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Review Article

Modulation of neuroinflammation: Role and therapeutic potential of TRPV1 in the neuro-immune axis

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ABSTRACT

Transient receptor potential vanilloid type 1 channel (TRPV1), as a ligand-gated non-selective cation channel, has recently been demonstrated to have wide expression in the neuro-immune axis, where its multiple functions occur through regulation of both neuronal and non-neuronal activities. Growing evidence has suggested that TRPV1 is functionally expressed in glial cells, especially in the microglia and astrocytes. Glial cells perform immunological functions in response to pathophysiological challenges through pro-inflammatory or anti-inflammatory cytokines and chemokines in which TRPV1 is involved. Sustaining inflammation might mediate a positive feedback loop of neuroinflammation and exacerbate neurological disorders. Accumulating evidence has suggested that TRPV1 is closely related to immune responses and might be recognized as a molecular switch in the neuroinflammation of a majority of seizures and neurodegenerative diseases. In this review, we evidenced that inflammation modulates the expression and activity of TRPV1 in the central nervous system (CNS) and TRPV1 exerts reciprocal actions over neuroinflammatory processes. Together, the literature supports the hypothesis that TRPV1 may represent potential therapeutic targets in the neuro-immune axis.

Contents

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1. Introduction

The transient receptor potential (TRP) channel gene was cloned from Drosophila in 1989 for the first time (Montell and Rubin, 1989) and the molecular structure and functional characteristics of the TRP super-family received a deeper understanding because members of this super-family are involved in many cell functions and have been identified as causal for many hereditary and acquired diseases (Nilius and Flockerzi, 2014). The TRP super-family has a diverse family of 28 cation channels, which is divided into six related sub-families, and shares a homologous function in mammalians (Moran et al., 2011).

As a member of the vanilloid receptor related TRP protein family, the TRPV1 channel, also named as the vanilloid receptor type 1 (VR1) or capsaicin receptor, which was first cloned and identified from rat dorsal root ganglia (DRG) by Caterina and his colleagues in 1997 (Caterina et al., 1997, 2000; Martins et al., 2014), is one of the most eminent members of the TRP super-family. Previously, neuroscientists identified the main function of TRPV1 in sensory transmission of the nociceptive neurons in the peripheral nervous system (PNS) (Ho et al., 2012; Martins et al., 2014). Recently, TRPV1 has been recognized to have a widespread distribution in the CNS where it is likely to constitute an atypical neurotransmission system involved in multiple functional properties through modulating neuronal and glial activities (Martins et al., 2014). Previous studies have suggested that TRPV1 is closely bound to immune processes and inflammatory signaling pathways in multiple organs or systems (Assas et al., 2014a). Dysfunction of TRPV1 is involved in the occurrence and development of numerous immune-mediated neurological disorders in the CNS, thus TRPV1 is regarded as a highly attractive potential therapeutic target for neurologic diseases.

TRPV1 is a well-characterized, ligand-gated non-selective cation channel that displays Ca^{2+} influx mainly with nearly equal permeability to Na^{+}, K^{+}, Cs^{+}, Li^{+}, and Rb^{+} along their electrochemical gradients, and it increases intracellular cation concentrations with the following membrane depolarization, triggering a variety of intracellular biochemical events (Caterina et al., 1997; Nilius and Flockerzi, 2014).

Functionally, the TRPV1 is a thermosensitive ion channel that possesses the ability to detect alterations in the environmental temperature, maintain normal body temperature (Alawi et al., 2015; Yamashita et al., 2008), and lead to painful, itching, burning and other sensations in conditions of tissue inflammation that are responsible for transducing physical, chemical, and thermal nociception (Caterina et al., 2000; Gu et al., 2017; Negri et al., 2006). It also participates in synaptic transmission (Saffarzadeh et al., 2016), neurogenesis (Ramirez-Barrantes et al., 2016) and seizure disorders in the nervous system (Huang et al., 2015). TRPV1 participates in various pathophysiologic responses in other systems and in tumors (Stock et al., 2012), such as in the respiratory system (Ternesten-Hasseus et al., 2015), cardiovascular system (Randhawa and Jaggi, 2017), digestive system (Linan-Rico et al., 2016), endocrine system (Lee et al., 2015), urogenital system (Coelho et al., 2015; Yoshiyama et al., 2015) and immune system (Parenti et al., 2016).

