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TRPV1 and the Intrinsic Neuronal Response to stress

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Abstract

By gating cation entry into cells, the TRP superfamily of ion channels aid in signal transduction of various stimuli. One particular TRP channel, TRPV1, activates upon exposure to certain noxious stimuli such as heat, low pH, and pressure. Although first characterized as a channel critical to nociception, TRPV1 is now known to participate in such diverse activities as mediating synaptic plasticity, initiating and regulating filopodia, aiding axonal guidance and migration, and participating in the neuronal stress response. Evidence from the literature, reviewed here, suggests that TRPV1 may promote neuronal survival under stress. Using glaucomatous neurodegeneration as a model of neuronal stress, a potential role of TRPV1-mediated neuroprotection is outlined here. Reasoning for this protective role draws upon TRPV1-/- data and the demonstrated abilities of TRPV1 to sensitize and translocate to the membrane in response to stressors, to localize to synapses, and to maintain synaptic structures via potentiating excitatory synaptic activity.

Keywords

TRP channels
TRPV1
Neuronal stress response
Neurotoxicity
Neuroprotection

TRPV1: A multifunctional TRP channel

Transient receptor potential (TRP) channels represent a diverse superfamily of proteins that gate cation entry into cells. Functional characteristics of TRP channels are so dissimilar that these proteins comprise six subfamilies grouped solely by amino acid homology rather than by function[1]. In mammals, these subfamilies include 28 different TRPs: canonical (TRPC1-7), vanilloid (TRPV1-6), melastatin (TRPM1-8), ankyrin (TRPA1), polycystin (TRPP1-3) and mucolipin (TRPML1-3)[2]. First characterized in the Drosophila phototransduction cascade[3], TRP channels are situated in the cell membrane, which positions them to transduce extracellular sensory information to the intracellular space. TRP channel subunits all possess six putative transmembrane (TM) domains with a stretch of hydrophobic amino acids between TM5 and TM6 that serves as a pore region (**Figure 1**). When these subunits tetramerize, they form a pore permeable to monovalent and divalent cations. Upon activation, TRP channels mediate Ca^{2+} flux across membranes, resulting in an increase in $[Ca^{2+}]_i$. Perturbations of neuronal Ca^{2+} signaling are a hallmark of neurodegenerative disease, thus it is particularly important to understand how TRP channels functionally influence neuropathic mechanisms[4].

One subfamily of TRP channels, the vanilloid TRPs (TRPVs) derive their name from the vanillyl functional group found on some of their ligands. Of the TRPVs, TRPV1 was the first discovered and remains the best characterized[5]. TRPV1 was first discovered based on its activation by the pungent component of chili peppers, capsaicin[6]. TRPV1 transduces information regarding other noxious stimuli, including heat (>42 °C temperatures), low pH (<6.0), and pressure[6, 7]. Within the peripheral nervous system, TRPV1 channels are expressed in primary sensory afferent fibers, allowing peripheral pain information to reach the central nervous system[6]. Accordingly, TRPV1 knockout mice exhibit a reduced pain response, which makes this channel of particular interest as a target for pain and hyperalgesia therapeutics[8, 9].

TRPV1 activity depends upon the sensitization state of the channel, which can be influenced by cellular signaling cascades. Phosphorylated TRPV1 represents a channel state that is more sensitive to activation[10]. Protein kinase A (PKA)[11], protein kinase C (PKC)[12], protein kinase D (PKD)[13], cyclin-dependent kinase 5 (Cdk5)[14] and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)[15] all sensitize TRPV1 by phosphorylation at serine, threonine, or tyrosine residues (**Figure 1**). This sensitization can be reversed by protein phosphatase 2B (calcineurin), which employs a Ca^{2+}-dependent phosphatase activity during this desensitization process[5]. When assessing TRPV1 function within injury or pathology, it is important to consider these modulatory effects by protein kinases and phosphatases.

