Roles of TRESK, a novel two-pore domain K⁺ channel, in pain pathway and general anesthesia

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Abstract: TRESK is the most recently reported two-pore domain K⁺ channel, and different from other two-pore domain channels in gene, molecular structure, electrophysiological and pharmacological properties. Although the current knowledge of this potassium channel is inadequate, researches have demonstrated that TRESK is remarkably linked to acute and chronic pain by activation of calcineurin. The fact that TRESK is sensitive to volatile anesthetics and localization in central nerve system implies that TRESK may play a very important role in the mechanism mediating general anesthesia. The further research of TRESK may contribute to explore the underlying mechanism of some pathological conditions and yield novel treatments for some diseases.

Keywords: TRESK; two-pore domain K⁺ channels; calcineurin; dorsal root ganglion

1 Introduction

The most recently identified K⁺ channel is a kind of two-pore domain K⁺ channel (K2P), which is very different from the other K⁺ channels including voltage-gated (Kv), calcium-activated (Kca) and inward rectifier (Kir) channels in molecular structure, electrophysiological and pharmacological properties^[1]. K2P is a collection of ion channel subunits exhibiting four transmembrane domains (TM1-4) and two pore-forming domains (P1, P2); while other K⁺ channel subunits are characterized by having two, six or eight transmembrane segments and one conserved pore-forming domain^[2-4]. The K2P currents are observed at all membrane potentials and can be activated instantaneously by a voltage step and show no voltage threshold for activation, which also distinguishes them from other K⁺ channels. So, it can produce leak current that help to set and stabilize the resting potential and thus

influences the cell excitability under physiological conditions^[5,6].

In the K2P channel family, there are six subfamilies according to the differences in channel structure and regulatory mechanism: (1) tandem-pore-domain weakly inward rectifying potassium channels (TWIK); (2) tandem-pore-domain halothane-inhibited potassium channels (THIK); (3) TWIK-related acid-sensitive potassium channels (TASK); (4) tandem-pore-domain alkaline-activated potassium channels (TALK); (5) TWIK-related arachidonic acid-sensitive and mechano-gated potassium channels (TREK); (6) TWIK-related spinal cord potassium channels (TRESK).

In this article, we reviewed recent advances in the research on TRESK, as well as the emerging physiological and pathological roles of TRESK in some diseases, and its therapeutic potentials. The review emphasizes the areas that we consider to be important for future researches.

2 Classification and molecular structure

TRESK is structurally unique among the members of K2P channels: the extended intracellular loops between TM2 and TM3 and short carboxyl-terminal segments (Fig. 1). All other K2P channels have short intracellular loops and long carboxyl termini. TRESK was first reported as a novel two-pore domain K⁺ channels in 2003 by Sano Y *et al.*^[7]. It differs

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from other K₂P channels in molecular structure, electrophysiological and pharmacological properties, activation and tissue distribution. TRESK is coded by 385 amino acids and shows low homology (13.5%-19.7%) with previously characterized two-pore domain K⁺ channels. Kang *et al.* cloned a TRESK from mouse cerebella RNA by RT-PCR in 2004. Since it had only 63% amino acid identity with human TRESK, this

mouse TRESK was reported as a new member of K₂P^[8]. But further research cannot demonstrate that they are two different subtypes, the human and mouse TRESK would be assumed to be orthologous.

3 Tissue distributions

Human TRESK was amplified initially only in the spinal

Fig. 1 TRESK sequence and predicted structure. **A**, Deduced amino acid sequence of TRESK. The four putative transmembrane regions (TM1-4) are underlined, and two pore regions (P1, P2) are boxed. Consensus sequences within the K⁺ channel [TXG(Y/F)G] are in bold-face. The potential N-glycosylation sites are circled. **B**, Hydroplicity plot of TRESK. The four putative transmembrane regions (TM1-4) and two pore-forming domains (P1, P2) are underlined. **C**, Deduced topology of TRESK. Extracellular N-glycosylation (N-Gly) sites are shown^[7].

cord^[7], but subsequent studies have proven that it is expressed in a number of neuronal populations in different regions of central and peripheral nervous systems including the cerebellum, dorsal root ganglia and cerebral cortex. TRESK mRNA was also detected in other organs such as spleen, thymus, pancreas, and kidney in rats^[9-11]. Mouse TRESK transcript level in the cortex and cerebellum was found four-fold higher than that in the spinal cord^[8,11]. The high content of TRESK in the brain suggests that it may participate in electronic actions of the cortex and play an important role in keeping the resting potential, which is a key factor for physiological excitation of neuron. Its extensive distribution in the spleen, thymus, pancreas, and kidney implies that this potassium channel may be involved in the immune cell secretion and gut hormone release through regulating background K^+ current.

