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Review

Pathophysiological Role of K_{2P} Channels in Human Diseases

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Abstract
The family of two-pore domain potassium (K_{2P}) channels is critically involved in central cellular functions such as ion homeostasis, cell development, and excitability. K_{2P} channels are widely expressed in different human cell types and organs. It is therefore not surprising that aberrant expression and function of K_{2P} channels are related to a spectrum of human diseases, including cancer, autoimmune, CNS, cardiovascular, and urinary tract disorders. Despite homologies in structure, expression, and stimulus, the functional diversity of K_{2P} channels leads to heterogeneous influences on human diseases. The role of individual K_{2P} channels in different disorders depends on expression patterns and modulation in cellular functions. However, an imbalance of potassium homeostasis and action potentials contributes to most disease pathologies. In this review, we provide an overview of current knowledge on the role of K_{2P} channels in human diseases. We look at altered channel expression and function, the potential underlying molecular mechanisms, and prospective research directions in the field of K_{2P} channels.

Introduction

Two-pore domain potassium (K_{2P}) channels have been identified and broadly characterized in the last decades. While the concept of background potassium currents was discovered by Bernstein in 1902, the first K_{2P} channel in drosophila, c.elegans, and mammalians was identified in 1996 by the groups of Goldstein and Lesage [1, 2]. Being initially recognized as a mere background leak channel, the relevance of K_{2P} channels to human disease was for a long time unknown. Today, K_{2P} channels are well known not only

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for contributing to potassium leak currents but also for maintaining the resting membrane potential and modulating diverse physiological functions in mammalian cells. There are fifteen members in the K_{2P} channel family, divided into six subgroups (THIK, TASK, TRESK, TWIK, TALK, and TREK) according to their distinct primary structures, physiological properties, and biological functions. All K_{2P} channel members share common structural features, with two pore-forming loops and four transmembrane domains (4TMD) with intracellular amino- and carboxyl-termini. Also, they function as homo- or heterodimers instead of tetramers as in other potassium channels [3].

The opening of K_{2P} channels is mainly voltage-independent but highly regulated by stimuli such as temperature, pH, mechanical stretch, lipids, and anesthetics [4, 5]. K_{2P} channels are insensitive to typical potassium channel blockers [6]. They are broadly expressed throughout the human body with specific expression profiles among the subgroups (Table 1). For example, almost all K_{2P} channels are highly expressed in the central nervous system (CNS), while only a few show prominent expression in liver, gallbladder, and lung. Among the different subgroups, TASK and TRESK subfamilies are highly expressed in endocrine and reproductive systems, whereas TWIK and TALK subfamilies are mainly observed in cardiac and gastrointestinal systems, lymphoid organs, and pancreas. The K_{2P} channel expression profile is an essential indicator of physiological function. On a cellular level, K_{2P} channel functions in excitable cells have been studied intensely, and lately, their influence on non-excitable cells became evident [7]. In excitable cells, K_{2P} channels modulate cellular activity and muscle tone through stabilizing the action potential in neuronal and cardiac systems and contributing to general physiological functions such as thermosensation, nociception, and muscle contraction/relaxation [8-12]. In non-excitable cells, their prominent expression in the pancreas, immune cells, kidney, and cancer cells associate them with a wide range of pathological conditions, including type 2 diabetes, multiple sclerosis (MS), cancer, and renal disorders [13-16]. In these diseases, the aberrant function of K_{2P} channels influences insulin secretion, T cell activation/proliferation, blood-brain barrier function as well as potassium re-absorption and homeostasis. Accordingly, $TASK1^{-/-}$ mice revealed an attenuated disease course in experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis, by reducing the activation and effector functions of T lymphocytes [17-19].

Table 1. K_{2P} channel RNA expression profile in human tissues. The table demonstrates the RNA expression levels of fifteen K_{2P} channels in human tissues following the online database The Human Protein Atlas (https://www.proteinatlas.org/). In general, the expression profile varies depending on the individual K_{2P} channel; some are expressed heterogeneously, whereas others are expressed in specific tissues. Channel names are based on the HUGO nomenclature. The indication of channel expression levels in different human tissues is categorized as abundant (+++), mild (++), and little (+). CNS: central nervous system, GI: gastrointestinal system

Channel HUGO name	CNS	Endocrine	Reproductive system	Liver	Cardiac	Kidney/ urinary bladder	GI	Lymphoid and blood
KCNK13	++	+++	+++			+		+
KCNK12	+++	+		++				+
KCNK9								
KCNK15		+	+++	++				
KCNK3	+	+++	+					
KCNK18	+		+					
KCNK1	++		+				+	
KCNK6		++	+++		++	++	+	+++
KCNK7							++	+
KCNK5		+	+	++		++	+++	
KCNK17		+	+		+			+++
KCNK16		+++					++	+
KCNK2	+	+++						
KCNK10	+++						+++	+++
KCNK4	+++							

A TASK3 channel blocker displayed its efficacy in inhibiting tumor formation by affecting cell cycle and proliferation in tumors [20, 21]. While some K_{2P} channels have been thoroughly investigated in various pathological conditions, others remain poorly characterized.

We here provide a comprehensive overview of current knowledge about the role of K_{2P} channels in human disease (Table 2) as well as novel ideas for mechanistic studies to further unravel the pathophysiological interrelations and identify potential therapeutic strategies (Table 3).

