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双孔钾通道研究进展

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摘　要

钾通道是选择性允许K^+跨膜通过的离子通道，而双孔钾通道是钾通道蛋白超家族的一个重要分支，其产生的电流为背景钾电流。因其具有十分重要且广泛的生理及病理学作用，近年来研究者们对双孔钾通道的研究进展较快。因双孔钾通道存在的亚型较多、功能复杂，现有研究较多，而现有综述性文献对其介绍不够清晰，本文即从分布与分类、生理病理及功能特性方面对其进行综述，以期为研究双孔钾通道的学者提供参考。

关键词

双孔钾通道，离子通道，钾离子通道

Research Progress of Two-Pore Potassium Channels

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Abstract

Potassium channel is an ion channel that selectively allows K^+ to pass across the membrane. Two-pore potassium channel (K2P) is an important branch of the potassium channel superfamily, and its current is the background potassium current. Due to its important and extensive physiological and pathological effects, researchers have made rapid progress in the study of two-pore potassium channels in recent years. Because there are many subtypes of two-pore potassium channels and their functions are complex, there are many studies on two-pore potassium channels, but the

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existing review literature is not clear enough. This article reviews the distribution and classification, physiological and pathological characteristics and functional characteristics of two-pore potassium channels, in order to provide a reference for scholars studying two-pore potassium channels.

Keywords

K2P, Ion Channel, Potassium Channel

1. 引言

双孔钾通道是钾通道蛋白超家族的一个重要分支，其于 20 世纪 90 年代发现并被克隆出，因含四个跨膜片段(4TMS)和两个孔区(2P)，因此被称为双孔钾通道(two-pore domain potassium channels, K2P)。K2P 家族包括 15 个成员，按其功能特性可分为 TWIK、TREK、TASK、THIK、TALK、TRESK 六类，分别由 KCNK1~KCNK18 基因编码(存在重复)。其中 TWIK1，TWIK2，TWIK3，TASK5 和 THIK2 五个亚型的通道，最初被认为是“沉默”通道[1] [2]，不表达功能活性。双孔钾通道可以在全部生理电压范围内被激活，因此又被称为背景钾通道或基线钾通道，通过产生背景电流来稳定细胞静息膜电位，调控细胞的兴奋性。

2. 双孔钾通道分类及分布

2.1. TWIK

TWIK 类是弱的内向整流型双孔钾通道，存在三个亚型，分别为 TWIK1 (KCNK1)，TWIK2 (KCNK6/KCNK8)，TWIK3 (KCNK7)。TWIK1 通道尚未被证明是功能通道[3]，可能需要其他非孔蛋白才能发挥作用，TWIK1 最初是从肾脏 cDNA 文库克隆而来的[4]，在大脑、胃、结肠、心脏、肝脏等多个组织广泛表达。TWIK2 通道蛋白被认为是一种开放整流剂，它受到花生四烯酸的刺激，并受到细胞内部酸化和挥发性麻醉剂的抑制[5]，在子宫内膜、食管、结肠、胎盘等多个组织中广泛表达。TWIK3 (KCNK7)通道也可能需要其他非孔形成蛋白才能发挥活性，在皮肤、食管和骨髓中偏向表达。TWIK1 和 TWIK3 主要在中枢神经系统中表达，而 TWIK2 优先在胰腺、胃、脾脏和子宫等外周组织中表达[6]。

2.2. TREK

TREK 类双孔钾通道被称为 TWIK 相关钾通道，属于脂质敏感机械门控通道，可被多不饱和脂肪酸和机械张力所激活，并通过蛋白激酶 A 磷酸化失活[7]，存在 TREK1 (KCNK2)，TREK2 (KCNK10)，TRAAK (KCNK4)三个亚型。TREK1 通道可以在某些麻醉剂、膜拉伸、细胞内酸中毒和加热条件下被打开，具有机械敏感特性，在肾上腺、甲状腺、大脑等组织中偏向表达，尤其在中枢神经系统分布较广。TREK2 通道是一种开放式整流器，主要在生理 K^+浓度下向外传递电流，并受到花生四烯酸的强烈刺激，在较小程度上受到膜拉伸、细胞内酸化和全身麻醉的刺激[8]，在大脑、十二指肠、肾脏、胃等多种组织中表达，在神经系统中，中枢和外周都有表达。TRAAK 通道受多不饱和脂肪酸、脂质膜的温度和机械变形的调节，