4 Electrophysiological and pharmacological properties

TRESK is a voltage-independent K^+ channel that contributes to the resting potential. S4 region, a possible voltage sensor, exists in other voltage-dependent channels including Na^+ , Ca^{2+} and K^+ (except for K2P) but is lacked in TRESK^[12]. TRESK is outwardly rectifying K^+ current and exhibits properties of a background K^+ current with a relatively small conductance, approximately 15pS in symmetrical 150 mmol/L KCl. TRESK is insensitive to the inhibition of typical K^+ channel blockers (triethanolamine, Cs^+ , 4-aminopyrine) and is blocked only by Ba^{2+} at millimolar concentrations. Quinidine, a nonspecific blocker of K^+ channels, strongly inhibits TRESK^[7]. Czirjak reported that both Zn^{2+} and Hg^{2+} were the selective blockers of TRESK among the mouse K2P channels, while human TRESK was resistant to Zn^{2+} ; mouse TRESK expressed in COS-7 cells was also inhibited by Zn^{2+} and Hg^{2+} and His132 of mouse TRESK was partly responsible for this difference^[13]. Zn^{2+} and Hg^{2+} may be the specific inhibitor for TRESK and could distinguish it from other two-pore-domain K^+ channels, which should help to further identify native TRESK in the future. However, differences in the sensitivity of TRESK to various pharmacological modulators (Zn^{2+} , anesthetic agents) between human and rodent must be considered. The human TRESK is much more sensitive than mouse TRESK in response to inhaled anesthetic agents such as isoflurane, which can increase the TRESK current; while

rodent TRESK shows about two-fold greater sensitivity to Zn^{2+} than human TRESK^[11]. Those differences impede the further exploration of TRESK in human, since it is difficult to extrapolate some research findings from rat to human.

In mouse and rat, TRESK current can be affected by changes of pH value: it is remarkably inhibited by the change of intracellular pH from 7.3 to 5.6 and enhanced by the change from 7.3 to 8.9. In addition, TRESK could be inhibited by intracellular and extracellular application of arachidonic acid, and intracellular application of other unsaturated free fatty acids, such as docosahexaenoic acid, linoleic acid, and oleic acid. Similar to other K2Ps, TRESK is insensitive to changes in temperature^[7] and saturated free fatty acids, .

5 Predicted physiological roles of TRESK

5.1 TRESK and pain It is very necessary to discover effective medications and methods to relieve pains by multimodal analgesia, which requires exploring all facets of the mechanism involved in this complicated process. It is far from completely understood though great progresses have been made in recent years. Previous research manifested that the hyperexcitability of axotomized dorsal root ganglion (DRG) neurons was accompanied with downregulation of some potassium channels^[14]. Many researches have revealed that K_v , K_{ca} and K_{ir} are involved in the ectopic discharge of DRG neurons and the C fiber of cornu dorsale medullae spinalis.

Until now, it remains unclear whether K2P participates in the neuropathic pain (NPP). TRESK is specifically located in the spinal cord in human whereas is mainly in the DRG in mouse, and which represent the most important background potassium channel in this tissue at the transcript level. All sizes of DRG neurons could be labeled with TRESK-specific probes by *in situ* hybridization. In TRESK[G339R] functional knock-out mice, the standing outward current $I_{K(so)}$ in DRG neurons was significantly reduced compared with that in TRESK wild-type littermates^[15]. Kang and Kim reported that TREKs and TRESK together contributed > 95% of the background K^+ conductance in DRG neurons at 37 °C. As TREKs and TRESK are modulatory targets of receptor agonists, they are likely to play active roles in regulating the excitability of DRG neurons. The major background K^+ channel at 24 °C in DRG neurons is TRESK^[9].