TRPV1 could be activated by a wide variety of exogenous and endogenous physical and chemical stimuli. The classical exogenous activators of TRPV1 include noxious heat (>43 °C) (Caterina et al., 1997), low pH (Jordt et al., 2000), capsaicin (Caterina et al., 1999), vanilloids (Brand et al., 1987), resiniferatoxin (Alawi and Keeble, 2010; Szallasi and Blumberg, 1989) and other biotoxins (Geron et al., 2017; Siemens et al., 2006). Its endogenous activators include N-arachidonoyl-ethanolamine, lipoxygenase compounds, N-acyldopamines, and other long-chain unsaturated fatty acids, such as endocannabinoid (Kumar et al., 2016; Raboune et al., 2014), endovanilloids (Huang et al., 2002), retinoids (Yin et al., 2013), leukotriene B4 and 15-hydroxyeicosatetraenoic acid (Koskela et al., 2012).

Many researches have demonstrated that the TRPV1 channel expresses in glial cells. Here, we have briefly summarized the recent knowledge on the TRPV1 channel that it exerts a modulatory function over neuroinflammatory processes and inflammation and, in turn, induces changes in TRPV1 in the CNS. The studies reviewed here point out that TRPV1 acts as a novel therapeutic target in the neuro-immune axis through the modulation of neuroinflammation and the results supply insight into changes in TRPV1 following neuro-immune associated diseases.

2. Role of TRPV1 in the neuro-immune axis

The neuro-immune axis produces a neurogenic inflammatory response that shares communication molecules and receptors and interfaces with the CNS and immune system to modulate homeostatic and inflammatory responses when confronted with external stimuli or self-disorders (Assas et al., 2014b; Hodes et al., 2015; Kraneveld et al., 2014).

TRPV1 functionally expresses in various cell types in the neuro-immune axis and in glial cells, in addition to neurons. To date, research progress on the expression and physiological roles in microglia and astrocytes has been reported by different investigators (Table 1).

2.1. Expression of TRPV1 in glial cells

The expression of TRPV1 in the CNS is still controversial. Many studies have suggested that TRPV1 expresses not merely in neurons, but also in glial cells in mammals, including humans (Ho et al., 2014; Miyake et al., 2015). However, the distribution of TRPV1 in glial cells remains debatable regarding the extent and localization, some initial seminal reports showed very low or no expression in the CNS (Caterina et al., 1997; Szallasi et al., 1995), while recently, the expression of TRPV1 in glial cells has been fully verified with the help of innovative approaches, including pharmacological characterization, immunohistochemistry, radio ligand binding, RT-PCR and *in situ* hybridization (Martins et al., 2014).

Functional expression of TRPV1 was reported in rodent and human microglial cells, mainly located in the hippocampus, cortex, hypothalamus, cerebellum, substantia nigra, olfactory system, mesencephalon, and hindbrain in the brain (Hironaka et al., 2014; Huang et al., 2014, 2015; Sun et al., 2013; Toth et al., 2005) and also in the spinal cord, retina and visual cortex (Sappington and Calkins, 2008; Talbot et al., 2012). Subcellularly, TRPV1 has been shown to express mainly in the cell membrane and cytoplasm (Huang et al., 2010). Miyake et al. discovered that TRPV1 functions on both the cytomembrane and the intracellular organelles, including the mitochondria, endoplasmic reticulum (ER), lysosomes, and golgi apparatus (Huang et al., 2010; Miyake et al., 2015); namely, the majority of TRPV1 is naturally expressed in microglia located in the endomembrane system rather than in the cytomembrane (Gallego-Sandin et al., 2009; Miyake et al., 2015).

TRPV1 was also detected in astrocytes located in the spinal cord, retina, and other brain regions (Benito et al., 2012; Doly et al., 2004; Toth et al., 2005). By double-immunofluorescence-labeling with glial fibrillary acid protein (GFAP) and S100β at the ultrastructural level, it showed that 7% of the total TRPV1 labeling was localized in astrocytes (Doly et al., 2004) and was mainly distributed in the cell membrane/cytoplasm (Huang et al., 2010; Rycerz et al., 2016). Subcellularly, immune- electronmicroscopy revealed that