roles of thiol- and cysteine- containing antioxidants in epileptic animals. Hence, the role of TRPV1 channels should be investigated in epileptic animals with respect to possible modulation by glutathione and N-acetyl cysteine.

As yet, the TRPV1 channel has not been fully recognizes as a potentially novel drug target by the drug industry. In the future, there is a need to investigate TRPV1 channel inhibitors as possible new antiepileptic drugs.

AUTHORS' ROLES

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DISCLOSER

There is no conflict to disclose in the current study.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

4-AP	=	4-aminopyridine
CB1	=	cannabinoid receptors type 1
CB2	=	cannabinoid receptors type 2
CNS	=	central nervous system
CPZ	=	capsazepine
DRG	=	dorsal root ganglion
FAAH	=	fatty acid amide hydrolase
IRTX	=	5'-iodoresiniferatoxin
LTD	=	long-term depression
LTP	=	long-term potentiation
NMDA	=	N-methyl-D-aspartate
PTZ	=	pentylenetetrazole
ROS	=	reactive oxygen species
TRP	=	transient receptor potential
TRP	=	transient receptor potential
TRPC	=	transient receptor cononcial
TRPM	=	transient receptor melastatin
TRPV1	=	transient receptor potential vanilloid type 1
VGCC	=	voltage gated calcium channels

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