TRESK is abundantly expressed in the DRG, as well as in the spinal cord^[11]. DRG is very important in transmitting

nociception and in the onset and development of chronic pain because it is a relay of pain signal transport from periphery to nerve central system. Previous studies have proved the hyperexcitability and ectopic discharge of DRG in several pain modals, such as chronic constriction injury (CCI) and partial sciatic nerve ligation model^[16-18]. It was reported that TRESK constitute a significant component of background potassium currents in murine dorsal root ganglion neurones. Thus, TRESK might play an important role in the development of NPP by regulating the background potassium currents of DRG. On the other hand, the glial cell membrane at rest is almost exclusively permeable to K⁺ ions whereas the neuron at rest is permeable to both K⁺ and Na⁺, so we speculate that the TRESK be a key ion channel to modulate the resting potential of glial cell. Recent studies have proved that glial cells play a key role in the process of NPP^[19-23]. Taken together, TRESK might be involved in the abnormal electrical action in DRG and spinal cord through down-regulating the resting potential, and consequently increase the magnitude and the time course of action potential, and so strengthen electrical signal conduction. The increasing cell excitability is known to be a key factor to produce the neuropathic pain, especially in the central nervous system (CNS)^[24,25].

In acute pain such as surgical intervention, the injury of tissues and neurons can induce pH change and the release of unsaturated free fatty acids. Several lines of evidences suggest that the attenuated TRESK current induced by accumulation of lactate or arachidonic acid might be responsible for some proportion of neuron hyperexcitability in both DRG and spinal cord. Acidosis will activate nociceptors and produce the pain that cannot be attenuated completely by current analgesic drugs and tools. This pain may transform into chronic pain, which would represent some abnormal pain sensations such as hyperalgia and allodynia^[26,27]. Gathered these evidences, TRESK may influence the process of NPP and acute pain by different mechanisms. The former is exerted by changing the level of background potential in a longer time whereas the later is caused by rapid fluctuation of microenvironment in a short time.

This information should be useful for future analgesic drug development and elucidation of pharmacy mechanism of some analgesic drugs used clinically, as well as their sub-cellular target sites, since the exact role of TRESK in pain

should be known before taking great advantage of its therapeutic potential.

5.2 Signal transduction pathway of TRESK and possible pain cure strategy

In general, the stimulations such as that of inflammatory factor exerted on the G protein-coupled receptor (GPCR) induce the Gαq activation following the elevated cytoplasmic cacluim. Calcineurin (calcium/calmodulin dependent phosphatase 2B) is activated with the enhancement of cacluim. Then TRESK shows a large calcium-dependent increase in current in response to calcineurin activation. Calcineurin has been shown to bind directly to an nuclear factor of activated T-cells (NFAT)-like docking site on TRESK channels and dephosphorylate them^[12,16,30] (Fig. 2). So the NFAT-like docking site may be a key for the phosphorylation of TRESK. The phosphorylation of TRESK in NFAT-like docking site can be inhibited by FK506, an inhibitor of calcineurin. It is a bi-directional influence of Ca²⁺ and calmodulin on the calcineurin activity. The strength and duration of particular stimulations such as the peripheral injury of nerves may cause apparently antagonistic functions of calcineurin to work in concert^[29,30] and then downregulate the TRESK. Thus we suppose the activation of calcineurin can relieve the pain in part because of the increase of TRESK current. Recently, calcineurin-inhibitor induced pain syndrome (CIPS), which is characterized by severe pain in the lower limbs after use of the calcineurin inhibitor, has been recognized in both organ and stem-cell transplantations^[31-35]. The possible mechanism for CIPS is that the inhibitor of calcineurin blocks TRESK channel which downregulate the background current and, thus, enhance the excitory signal transduction of neurons by affecting the velocity of action potential propagation.

At present, the pathway(s) phosphorylating TRESK at rest and keep their basal activity is unknown and the specific activator of TRESK is not confirmed completely, which impede the further researches on the physiological role and probable therapy usage of TRESK. It was reported that the extract of *Fructus cannabidis* (EFC, a Chinese traditional medicine) was an activator of calcineurin^[36], though whether EFC has pronounced effect on the pain induced by increase of TRESK current is needed to further investigate. The agonist of calcineurin and TRESK channel might develop a potential new treatment for pain.