K_{2P} channels in oncology

Background

Cancer is a phenomenon of uncontrolled cell growth and metastatic dissemination. It is caused by both genetic and environmental factors [22, 23] that lead to distinct cellular alterations such as abnormal cellular metabolism, epigenetic changes, and increased angiogenesis [24, 25]. Oncogenes have been suggested to activate potassium channels and promote tumorigenesis [26, 27]. Thirteen out of fifteen K_{2P} channel was found to associate with carcinogenesis, each K_{2P} channel plays a distinct role in tumor development, depending on its biophysical characteristics, sensitivity to different stimuli (pH, hypoxia, reactive oxygen species, stretch, calcium and glucose levels), and expression patterns.

Human data

Summary. In 2013, a systemic screening of the mRNA expression of fifteen K_{2P} channels was conducted in 20 types of cancer by using Oncomine, an online cancer microarray database, together with a meta-analysis. Despite heterogeneous expression of K_{2P} channels among different cancers, overexpression of *KCNK1* and *KCNK15* was observed in most cancers (bladder, breast, cervical, lung, pancreatic, head and neck cancer, and leukemia), whereas *KCNK3* and *KCNK10* were downregulated in breast, lung, pancreatic cancer, and sarcoma [13, 28].

Breast cancer. Ten out of fifteen K_{2P} channels showed altered expression in breast cancer. Among those ten genes, eight were upregulated (*KCNK1, KCNK3, KCNK5, KCNK6, KCNK9, KCNK13*, *KCNK15*, and *KCNK17*), whereas *KCNK2* and *KCNK10* were downregulated. Upregulation of *KCNK5*, *KCNK9*, and *KCNK2* was associated with triple-negative type breast cancer (TNBC), which is characterized by poor prognosis and limited treatment options [28, 29]. Therefore, targeting K_{2P} channels might be a potential therapeutic strategy. Functionally, K_{2P} channels modulate breast cancer development in cell proliferation, metastasis, and apoptosis [30, 31]. *KCNK2* was upregulated in the MDA-MB-231BO human metastasis cancer cell line and is highly related to the metastasis towards bone by modulating bone sialoprotein (BSP) and its downstream factor αvβ3 integrin [32].

Leukemia. Overexpression of *KCNK3*, *KCNK10,* and *KCNK12* and downregulation of *KCNK6* was found in patients with leukemia, resistant hematopoietic cancers, and acute myeloid leukemia (AML) [13, 28]. *KCNK15* was linked with acute lymphoid leukemia by altering DNA methylation in peripheral blood mononuclear cells (PBMCs) from patients [33]. On the other hand, TRESK was detected in patients with acute lymphoblast leukemia and lymphoma, indicating a regulatory role in lymphocyte proliferation and tumorigenesis [34].

Melanoma. TASK3 intracellular positivity was found in human melanoma tissue and three primary and metastatic human melanoma cell lines (WM35, HT199, and HT168-M1) [35], while *KCNK5* was downregulated in melanoma patient samples [13]. *KCNK7* was suggested as a disease biomarker and molecular target in melanoma patient specimens from a study concerned with the in silico identification and experimental validation [36].

Table 2. Role of K_{2P} channels in different pathological conditions The table summarizes all the findings on K_{2P} channels relevant to human diseases, including altered channel expression, channel mutation, and genetic variants associated with different pathological conditions. The channel name is based on the IUPHAR nomenclature. TNBC: triple-negative breast cancer, ALL: acute lymphoblastic leukemia, HCC: hepatocellular carcinoma, MS: multiple sclerosis, SNP: single nucleotide polymorphism, SCD: sickle cell disease, PAH: pulmonary artery hypertension, IVF: idiopathic ventricular fibrillation, LQTS: long QT syndrome, FHEIG: facial dysmorphism, hypertrichosis, epilepsy, intellectual/developmental delay, and gingival overgrowth syndrome, BBMRS: Birk Barel mental retardation syndrome, SSRIs: selective serotonin reuptake inhibitors, MDD: major depressive disorder, IGE: Idiopathic generalized epilepsies, T2D: type 2 diabetes, MODY: maturity-onset diabetes of the young, BEN: Balkan endemic nephropathy, DO: detrusor overactivity, LUTS: lower urinary tract symptoms, HSCR: Hirschsprung disease. CNS: central nervous system, GI: gastrointestinal system