Although TRPV1 was first characterized as a molecular detector of noxious stimuli, the discovery of widespread TRPV1 expression throughout the brain suggested

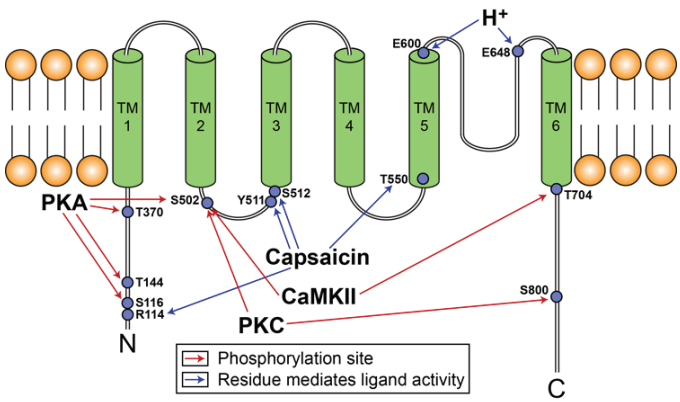

Figure 1. TRPV1 channel structure and functionally important residues. TRPV1 is a membranous ion channel characterized by intracellular N- and C-termini, 6 transmembrane (TM) domains, and a cation-permeable pore region between TM5 and TM6. Protein kinases phosphorylate specific residues (red arrows) in order to sensitize TRPV1 to ligand interactions (blue arrows). Figure constructed from reviewed information[16].

that the channel may possess additional functions beyond nociception[17]. It was proposed that there must be a class of endogenous ligands (endovanilloids) that regulated this signaling[18]. This class of ligands exists, and includes endocannabinoids such as anandamide and N-arachidonoyl-dopamine (NADA), lipoxygenase products, as well as endogenous inhibitors like PIP_2. The endocannabinoids are particularly interesting because anandamide and anandamide-like structures can often act at both TRPV1 and the cannabinoid (CB1 and CB2) receptors[10]. These promiscuous interactions indicate that there may be some interplay between the cannabinoid system and TRPV1.

Functions of TRPV1 in the central nervous system

Although TRPV1 is well-characterized with respect to pain perception at the periphery, data regarding its function within the CNS is limited. Examination of TRPV1 knockout mice revealed a reduction in anxiety, conditioned fear responses, long-term potentiation (LTP) in the hippocampus, and long-term depression (LTD) in the dentate gyrus[19, 20]. These alterations in behavior and neurophysiology suggest the relevance of TRPV1 to synaptic plasticity and neuronal networks. Within the CNS, TRPV1 activation in dorsolateral periaqueductal gray neurons increases neuronal activity by potentiating input from glutamatergic synapses[21]. Despite TRPV1's involvement in modulating synaptic transmission, it was not known if TRPV1 itself was located in synaptic terminals. Recently, it was determined that TRPV1 is present in synaptic structures by colocalization with pre- and post-synaptic markers as well as presence within biochemical fractions of synaptosomes and the post-synaptic density[22].

TRPV1 functions in developmental aspects of the CNS, such as regulation of the neuronal growth cones and filopodia. These TRPV1-positive filopodia contain synaptic vesicular and scaffolding proteins, thus it is likely that TRPV1 plays a role in synapse formation[23, 24]. These studies were complemented by another developmental study which indicated that TRPV1 mediates LTD in the developing superior colliculus via the depression of glutamatergic retinocollicular synapses[25]. Altogether, these examples show that TRPV1 is involved in plasticity and activity of synapses.

TRPV1 and the neuronal stress response

TRPV1 expression and localization in neurons is affected by injurious stressors and pathology. Increases in TRPV1 protein were observed in models of neuronal injury such as lingual nerve injury[26], chronic constriction injury[27], and gentamicin-induced ototoxicity[28]. In human tissue, increases in TRPV1 protein levels were found in aged and photoaged skin and its associated nerve fibers[29], as well as in tissue collected from patients with traumatic and diabetic neuropathy[30].

