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Review

Role of leak potassium channels in pain signaling

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ABSTRACT

Potassium (K^+) channels are membrane proteins that allow rapid and selective flow of K^+ ions across the cell membrane, generating electrical signals in neurons. Thus, K^+ channels play a critical role in determining the neuronal excitability. Two-pore domain (K2P) "leak" K^+ channels give rise to leak K^+ currents that are responsible for the resting membrane potential and input resistance. The wide expression of leak K^+ channels in the central and peripheral nervous system suggests that these channels are critically involved in pain signaling and behavior. Indeed, it has become apparent in the past decade that the leak K^+ channels play essential roles in the development of pain. In this review, we describe evidence for the roles of TASK1, TASK3, TREK1, TREK2, TRAAK and TRESK channels in pain signaling and behavior. Furthermore, we describe the possible involvement of TASK2 and TWIK1 channels in pain.

Contents

1. Introduction

Pain is a symptom, which may be caused by different diseases of the brain, spinal cord, and nerves that make up the nervous system. The International Association for the study of pain defined the pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (International Association for the Study of Pain, 1986). The pain is a self-protective mechanism. Indeed, the sensation of pain alerts us to real or impending injury and triggers appropriate protective responses (Julius and Basbaum, 2001; Vlaeyen, 2015). The pain sensation is transmitted from the peripheral tissue to the central nervous system: the pain-causing signals such as heat, pressure, chemical agents and tissue damage are detected by ion channels and receptors which are distributed at the nociceptor peripheral terminals and then transmitted to the central nervous system via dorsal root ganglion (DRG) or trigeminal ganglion neurons (Waxman et al., 1999; Waxman and Zamponi, 2014).

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Therefore, identification of ion channels involved in peripheral nociceptor activation is pivotal to understanding of pain perception mechanisms (Eglen et al., 1999; Julius and Basbaum, 2001; Wood et al., 2004). To date, many studies have demonstrated that various ion channels in the nervous system are involved in the development of pain (Eglen et al., 1999; Julius and Basbaum, 2001; Wood et al., 2004; Baron, 2006). In general, ion channels are responsive to various stimuli such as heat, pressure and nerve injury. Most of ion channels are located at the peripheral terminals of nociceptor sensory neurons (Julius and Basbaum, 2001). Following nerve injury, these ion channels affect neuronal excitability, resulting in modulation of pain sensation (Eglen et al., 1999). In recent years, the molecular basis of ion channels has been elucidated through the development of the molecular cell biology and genetic engineering method. Consequently, it has become widely known that voltage gated Na^+, K^+ and Ca^{2+} channels, acid-sensing ion channels (ASICs), transient receptor potential (TRP) channels, ligand gated ion channels, P2X, *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors are involved in the pathogenesis of pain (Wood et al., 2004; Baron, 2006; Eijkelkamp et al., 2012; Tsantoulas and McMahon, 2014). The role of TRP, ASIC channels and P2X receptors in pain is relatively well established (Wood et al., 2004; Baron, 2006). However, the roles of leak K^+ channels in pain signaling and behavior remains largely unclear (Enyedi and Czirjak, 2010).

K^+ channels are crucial determinants of neuronal excitability throughout the nervous system (Tsantoulas and McMahon, 2014). A large number of research has revealed a crucial role of K^+ channels in nociceptive processing, particularly in modulating peripheral hyperexcitability (Tsantoulas and McMahon, 2014). The K^+ channel conduction inhibits peripheral excitability by counteracting action potential initiation at peripheral nerve terminals, decreasing conduction fidelity across the axon, or limiting neurotransmitter release at axon terminals (Hille, 2001). Furthermore, a negative membrane potential is important for suppressing peripheral excitability, and it has been elucidated that this key mechanism is provided to a considerable degree by leak K^+ channels, which cause K^+ leak currents and are major contributors to resting membrane potential (Goldstein et al., 2001). The painful stimuli activates peripheral terminals of DRG and trigeminal ganglion through various nociceptive ion channels such as ASIC, TRPV1 and TRPA1, depolarizing the membrane potentials of the peripheral nerve terminals. When the membrane potential reaches the threshold, an action potential is induced through activation of voltage-dependent Na^+ channels. By contrast, leak K^+ channels hyperpolarize the membrane potential of peripheral nerve terminals and prevent the neuron from generating an action potential (Enyedi and Czirjak, 2010). When the activity of leak K^+ channels decreases during inflammatory and neuropathic pain conditions, the pain sensation can be upregulated (Mathie and Veale, 2015) (Fig. 1). Thus, the leak K^+ channels play an important role in pain processing. In this review, we will discuss the possible roles of leak K^+ channels in the mechanisms of pain processing.