Disease type	Channel name	Remarks and effect	References
Oncology	THIK1 (K_{2P}13.1)	Upregulation in breast cancer	[13, 28]
	TASK4 (K_{2P}12.1)	Upregulation in resistant hematopoietic tumors and leukemia Downregulation in astrocytoma and glioblastoma	
	TASK3 (K_{2P}9.1)	Upregulation in breast cancer, TNBC, and melanoma	[29, 35]
	TASK5 (K_{2P}15.1)	Association of DNA demethylation in leukemia, breast, gastric, and pancreatic cancers	[33, 39, 45]
	TASK1 (K_{2P}3.1)	Upregulation in leukemia, lymphedema, breast, and kidney cancers	[13]
	TWIK1 (K_{2P}1.1)	Upregulation in most cancers Downregulation in melanoma, prostate cancers, and sarcoma	[13]
	TWIK2 (K_{2P}6.1)	Downregulation in AML, colorectal, esophageal cancers, leukemia, and melanoma Upregulation in breast and ovary cancer	
	KCNK7 (K_{2P}7.1)	Downregulation in cervical cancer and potential marker for melanoma	[43]
	TRESK (K_{2P}18.1)	Upregulation in acute lymphoblast leukemia and lymphoma	[28, 34]
	TASK2 (K_{2P}5.1)	Downregulation in melanoma Upregulation in breast, pancreatic cancer, and HCC	[13, 29, 37]
	TASK4 (K_{2P}12.1)	Upregulation in breast cancer Downregulation in HCC and CNS cancers	[13, 28, 37]
	TREK1 (K_{2P}2.1)	Downregulation in breast cancer and HCC Upregulation in prostate cancer	[28, 37, 43]
	TREK2 (K_{2P}10.1)	Downregulation in most cancers and mediate breast cancer via estrogen receptor	[13]
Autoimmune disease	TASK1 (K_{2P}3.1)	Downregulation in MS patient samples	[19]
	TASK2 (K_{2P}5.1)	Upregulation in MS and Rheumatoid arthritis patient samples	[18, 54]
	TASK3 (K_{2P}9.1)	Downregulation in MS and UC patient samples	[19, 53]
Hematologic disease	TWIK2 (K_{2P}6.1)	KCNK6 is associated with the SNPs in SCD patients	[69]
Cardiovascular disorders	TASK1 (K_{2P}3.1)	Common target for class III antiarrhythmic drugs and A293 Missense mutation is associated with PAH	[90, 93, 95]
	TASK2 (K_{2P}5.1)	Risk genes for coronary arterial disorders and myocardial infarction patients	[89]
	TALK2 (K_{2P}17.1)	Mutation with loss of channel functions in IVF, heart failure, and LQTS patients Genetic variants in cerebral hemorrhage and ischemic stroke	[84, 85, 100, 103]
	TREK1 (K_{2P}2.1)	Downregulation in atrial fibrillation, and tachycardia patients	[97, 100]
CNS disease	TRAAK (K_{2P}4.1)	Missense mutations contribute to neurodevelopmental disease, FHEIG	[117]
	TASK3 (K_{2P}9.1)	Genetic mutation and channel dysfunction associated with BBMRS and schizophrenia	[118]
	TASK5 (K_{2P}15.1)	Therapeutic evaluation marker in male schizophrenia patients	[120]
	TREK2 (K_{2P}10.1)	Involvement in Schizophrenia development	[121]
	TREK1 (K_{2P}2.1)	Channel inhibition by SSRIs and genetic variants in MDD patients Channel inhibition in clinical anesthetic agents	[122]
	TRESK (K_{2P}18.1)	Channel dysfunction might increase the susceptibility to familial migraine	[123, 126]
	TASK2 (K_{2P}5.1)	Association with ion homeostasis and migraine	[128]
	TALK1 (K_{2P}16.1)	Genetic association with IGE	[129]
Metabolic disorder	TALK1 (K_{2P}16.1)	Channel genetic locus associated with T2D and MODY among different populations	[148, 149, 150]
Kidney and urinary system disorders	TASK2 (K_{2P}5.1)	Genetic mutation contributes to a renal disease, BEN	[16]
	TREK1 (K_{2P}2.1)	Reduced channel expression in DO and LUTS	[161, 164]
GI disorders	TREK1 (K_{2P}2.1)	Downregulation in HSCR patient samples	[168]
	TRAAK (K_{2P}4.1)		[169]

Table 3. Pathophysiological contributions of K_{2P} channels to human diseases The table lists currently-known mechanisms of K_{2P} channels that lead to different pathological conditions. The general pathomechanisms include dysfunction in cell proliferation, volume homeostasis, barrier integrity, endocrine signaling, and electrical activities in both neurons and smooth muscle cells. MS: multiple sclerosis, RA: rheumatoid arthritis, SCD: sickle cell disease, FHEIG: facial dysmorphism, hypertrichosis, epilepsy, intellectual/developmental delay, and gingival overgrowth syndrome, HSCR: Hirschsprung disease, T2D: type 2 diabetes, IBS: irritable bowel syndrome. CNS: central nervous system, GI: gastrointestinal system

Pathomechanism	Disease type	Disease name
Aberrant cell proliferation, differentiation and activation	Oncology	Cancer
	Autoimmune disease	MS and RA
	Neurodevelopmental disorder	FHEIG
Impaired volume regulation	Hematological disease	SCD
Dysfunction in endothelial/ epithelial barrier integrity	Autoimmune disease	MS
	GI disorder	HSCR
Altered intracellular endocrine signaling	CNS disease	Depression
		Schizophrenia
	Metabolic disease	T2D
Imbalanced electrochemical activities and dysregulated cellular excitability	CNS disorder	Pain/migraine
		epilepsy
	Cardiovascular disorder	Arrhythmias
	GI disorder	IBS
	Kidney and urinary disorder	Detrusor overactivity

Hepatocellular carcinoma. With the help of bioinformatics and biochemical assays, downregulation of *KCNK5*, *KCNK17,* and *KCNK2* was observed in hepatocellular carcinoma (HCC) specimens, suggesting K_{2P} channels as a diagnostic biomarker for HCC [37].