主要在中枢神经组织中表达，可能参与调节背根神经节神经元的有害输入阈值[9]。

2.3. TASK

TASK 为 TWIK 相关酸敏感性外向整流钾通道，包含 TASK1 (KCNK3)、TASK2 (KCNK5)、TASK3 (KCNK9)、TASK4 (KCNK17)和 TASK5 (KCNK15)五种亚型，其中 KCNK17 亦称 TALK2，可将其归为 TALK 类型中。TASK 通道在神经系统和外周组织中均有表达，包括可兴奋性和非兴奋性细胞，并广泛参与病理生理现象。TASK1 对细胞外 pH 值的变化敏感，并受到细胞外酸化的抑制，由麻醉剂氟烷和异氟烷激活，在肾上腺、胎盘、前列腺等组织中偏向表达，肾上腺皮质中强烈表达[10]。TASK2 通道蛋白对外部 pH 高度敏感，结合其表达模式，表明它可能在肾钾转运中起重要作用，其在小肠、肾脏、胆囊、十二指肠等多个组织中广泛表达，主要在皮质远端小管和肾脏集合管中表达。TASK3 作为 pH 依赖性钾通道发挥作用，其在许多呼吸神经元群中表达，它们可以解释天然 pH 敏感的背景 K 电流，这些电流赋予细胞外质子对神经元兴奋性的动态调节[11]。在几种类型的人类癌症中已经观察到该基因的扩增和过表达，该基因印在大脑中，优先表达来自母体等位基因。TASK4 (KCNK17)通道是一个开路整流器，主要在生理 K^+浓度下向外传递电流，在碱性 pH 下被激活，在肺、胃、胎盘、胆囊、心脏等多种组织中广泛表达。TASK5 (KCNK15)产物尚未被证明是功能通道，它可能需要其他非孔形成蛋白才能发挥活性[12]，在睾丸、子宫内膜、卵巢、脑等多组织中广泛表达。

2.4. THIK

THIK 属于氟烷可抑制的钾离子通道，其包含 THIK1 (KCNK13)、THIK2 (KCNK12)两种亚型，THIK1 和 THIK2 在哺乳动物肾脏的近端和远端肾单位中大量表达[13]。THIK1 是开放通道，可以被花生四烯酸刺激，并被麻醉剂氟烷抑制，在睾丸、肾脏及其他组织中偏向表达。THIK2 属于双孔钾通道家族的“沉默”通道，它在大脑的许多细胞核中高度表达，但迄今为止对其功能的研究仍然较少[3]。THIK2 在大脑、胎盘、睾丸、肾上腺等组织中偏向表达。

2.5. TALK

TALK 类双孔钾通道属于 TWIK 相关碱敏感钾通道，在碱性 pH 下被激活，包含 TALK1 (KCNK16)和 TALK2 (KCNK17, TASK4)两种亚型。TALK1 通道是一个开放整流器，主要在生理钾离子浓度下的向外传递电流，该基因在胰腺、胃、十二指肠、小肠中表达，在外分泌胰腺中高度特异性表达[14]。

2.6. TRESK

TRESK 类双孔钾通道属于 TWIK 相关脊髓表达、脂肪酸抑制钙活化的通道，其包含一个亚型，由 KCNK18 基因编码，在大脑、睾丸组织中表达水平较低，主要在脊髓中表达。

3. 双孔钾通道的生理病理及功能特性

3.1. TWIK

TWIK-1，TWIK-2，KCNK7，TASK-5 和 THIK-2，最初被认为是“沉默”通道，因为在天然细胞中无法记录与这些通道蛋白相关的电流，并且在异源表达系统中无法测量电流(或只有非常小的电流) [3]。有研究将 TWIK1 作为乳腺癌潜在预后生物标志物和治疗靶点[15]，TWIK1 在心脏功能中具有高度保守的作用，是正常心率和心房形态所必需的[16]。TWIK2 为 DFNA6 的位置候选基因[17]，不少研究表明，TWIK2 对血压调节尤其肺动脉高压起到重要作用，增强 TWIK2 活性可能是未来治疗肺部高血压疾病的潜在靶标[18] [19]，TWIK2 钾通道还可能是 NLRP3 相关炎症性疾病的潜在药物靶标[20]。

3.2. TREK

TREK1 作为背景钾电流通道，无时间、电压依赖性，参与维持细胞静息电位、细胞兴奋性、感觉传导过程以及代谢调节，在神经保护[21]、麻醉，疼痛感知和抑郁的细胞机制中起关键作用[22]，并可能为肝纤维化[23]、胰腺癌[24]等提供潜在治疗靶点。并且通过激活 TREK1 通道激活镇痛时，没有阿片类药物的不良反应[25]。

TREK2 在脑缺血、神经保护、记忆障碍等生理病理状态中起重要作用[26]，并参与神经性疼痛[27]、热刺激疼痛[28]、人膀胱癌细胞体外增殖[29]等过程。TRAAK 是一种机械敏感性双孔钾通道，其在机械和热异常性疼痛、神经发育障碍 FHEIG [30]，以及维持静息膜电位和快速动作电位传导方面发挥作用[31]。