5.3 TRESK and volatile anesthetics

Clinical dose of isoflurane, halothane, sevoflurane, or desflurane could

Fig. 2 The signal transduction pathway of TRESK. The condition of TRESK current is regulated by calcineurin (calcium/calmodulin dependent phosphatase 2B)^[12].

strongly increase TRESK currents to three-fold. The single-channel data also indicate that volatile anesthetics increase TRESK currents by enhancing the channel gating to improve the open probability of channels rather than increasing the single-channel conductance or changing the number of channels on the membrane. This could explain the pain-inhibition effect of volatile anesthetics under general anesthesia and pain therapy. Because TRESK is abundant in spinal cord tissue, TRESK channels may play an important role in the immobility of body to surgical stimulations induced by volatile anesthetics^[10]. To date, several channels, such as TRESK, GABAA and NMDA, have been identified to be sensitive to anesthetics^[10,11,37]. However, the further research about the systemic roles of these channels including TRESK in the mechanism of volatile anesthetic is still undergoing, so it remains unclear what proportion of TRESK participate in the progress of general anesthesia and how important is it. In addition, because of identifying TRESK transcript in brain RNA, rich in the cortex and cerebellum, a role for TRESK in mediating the volatile anesthetics and other components of

general anesthesia in the CNS is possible through direct depression of the electrical action of cortex. Localization studies in the spinal cord and brain is needed for more fully assessing the role of TRESK in general anesthetic mechanisms. Future *in situ* hybridization and immunohistochemical localization studies should identify in which cells and at what levels TRESK is expressed in the CNS.

Some researches suggested that volatile anesthetics impaired the memory of surgical patient by inhaled anesthetics^[38]. Calcineurin which regulates the dephosphorylation of TRESK, is also proved to negatively affect the memory by modulating the neuron plasticity, though it is critical in the form of the learning and memory in normal condition^[29,30,39]. The activator of calcineurin has proved to improve the impaired memory in experimental animal^[36,39]. Though many receptors and channels are involved in the mechanism of volatile general anesthesia, the special activation pathway in TRESK affected by calcineurin and the relationship between calcineurin and memory make us to predict that TRESK may be relevant to the memory impair induced by volatile

anesthetics. Now, no direct evidence support that the memory impair induced by inhaled anesthetic is greatly related to the activation of calcineurin. Given that the enhancement of TRESK current induced by volatile anesthetic is modulated by calcineurin, we can predict that TRESK activation may be a common mechanism for the memory impair mediated by inhaled anesthetic.

6 Conclusion

To summary, the novel two-pore potassium channels, TRESK, is special in the topology, distribution, electrophysiological and pharmacological properties compared to other K2P channels and sensitive to inhaled anesthetics. The intracellular regulatory pathway of TRESK is greatly associated with the calcineurin/NFAT system, suggesting TRESK might be involved in some biological processes modulated by calcineurin dephosphorylation. The specific location and function of TRESK in the central and periphery nervous system imply its extensive roles in the physiological functions such as pain pathway and general anesthesia. The further study for TRESK should be focused on exploring the overall function in human body, revealing the probable mechanism of some pathological condition, and finding new drug therapy target to some disease.

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一种新发现的双孔钾通道—TRESK在疼痛及全身麻醉中的作用

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摘要: TRESK 是最近新发现的一种双孔钾通道, 其在基因、分子结构、生理药理学特性方面不同于其他类别的双孔钾通道。本文总结了TRESK的研究现状, 并根据目前的研究资料推测TRESK有可能通过激活钙调神经磷酸酶参与了急性和慢性疼痛的发生, 是吸入性全身麻醉药的作用靶点, 有可能通过对钙调神经磷酸酶的激活影响记忆, 从而参与吸入性全身麻醉药的术后遗忘效应。对TRESK的深入研究有可能揭示某些病理生理状态的内在机制。

关键词: TRESK; 双孔钾通道; 钙调神经磷酸酶; 背根神经节