Other cancers. Demethylation of long non-coding RNA (lncRNAs) in *KCNK15* and *WISP2* antisense *RNA 1* (*KCNK15-AS1*) was observed in pancreatic cancer specimens, indicating a correlation between epigenetic changes in *KCNK15* and pancreatic carcinogenesis and metastasis [38]. Also, similar demethylation was found in gastric cancer patient samples and was due to inhibition of DNA methyltransferase 1-mitogen-activation protein kinase (DMNT1-MAPK) and histone deacetyltransferase 1-AKT (HDAC1-AKT) [39]. Moreover, the *KCNK15-AS1* lncRNA axis was found to contribute to the tumor progression in lung adenocarcinoma tissues via MicroRNA-202 (miR-202) and miR-307 [40]. These results indicate that CpG island methylation and histone acetylation might be common mechanisms of *KCNK15* modulation in post-transcription of oncogenes and tumor-suppressor genes [39] in several cancers despite different tumor microenvironments.

In addition to *KCNK15*, *KCNK5* upregulation was observed in specimens from a systemic screening of non-small-cell lung cancer (NSCLC) and pancreatic cancer [29]. TASK3 is recognized as an oxygen-sensing potassium channel in the human lung cancer cell line H146, suggesting TASK3 as a potential modulator of solid tumor formation [40, 41]. Also, strong TASK3 immunoactivity was observed in human gliomas specimens and TASK3 channel demonstrated functional relevance to isoflurane–induced cell death in U373 and LN393 human cell lines [42]. *KCNK2* upregulation was found in the human prostate cancer cell lines PC3 and LNCaP due to increased cell proliferation [43]. *KCNK6* was upregulated in cells from ovarian cancer patients, while it was downregulated in patients with colorectal and esophageal cancers. In CNS cancers, *KCNK12* downregulation was observed in astrocytoma and glioblastoma specimen [13, 28, 29].

Key mechanistic studies

The estrogen receptor α was found to mediate cell cycle checkpoints in cancer and cell proliferation by elevating *KCNK5* expression in the breast cancer cell lines MCF-7 and T47D [44]. Also, *KCNK*9 upregulation promoted solid breast tumor formation due to its resistance to hypoxia and serum deprivation in C8 mouse embryonic fibroblast cells and Mus musculus mammary gland (NmuMG) epithelial cell-transferred mice [28]. As proof of concept, TASK3 blocking agents (zinc and methanandamide) induced cell apoptosis and reduced cell proliferation in the ovarian cancer cell lines SKOV-3 and OVCAR-3 [20]. A TASK3 monoclonal antibody was proven to reduce tumor growth due to channel internalization and dysfunctions. In addition to breast cancer, TASK3 genetic knockdown was found to dampen tumor invasion in the human gastric cancer cell lines KAYO-III and MKN-45. BL1249, a TREK1 activator, was identified to inhibit tumor proliferation and migration via hyperpolarization in the human pancreatic ductal adenocarcinoma cell line BxPC-3 [45]. Several studies have also demonstrated the importance of intracellular potassium levels in T cell effector functions, tumor clearance, and cell survival through protein phosphatase A (PP2A)-mediated Akt-mTOR phosphorylation [46], indicating K_{2P} channels as a promising candidate for anti-tumor effects in cancer therapy [31, 47].

K_{2P} channels in autoimmune diseases

Background

Autoimmunity is characterized by a loss of immune system self-tolerance towards own healthy cells and tissues. The etiology is only sparsely understood, however genetic (loss and gain of function mutations) and environmental factors (autoantibodies, UV exposure, and gut microbiome) are critically involved in disease development [48]. Altered expression and dysfunction of potassium channels in autoimmune diseases indicate a potential role in the disease pathology. For example, elevated Kv1.3 expression has been shown in autoreactive T cells from patients with type 1 diabetes, multiple sclerosis (MS), and rheumatoid arthritis [49, 50].

Also, the upregulation of Kv.7 was found in ulcerative HSCR patients, contributing to basolateral conductance [51]. In general, potassium channels contribute to the inflammatory responses in autoimmune diseases by regulating hyperpolarization-induced calcium influx together with Ca2+ release-activated Ca2+ (CRAC) channels and stromal interaction molecules (STIM) [52].

Human data

Reduced TASK1 and TASK3 channel expression were found in the inflammatory lesions of MS patients, particularly in $CD11b^+$ macrophages and granulocytes. TASK channels might regulate cell apoptosis by initiating apoptotic volume decrease (AVD) and reducing the inhibition towards pro-apoptotic enzymes [19]. On the other hand, *KCNK9* upregulation was found in the colon of ulcerative colitis (UC) patients, implicating the contribution of *KCNK9* genetic variants in UC pathogenesis [53]. TASK2 upregulation in $CD8^+$ T lymphocytes was observed in the CNS of relapsing-remitting multiple sclerosis (RRMS) patients in both acute and chronic phases. Correspondingly, TASK2 blockers and siRNA both confirmed their therapeutic potential in MS by modulating T cell effector functions [18]. In addition to findings in MS, comparable TASK2 upregulation was discovered in the blood- and synovial fluid-derived $CD4^+$ T cells from RA patients and positively correlates with the DAS28 scores [54]. These findings indicate that TASK channel modulation might be beneficial to autoimmune diseases due to potassium-mediated T cell inflammatory responses.