3.3. TASK

TASK 通道在神经系统和外周组织中均有表达，包括可兴奋性和非兴奋性细胞，并广泛参与病理生理现象，如呼吸刺激、肺动脉高压、心律失常、醛固酮分泌、癌症、麻醉、神经系统疾病、葡萄糖稳态和视觉敏感性[32]，是多种疾病的治疗靶点。TASK1 通道与呼吸控制[33]、肺动脉高压[34]、心房颤动[35]、醛固酮分泌[36]等密切相关，还可能参与调节非小细胞肺癌亚群的凋亡和增殖[37]，并可用于多发性硬化症的动物模型[38]。TASK2 可能在肾钾转运中起重要作用，并与醛固酮增多症[39]、巴尔干地方性肾病(BEN) [40]等相关，另有研究表明 TASK2 有驱动人自然杀伤细胞增殖和细胞溶解功能[41]。TASK3 在不同的癌细胞类型和神经元中表达，在三叉神经[42]、子宫腺肌病[43]、胃癌[44]、卵巢癌[45]、乳腺癌[46]、黑色素瘤[47]等多种疾病中发挥作用，该基因的突变与还 Birk-Barel 畸形综合征(KCNK9 印记综合征) [48]相关。TASK4 通道主要与脑出血、心脏传导障碍等[49]相关。TASK5 本身不会产生功能性质膜 K^+电流[12]，但可能与中枢听觉通路相关[50]。

3.4. THIK

THIK 通道受氟烷抑制，THIK1 和 THIK2 在哺乳动物肾脏的近端和远端肾单位中大量表达[13]。研究发现，THIK1 离子通道参与了一系列重要的病理生理过程，其在背根神经节(dorsal root ganglia, DRG)大中小神经元中均有表达，而 DRG 作为初级传入神经元对疼痛的传导至关重要，CFA (complete Freund's adjuvant)诱导的皮肤炎症在不同时间选择性地下调 DRG 小神经元中的 THIK1 表达，且 CFA 1 时 DRG 小神经元中同侧 THIK1 平均强度百分比与自发足提升(SFL)持续时间(自发性疼痛的标志物)呈强烈负相关，因此其可能参与炎症后的疼痛处理[51]以及神经系统疾病的发生。此外，THIK 作为受氟烷抑制通道，还参与吸入麻醉药的作用机制。另有研究表明 THIK1 是响应 ATP 的 NLRP3 炎症小体激活的调节因子，并确定 THIK1 作为炎症性疾病的潜在治疗靶点[52]。与其他“沉默”通道类似，THIK2 在存在于许多组织中，胰腺中有高表达，但其仍然尚未被证明是功能通道[53]，另有研究表明 THIK2 沉默依赖于细胞内保留和质膜处的低内在活性[54]。

3.5. TALK

TALK1 通道主要在胰腺中表达，研究主要围绕其在胰腺中的作用展开。胰腺 β 细胞中糖尿病相关 TALK1 由骨桥蛋白激活[55]，TALK1 可调节 β 细胞电兴奋性、第二期胰岛素分泌和葡萄糖稳态[56]。另有研究将 TALK1 通道确立为 β 细胞内质网 Ca^{2+}的关键调节因子，并认为糖尿病发病过程中，TALK1 可能是减少 β 细胞内质网 Ca^{2+}处理缺陷的治疗靶点[57]。

3.6. TRESK

TRESK 通道的研究主要与先兆性偏头痛和智力障碍相关[58]，TRESK 背景 K 通道是初级感觉神经

元兴奋性的主要决定因素，被蛋白激酶 C 通过去磷酸化激活[59]。TRESK 与其他 K2P 通道的结构和功能相似性最低，是唯一通过钙调神经蛋白介导的去磷酸化而受细胞内 Ca^{2+}浓度调节的 K2P 通道[60]。TRESK 在免疫相关细胞和神经元细胞中高表达，特别是在背根和三叉神经节的感觉神经元中[61]。由于诱导的超极化，TRESK 影响神经元放电，炎症介质的释放和不同免疫细胞的增殖，因此，该通道可能是偏头痛、癫痫、神经性疼痛或不同免疫疾病药物干预的合适靶标[60]。

4. 总结与展望

双孔钾通道的发现与研究极大地促进了离子通道功能的研究。近年来，研究者们对双孔钾通道的研究已从结构、分布逐渐向功能和调控方向发展。越来越多的研究强调了它们对生理病理机制的影响。例如，双孔钾通道是许多生物过程中的核心参与者，包括离子稳态、激素分泌、细胞发育和兴奋性等，涉及多种如细胞体积调节、细胞凋亡、血管舒张、中枢化学敏感性、神经元兴奋性和疼痛感知等生理功能。对双孔钾通道的研究虽然取得了很大的进展，但对 K2P 各种亚型的细节研究还远远不够。因此，对双孔钾通道的进一步研究不仅有助于了解许多生理病理机制，也会越来越多地在临床应用上解决现有的诊断与治疗难题。

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