2. Leak K^+ channels

In excitable cells such as neurons, a negative membrane potential is critical for electrical signaling, and it has long been considered that this key mechanism is largely mediated by leak K^+ currents (Goldman, 1943). However, the molecular basis for characterizing functional properties of leak K^+ channel subunits remained unknown over many years. In the 1990s, the discovery of the *KCNK* gene family has been described whose members generate the hallmark properties of leak K^+ currents (Goldstein et al., 2001). In mammalians, fifteen subunits have been identified and were further divided into six subfamilies (TWIK, tandem of P domains in a weak inward rectifying K^+; TREK, TWIK-related K^+; TASK, TWIK-related acid-sensitive K^+; THIK, TWIK-related halothane-inhibited K^+; TRESK, TWIK-related spinal cord K^+ and TALK, TWIK-related alkali-activated sensitive K^+) on the basis of sequence similarity and functional resemblance (Goldstein et al., 2001; Enyedi and Czirjak, 2010) (Table 1). The TWIK group includes the weakly inwardly rectifying channels (TWIK1, TWIK2, and the nonfunctional *KCNK7*); the THIK group includes halothane-inhibited THIK1 channel and related non-functional THIK2; the TREK group includes the arachidonic acid and mechanosensitive channels (TREK1, TREK2, and TRAAK); the TALK group includes the alkaline-activated channels (TASK2, TALK1, and TALK2/TASK4); the TASK group includes acid-sensitive channels (TASK1, TASK3, and the nonfunctional TASK5); the TRESK group includes Ca^{2+}-activated channels (TRESK1). Until now, TASK1, TASK2, TASK3, TREK1, TREK2, TRAAK, TWIK1 and TRESK channels have been demonstrated to be possibly involved in pain signaling and behavior as described below (Table 2).

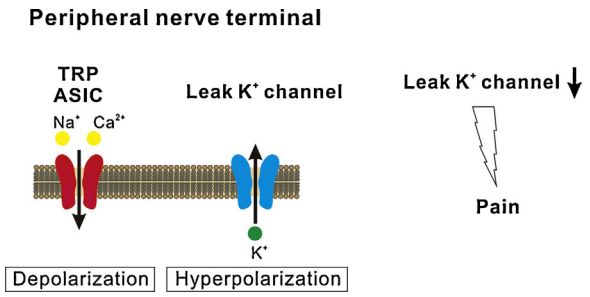

Fig. 1. Role of leak K^+ channels in pain signaling.
Nociceptive stimuli activate peripheral terminals through various nociceptive ion channels such as ASIC, TRPV1 and TRPA1 and thereby causing the membrane depolarization. When the membrane potential reaches the spike threshold, an action potential is induced through activation of voltage-dependent Na^+ channels. By contrast, leak K^+ channels hyperpolarize the membrane potential of peripheral nerve terminals and prevent the neuron from generating an action potential. If the activity of leak K^+ channels decreases during inflammatory and neuropathic pain conditions, pain sensation could be enhanced.

3. Leak K^+ channel subfamilies involved in pain

3.1. *TASK1 and TASK3 channels*

TASK channels are two pore domain K^+ channels that generate pH-sensitive K^+ currents with little time-dependence and weak rectification (Goldstein et al., 2001; Bayliss et al., 2003). In heterologous expression systems, TASK1 and TASK3 channels were able to form functional homomeric channels *in vitro* and *in vivo* (Czirjak and Enyedi, 2002; Berg et al., 2004; Lazarenko et al., 2010) whereas TASK5 channels were found to be inactive (Kim and Gnatenco, 2001). TASK1 and TASK3 channels show different extracellular pH sensitivity. The pK for TASK1 channel inhibition is ~7.4 while that for TASK3 channel is ~6.7 (Kim et al., 1999, 2000; Bayliss et al., 2003; Bayliss and Barrett, 2008). TASK1 and TASK3 channels are inhibited by extracellular acidification and local anesthetics (Bayliss et al., 2003; Bayliss and Barrett, 2008; Enyedi and Czirjak, 2010). These channels are also inhibited by hormone and transmitters (*e.g.*, muscarinic M3, thyrotropin-releasing hormone 1 and AT1a angiotensin II receptors) that act through $G_{q/11}$-coupled receptors (Czirjak et al., 2000; Millar et al., 2000; Chen et al., 2006). It had been reported that depletion of the PLC substrate, phosphatidylinositol-4,5-bisphosphate, PIP2, may be the signal triggering channel deactivation (Lopes et al., 2005). However, it has recently been shown that diacylglycerol (DAG) inhibits TASK channels, and channel activity is independent of PIP2 (Wilke et al., 2014). In contrast, TASK1 and TASK3 channels are activated by