Key mechanistic study

In the EAE model, TASK1 and TASK3 channels were found to mediate T cell proliferation and cytokine production by regulating intracellular calcium concentration via hyperpolarization [19]. Also, TASK1 was found to regulate oligodendrocyte differentiation *in vitro* and myelination *in vivo* via LINGO-1/ WNK1 phosphorylation [55]. TASK3 was discovered to modulate cell apoptosis and neurodegeneration via inflammation-mediated TNF-α activation [56]. Beyond MS pathology, TASK2-mediated intracellular Ca^{2+} signaling alternations in T cell subsets was observed in a mouse model of inflammatory bowel disease (IBD) [57]. KCNK2 downregulation on mRNA level was identified in murine dorsal root ganglia (DRG) neurons, leading to increased colon mechanosensitivity and UC development [58]. Also, TASK1 inhibition (anandamide and A293) was beneficial to EAE due to reduced calcium-dependent T cell activation, proliferation, and cytokine production [17, 19, 59]. However, TASK2 deficiency in mice showed no impact on EAE pathology due to the compensatory effects of TASK1 and Kv1.3 [60]. On the contrary, $TREK1^{-/-}$ mice demonstrated exacerbated EAE phenotypes accompanied by elevated CNS T cell infiltration, altered endothelium integrity, and higher expression of adhesion molecules (VCAM1, ICAM1, and PECAM1) [61]. Similarly, suppressed TREK1 expression in intestinal epithelial cells worsened the colon inflammation by disrupting barrier integrity via histone deacetylation 1 (HDAC) and p38/mitogen-activated protein kinase (MAPK) pathway [62]. In summary, K_{2P} channels are involved in the development of autoimmune diseases by modulating calcium-mediated T cell activation, loss of barrier integrity, cell apoptosis, and eventually neurodegeneration.

K_{2P} channels in hematologic diseases

Background

Hematologic diseases affect blood and blood-producing organs and comprise anemias, sickle cell disease, glucose-6-phosphate dehydrogenase deficiency, and coagulopathies [63, 64]. Sickle cell disease (SCD) is one of the most common inherited hematologic diseases in regions affected by malaria worldwide and is caused by a genetic mutation in β-globin. SCD patients are characterized by sickle hemoglobin (HbS) and compromised red blood cell functions. Calcium-activated potassium channels (Gardos channels, KCNN4) contribute to the loss of potassium and erythrocyte dehydration in SCD. Inhibition of Gardos channels proved to alleviate red blood cell (RBC) dehydration and showed anti-sickling effects [65]. Also, a genetic mutation in Gardos channels contributes to rare anemias. For instance, R352H in KCNN4 was associated with decreased K^+ content, increased conductance, and cell dehydration in hereditary xerocytosis [66, 67]. On the other hand, dehydration also occurred due to the loss of K^+ via KCl channels [68], indicating a central role of potassium channels in the development of hematological diseases.

Human data

KCNK6, as a member of the K_{2P} channel family, was highly expressed in $CD34^+$ cells and identified as a disease-contributing gene in the inherited polymorphisms (SNPs) of SCD patients from a Genome-wide Association Study (GWAS). *KCNK6* might regulate the disease pathogenesis by affecting erythroid differentiation and vaso-occlusive processes in SCD [69].

Key mechanistic study

Early in the 1990s, scientists suggested the association of cation ions with SCD [70, 71], particularly potassium loss in RBC dehydration [72, 73]. TWIK2 channels are highly expressed in $CD34^+$ stem cells, the cell population associated with erythroid differentiation. Besides, the potassium homeostasis of erythrocytes is critical for HbS polymerization, RBC hemolysis, and the development of SCD [69]. However, the detailed mechanism of TWIK2 channel contribution to SCD disease is still unclear and requires further mechanistic studies.

K_{2P} channels in cardiovascular disorders

Background

Cardiovascular diseases include blood vessel blockage, myocardial dysfunctions, and arrhythmias [74, 75]. For example, ischemic stroke is associated with blood clot formation and vessel blockage [76]. Diseases with myocardial dysfunctions include atherosclerosis, coronary arterial disease (CAD), myocardial infarction (MI), and left ventricular (LV) dysfunctions [77, 78]. Arrhythmias refer to disorganized electrical activities in the cardiac system such as tachycardia, idiopathic ventricular fibrillation (IVF), atrial fibrillation (AF), and congenital long QT syndrome (LQTS) [79, 80].

The physiological functions of the cardiovascular system rely on depolarization-mediated smooth muscle tone for which K_{2P} channels play a critical role by coordinating voltage-gated calcium channels (VGCC) and stabilizing the membrane potential [82]. Hence, K_{2P} channels contribute to the development of cardiovascular diseases.

Human data

In the 2000s, a growing number of K_{2P} channel studies related to the cardiovascular system were conducted based on the high expression in pulmonary artery smooth muscle cells (PASMC) [82, 83]. In addition to the high expression, several K_{2P} channels are associated with the development of cardiovascular disorders. For instance, *KCNK17* genetic variants were associated with vessel blockage, susceptibility to ischemic stroke in Caucasian, and cerebral hemorrhage in Chinese populations [38, 84, 85]. In addition to *KCNK17*, multiple *KCNK5* genetic variants were found to be a common risk factor of CAD and migraine, suggesting overlapping mechanisms in disease pathogenesis [86, 87]. Also, the TASK2 genetic variant rs10947789 was discovered as an overlapping risk gene in the blood samples of CAD and MI patients and was associated with increased platelet counts and volume [88]. Apart from being a risk factor, TASK2 channels regulated myocardial functions by modulating membrane potentials and respiration via oxygen chemosensitivity [89].