In multiple instances, TRPV1 has been implicated in physiological stress responses. Injured cells release ATP into the extracellular space, which can bind metabotropic ATP receptors[31]. These ATP receptors in turn sensitize TRPV1 via PKC-dependent phosphorylation[32]. Additionally, neurodegenerative diseases often have a sustained neuroinflammatory component that contributes to pathology[33]. Proinflammatory chemokines bind G protein-coupled receptors, which can cause downstream sensitization of TRPV1 by PKC[34]. Another proinflammatory mediator, nerve growth factor (NGF), promotes an increase in membrane current carried by TRPV1 by increasing the number of TRPV1 channels inserted in the membrane[35]. NGF binds the TrkA receptor, which activates a signaling cascade that ultimately phosphorylates TRPV1 at tyrosine residue Y200 via Src kinase. Tyrosine phosphorylation is involved in trafficking ion channels[36] and receptors[37], and is responsible for increasing the number of TRPV1 channels at the membrane following NGF binding[35]. These examples show that neuronal stressors can affect TRPV1 both by sensitizing the channel to activation as well as increasing levels of TRPV1 at the membrane, where it enhances current.

TRPV1: functionally neurotoxic or neuroprotective?

For many years, it has been known that capsaicin treatment causes degeneration of primary sensory neurons[38] as well as many neurons of the central nervous system[39]. Both in vivo and in vitro data gathered from mesencephalic dopaminergic neurons indicate that direct activation of TRPV1 with capsaicin or the endogenous ligand anandamide mediates cell death[40]. Such treatment produces a large increase in $[Ca^{2+}]_i$, subsequent mitochondrial damage, and cell death. However, the pathway mediated by anandamide may not actually act through TRPV1 due to the inability of TRPV1 antagonist capsazepine to prevent anandamide-induced cell death[41]. This is particularly important to consider in relation to cellular signaling occurring in neuropathy—anandamide may contribute to neurotoxicity independently of TRPV1. Although direct activation of TRPV1 via capsaicin is neurotoxic, there is some evidence that TRPV1 can be functionally neuroprotective. In a global ischemia model, TRPV1 antagonist capsazepine was able to block the neuroprotective effects of CB1 receptor antagonist rimonabant in CA1 hippocampal neurons[42]. The ability of capsazepine to block neuroprotection in this case suggests that TRPV1 at least partially mediates the neuroprotective effects of rimonabant[43]. This data concerning neurotoxic versus neuroprotective functions must be considered with the understanding that perturbing neurons with TRPV1 agonists and antagonists (some of which are not endogenous) does not necessarily represent functions that actually occur in stressed or degenerating neurons in vivo. While evidence supports neurotoxic and neuroprotective roles of TRPV1, it is of primary importance to understand that channel function is dictated by the neuronal signaling milieu. This signaling inevitably varies between classes of neurons as well as between different injury and disease states.

TRPV1 function in retinal ganglion cells: potential neuroprotection

The role of TRPV1 in neuronal survival remains controversial, especially with respect to disease and injury states in vivo. Glaucoma, an irreversible optic neuropathy, presents an especially interesting system in which to study TRPV1. In glaucoma, intraocular pressure (IOP) is the primary modifiable risk factor[44], so many animal models of this neurodegenerative disease require inducing elevated IOP[45, 46]. It is known that this channel contributes to pressure-induced changes in Ca^{2+} signaling in retinal ganglion cells (RGCs)[47] and retinal microglia[7]. Preliminary data from TRPV1 knockout mice suggests a neuroprotective role of TRPV1 against pressure-induced neurodegeneration of RGCs (Ward - unpublished data). These TRPV1-/- mice, when subjected to IOP elevation, exhibited increased optic nerve pathology when compared to wildtype controls. This is unusual, given that pressure is known to activate TRPV1 in RGCs, and that such Ca^{2+} influx can cause neurotoxicity. It seems logical that loss of TRPV1 would render RGCs less susceptible to pressure-induced death in vivo; however, this would not be the case if TRPV1 activation is actually neuroprotective. The potential for a TRP channel to exhibit neuroprotective activity in retinal injury is not unprecedented, as a recent study of retinal ischemia/reperfusion injury indicated that TRPC6 is protective[48].