TASK1 channels are a common molecular target for treating arrhythmias (amiodarone, vernakalant, flecainide, and carvedilol), and A293, a potent and specific TASK1 blocker, displayed potent antiarrhythmic effects [90, 91]. Also, TASK1 inhibition was found to attenuate cardiovascular dysfunctions in AF patients by prolonging action potentials [92, 93], and TASK1 missense mutation and reduced currents were observed in patients with pulmonary arterial hypertension [94, 95]. As a proof of concept, phospholipase inhibitor ONO-RS-082 was able to increase TASK1 currents in human PASMC via channel activation [96]. Also, decreased atrial *KCNK3* expression was observed in patients with left ventricular (LV) dysfunction but was increased in chronic AF (cAF) patients. *KCNK3* channel inhibition prolonged action potential (AP) duration and showed beneficial effects in cAF patients [97]. Therefore, TASK1 inhibitors and activators both might be beneficial for treating cardiovascular disorders depending on the different pathological conditions. In whole-exome sequencing (WES) research, mechanosensitive TREK1 and TREK2 channels are highly expressed throughout the cardiac system. Atrial and ventricular TREK1 downregulation was found in AF patients and contributed to cardiac rhythmic regulation [97]. Also, a later study confirmed significant mRNA reduction (-80%) in the atrium of AF and HF patients, leading to prolonged atrial effective refractory periods [97, 98]. In whole blood samples, a point mutation in TREK1 increased potassium permeability, mechano-sensitivity, and contributed to right ventricular outflow tract (RVOT) tachycardia [99]. G88R mutation and genetic variants in *KCNK17* were discovered in whole blood samples and induced pluripotent stem cell-derived cardiomyocytes to enhance channel currents, hyperpolarization, and contribute to the pathologies of IVF and LQTS [100, 101]. Moreover, *KCNK17* was found to be sensitive to antiarrhythmic drugs and involved in drug working mechanisms [102]. On the other hand, reduced TALK2 currents in atria and ventricles were observed in patients with heart failure (HF) and atrial fibrillation [103]. Therefore, TALK2 activators and blockers both showed therapeutic potentials in treating arrhythmias and heart failure. In summary, K_{2p} channels are a promising target for treating a range of cardiovascular disorders.

Key mechanistic study

Although the mechanism of how *KCNK17* modulate the susceptibility to ischemic stroke is still unclear, TREK1 silencing by short-hairpin RNA displayed protective effects in rat cardiomyocytes by decreasing cell apoptosis under ischemic injury conditions [104]. Also, in the transient middle cerebral artery occlusion (tMCAO) model, $TASK1^{-/-}$ mice displayed larger infarcted volumes, but $TRAAK^{-/-}$ mice showed preserved brain metabolism and pH. Therefore, TASK1 channel-induced hyperpolarization might be an intrinsic defense mechanism, while high levels of organic osmolytes in $TRAAK^{-/-}$ mice avoided ischemic-induced cell death [105, 106].

For K_{2P} channel modulation in myocardial functions, a naïve TREK-1-like current discovered in rat ventricular cardiomyocytes is activated by ATP through cytosolic phospholipase A_2, cAMP-mediated protein kinase A (PKA), and tyrosine kinase pathways [107]. Also, endothelin-1 (ET-1) was discovered as a TREK1 upstream regulator in calcium-mediated vasocontraction via Gq protein-coupled protein kinase C (PKC) signaling [108]. β(IV) spectrin, an actin-associated protein, was found to regulate TREK1 membrane trafficking by colocalization with the channel [109, 110]. Therefore, TREK1 channels might coordinate with G protein coupled receptors and its downstream effector proteins to regulate myocardial functions under physiological conditions. On the other hand, histone deacetylase (HDAC) inhibitors increased TREK1 expression and prolonged action potential duration in murine atrial cardiomyocytes, indicating that epigenetic changes also modulate TREK1 functions [111].

Although atrial KCNK2 expression was reduced in the AF mouse model, TREK1 specific deletion in fibroblasts attenuated cardiac fibrosis and dysfunctions through PKC-mediated oxidative stress and Jun N-terminal kinase (JNK)-mediated cell death [97, 112]. Besides, reduced atrial TASK1 expression was observed in an AF mouse model (CREM transgenic mice) and a HF disease model (transverse aortic constriction) [113] Furthermore, in $TASK1^{-/-}$ mice, prolonged action potential and QT intervals were observed in electrocardiograms, accompanied by reduced autonomic variability and sympathetic overactivity [114, 115]. However, there is currently no genetic knockout mice study or mechanistic data for the role of TASK2 channels in cardiovascular disorders. Propafenone, a commonly used antiarrhythmic drug, was found to activate the TALK2 channel with a 7.8-fold current increase in mammalian Chinese hamster ovary (CHO) cells. Also, TALK2 expressed in Xenopus oocytes showed sensitivity to most antiarrhythmic drugs, such as propafenone, quinidine, mexiletine, and metoprolol [102]. However, mechanistic studies of TALK2 in arrhythmias are largely missing.

K_{2P} channels in CNS diseases

Background

Central nervous system (CNS) diseases include disorders of the brain, spinal cord, and nerves. Neurodevelopmental diseases affect CNS development, where mutations lead to abnormal brain size and dysfunctions. Psychiatric disorders are brain disorders characterized by abnormal mental and behavioral phenotypes. Further CNS-related diseases such as pain, migraine, and epilepsy are based on neuronal hyperexcitability, abnormal biochemical metabolisms, and aggregations. Potassium channels are a critical modulator of electrochemical and ion homeostasis, and the high expression and central functions of K_{2P} channels in the CNS argue for an essential role in CNS diseases.

Human data

Neurodevelopmental disorders are mainly caused by familial mutations. For instance, FHEIG (Facial dysmorphism, Hypertrichosis, Epilepsy, Intellectual disability, Gingival overgrowth) is related to the *KCNK4* missense mutation negatively affecting lateral intramembrane fenestration during CNS development [116]. Birk Barel Mental Retardation Syndrome (BBMRS) is a maternally transferred disease characterized by mental retardation,

hypotonia, and dimorphisms and caused by a *KCNK9* missense mutation leading to impaired channel functions. Flufenamic acid (FFA) application was found to enhance TASK3 channel currents and improve the symptoms in younger BBMRS patients [117].

Emerging evidence also suggests a role of TASK3 channels in psychiatric disorders. For example, rs4736253a, a genetic locus near *KCNK9,* was associated with schizophrenia [118]. Furthermore, hypomethylated *KCNK15* was associated with remission in male schizophrenia patients [119]. Similarly, demethylation in *KCNK10* was associated with neuronal growth and cerebellum development in schizophrenia patients [120]. Genetic variants in *KCNK2* were identified to influence treatment resistance in patients with major depressive disorders (MDD) [121].

Migraine, pain, and epilepsy are related to neuronal hyperexcitability. In migraine with and without aura (MA and MO), several *KCNK18* mutations were associated with reduced neuronal current threshold and high spike frequencies [122]. Some contradictory studies discovered that the *KCNK18* variants A34R and C110R were detectable in both migraine patients and controls [123, 124], suggesting that a single TRESK mutation is not sufficient to cause migraine. Afterward, the C110R variant in TRESK was confirmed to show preserved currents in human nociceptors, and only the frameshift mutation F139WfsX24 led to a loss of TRESK function [125]. Bupivacaine, a clinical anesthetic agent, was found to inhibit TREK1 channels. Also, Aristolochic acid (AristA), a plant extract medicine to treat pain, enhanced TREK1 and TREK2 currents but inhibited TRESK currents [126]. *KCNK5* was also identified as a risk factor for migraine from a GWAS [127], whereas *KCNK16* and *KCNK17* variants were suggested to be risk factors for idiopathic generalized epilepsy (IGE) due to altered channel currents and spike frequencies [128].

Key mechanistic study

There is currently no mechanistic study of K_{2P} channels in neurodevelopmental disorders. However, potential mechanisms of K_{2P} channels contributing to psychiatric disorders were suggested. For example, a TREK2 mutation in the protein kinase A (PKA) phosphorylation site abolished the norepinephrine-mediated suppression of neuronal excitability and the development of schizophrenia [129]. Besides, selective serotonin reuptake inhibitors (SSRIs), a group of commonly used antidepressants, are effective through TREK1 channel inhibition, among other mechanisms [130, 131]. Correspondingly, a depression-resistant phenotype was observed in TREK1$^{-/-}$ mice due to higher efficiency of 5-HT neurotransmission and reduced stress-mediated corticosterone levels in serum [132, 133]. In addition, spadin, a specific TREK1 blocker, was discovered to show anti-depressive effects by activating the 5-HT1A receptor, the cAMP-response element (CREB), brain-derived neurotrophic factor (BDNF) signaling, and hippocampal neurogenesis [134, 135]. In contrast, ostruthin, an element extracted from plants, showed anxiolytic and anti-depressive effects by activating TREK1 channels, increasing channel currents, and reducing stress-mediated c-Fos signaling [136].

Also, TREK1$^{-/-}$ mice displayed hyperalgesia toward mechanical and thermal stimuli [137], while μ-opioid receptor-mediated TREK1 activation showed morphine-mediated analgesic effects without opioid-induced adverse effects [138]. Further, 11-Deoxy prostaglandin F2α, a TREK2 selective activator, showed analgesic effects by reducing the calcium influx in mouse primary dorsal root ganglia (DRG) [139], whereas TREK2 downregulation by siRNA induced depolarization of the nociceptors in DRG neurons and exacerbated hyperalgesia in rats [140]. Similarly, TRESK mutations in mouse trigeminal ganglion (TG) cells showed lower current threshold among action potential initiation, increased spike frequencies, and increased migraine susceptibility [141], whereas TRESK overexpression led to reduced spike formation and excitability [142].

K_{2P} channels in metabolic disorders

Background

Metabolic disorder refers to a deficiency in enzymes during metabolic processes, e.g., the metabolism of glucose, carbohydrates, amino acids, and fatty acids. Type 2 diabetes (T2D) is a common metabolic disorder associated with family history, chronic diseases, age, and obesity and is characterized by disrupted glucose-mediated insulin secretion. The correlation between potassium and glucose metabolism has been proposed since the late 1900s. For instance, potassium depletion leads to impairment in insulin secretion and glucose tolerance through depolarization [143, 144], while higher potassium intake reduces the risk of T2D development [145, 146].

Human data

In pancreatic beta cells, *KCNK16* was identified as susceptibility locus of T2D from several GWAS in East Asian, Indian, and European populations and is involved in pancreatic β cell development and insulin secretion [147, 148]. Moreover, the association of *KCNK16* with T2D was strengthened from the results of small RNA sequencing [149]. Lately, a *KCNK16* gain of function was also identified in patients with maturity-onset diabetes of the young (MODY) by affecting calcium signaling and glucose-stimulated insulin secretion (GSIS) [150].