Our working hypothesis is that TRPV1 functions as an intrinsic stress responder that slows down RGC degeneration by increasing excitatory activity at RGC synapses. In the DBA/2 mouse model of glaucoma, RGCs experiencing degeneration regularly exhibit dendrites with decreased complexity that lack higher-order branching, an indication of dendritic pruning[49]. Likewise, it is known that synaptic activity is a crucial factor in long-term synapse maintenance[50]. Increased TRPV1 activity at RGC synapses may counter the dendritic pruning seen in glaucoma, as retention of synapses requires maintenance of synaptic activity. In fact, eyes with elevated IOP exhibit increased levels of TRPV1 in the inner plexiform layer (IPL) of the retina[47] (**Figure 2**), which supports the idea of increased synapse potentiation in response to stress. The IPL includes extensive synaptic connections between RGC dendrites and bipolar cells, so this observed localization to the RGC dendrites may involve potentiation of synaptic connections under IOP stress.

As described in this review, TRPV1 exhibits a functional profile that fits with this working hypothesis. First, TRPV1 exhibits an intrinsic stress response that often includes increased levels of channel expression in injured and degenerating neurons[26-30]. Second, under stressed conditions, TRPV1 is sensitized by phosphorylation and relocalization to the membrane, where it increases membrane currents[32, 34, 35]. Third, within neuronal networks in the CNS, TRPV1 is known to modulate synaptic plasticity[19, 20] and to potentiate input from glutamatergic synapses[21]. Finally, the potential for TRPV1-mediated neuroprotection is supported by our preliminary data, where TRPV1-/- mice exhibit reduced RGC survival despite elevated IOP. Altogether, these functions indicate that TRPV1 may exhibit neuroprotective activity in glaucoma.

This hypothesis specifically addresses a potential TRPV1-mediated mechanism for intrinsic neuroprotection. Examination of TRPV1 function outside the neuron itself may provide even more information regarding how this channel mediates RGC survival. For example, retinal

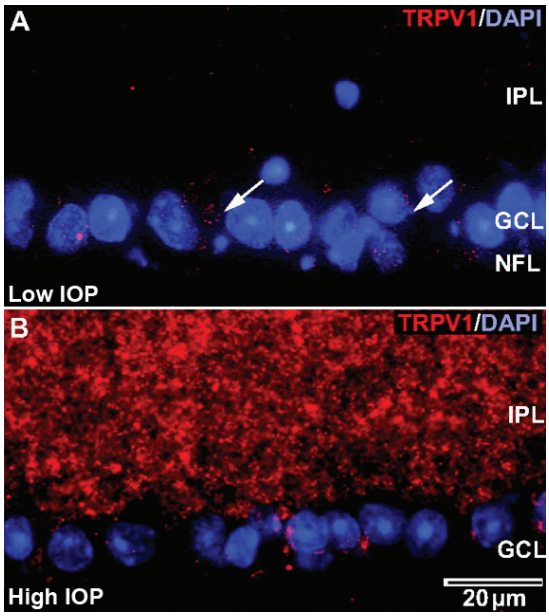

Figure 2. TRPV1 expression increases in RGC dendrites with elevated IOP. A. Immunolabeling for TRPV1 in a 6 month DBA/2J mouse retina from an eye with normal IOP. TRPV1 localizes primarily to the ganglion cell layer (GCL). B. TRPV1 immunolabeling increases in an age-matched retina with elevated IOP. Labeling persists in the GCL and increases in the inner plexiform layer (IPL), where RGC dendrites ramify. Figure modified for use with permission from author[47].

microglia exhibit pressure-dependent release of IL-6, a cytokine that is protective against pressure-induced RGC death[51]. Specific antagonism of TRPV1 revealed that this release was partially mediated by TRPV1-induced Ca^{2+} influx[7]. It is therefore likely that TRPV1-mediated neuroprotection is not simply intrinsic to RGCs, but may also involve glial cells.

Conclusions

Transduction of stimuli from the extracellular environment is a critical component of the neuronal response to stressors. The responses of TRPV1 to stress, reviewed here, indicate a potential role of TRPV1 in neuroprotection. TRPV1 activation is known to potentiate glutamatergic synapses, thus relocalization of TRPV1 to RGC dendrites may be involved in slowing the progression of dendritic pruning in glaucoma. Neurodegenerative diseases such as glaucoma do not push neurons unidirectionally toward death without a response from intrinsic cellular mechanisms that counter dysfunction. It is therefore important to characterize intrinsic stress responders such as TRPV1 in order to assess the potential for therapeutic interventions.

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FURTHER INFORMATION

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