Key mechanistic study

Enriched TASK1 channel expression was found in the plasma membrane of β cells in both humans and rodents. TASK1 can regulate hyperpolarization by interacting with voltage-dependent calcium channels (VDCC), suggesting TASK1 as a modulator of calcium signaling and the development of T2D. As a proof of concept, TASK1 conditional deletion in pancreatic β cells led to increased glucose-stimulated depolarization, GSIS, and improved glucose tolerance [151].

The genetic polymorphism of TALK1 channel rs1535500 was associated with T2D. In $TALK1^{-/-}$ mice, increased β-cell depolarization, enhanced GSIS reduced calcium-mediated ER stress, and islet dysfunction were observed [152, 153]. Besides, cytokine-mediated TALK1 inhibition showed protective effects on β-cells by facilitating calcium influx and GSIS under inflammation [1554, indicating modulatory functions of K_{2P} channels in glucose tolerance and T2D development.

K_{2P} channels in kidney and urinary system disorders

Background

Kidney and urinary-tract disorders include kidney dysfunctions, abnormal urinary filtration, and urination. Potassium channels are central modulators of resting membrane potential in smooth muscle cells, renal vascular cell contractility, and ion homeostasis, supporting a critical role in various human kidney and urinary system disorders [155, 156]. For instance, reduced urinary potassium excretion is associated with reduced renal mass and dysfunction in glomerular filtration [157]. On the contrary, elevated urinary potassium excretion and high potassium diet lowered the risk of chronic kidney disease development [158].

Human data

pH-sensitive TASK2 channels are highly abundant in the nephron of human kidneys, especially in tubular epithelia, and are inhibited by external acidic pH [159]. Correspondingly, T108P, a missense variant in *KCNK5* leading to a loss of channel function, is associated with Balkan endemic nephropathy (BEN), a familial and chronic kidney disease [16].

For TREK1 channels, downregulated expression and reduced currents were observed in human detrusor overactivity (DO), an abnormal response of the bladder to physiological

stretches. Furthermore, DO myocytes failed to dilate while exposed to TREK1 channel openers, which supports the role of TREK1 in regulating bladder contraction by interacting with cytoskeletal proteins [160]. In addition, diminished TREK1 expression was also found in the SNPs of patients with lower urinary tract symptoms (LUTS) and was associated with urinary defects [161].

Key mechanistic study

In TASK2 deficient mice, the pH and concentration of $HCO3^-$ was reduced in the blood but increased in the urinary system, indicating channel inhibition and metabolic acidosis due to renal bicarbonate loss [162]. In $TREK1^{-/-}$ mice, elevated muscle tone and more contractile force in response to stimulations were found in myocytes. Also, $TREK1^{-/-}$ animals revealed increased micturition durations and bladder capacity. However, a mixed effect was observed in global knockout mice, suggesting that further studies are required with conditional knockout animals [163]. Besides, significant TREK1 downregulation was found in the obstructor myocytes of the DO mouse model after bladder obstruction [164], whereas channel upregulation was observed in the rat model [165], indicating the urgent need of a promising DO animal model for representing human patients.

K_{2P} channels in gastrointestinal (GI) disorders

Background

Gastrointestinal (GI) disorder refers to defects in GI tracts, including the esophagus, stomach, intestines, and rectum. Potassium homeostasis is one vital factor, maintaining the physiological functions of muscle tone and motility of GI tracts. Particularly the mechanosensitive K_{2P} channels are highly expressed in mechanosensory smooth muscle cells and Cajal cells in the human GI system [58, 166, 167], suggesting a potential for K_{2P} channel modulation in the GI system.

Human data

Hirschsprung disease (HSCR) is a congenital disorder within the GI system due to reduced TREK1 expression and missing intestinal aganglionic and ganglionic neurons [168]. Also, TRAAK downregulation was observed in aganglionic and ganglionic neurons in the colon, indicating disrupted K_{2P} channel functions for maintaining epithelium barrier integrity and contributing to the disease development of HSCR [169]. The role of mechanosensitive K_{2P} channels in other GI disorders remains unknown and requires further investigations.

Key mechanistic study

The association of mechanosensitive K_{2P} channels with GI disorders was discovered in the context of high channel expression in murine small and large intestines [170]. For example, abundant TASK2 expression was found in the murine intestinal epithelium and played a critical role in maintaining the anion and fluid secretions. Tetrapentylammonium, a TASK2 inhibitor, was found to abolish the anion secretory current [171]. Besides, altered potassium channel-mediated muscle contraction induces irritable bowel syndrome (IBS) [172]. Riluzole, a mechanosensitive channel activator, reduced the hypercontractility of colon myocytes, indicating TREK1 as a potential therapeutic target for the hypercontraction in IBS [167]. Although it is known now that mechano-gated K_{2P} channels regulate the GI system by maintaining epithelial barrier integrity and smooth muscle tone contraction, the underlying molecular mechanisms and related signaling pathways are still unclear.

Outlook

The growing research on K_{2P} channels not only brings new insights into the field but also reveals obstacles for both researchers and physicians. The major difficulties include translational roadblocks, lack of modulators with high specificity, and risk of adverse effects. There are already several examples of failed translation in K_{2P} channel research: TASK1 deficient mice showed reduced T cell effector functions and ameliorated motor dysfunction, whereas TASK1 downregulation was found in MS patients with elevated inflammatory responses. Moreover, TASK2 upregulation was observed in both RA and MS patients; however, $TASK2^{-/-}$ mice showed a EAE disease course comparable with WT. The usage of patient-derived and -induced pluripotent stem cells and computer-based prediction models might be helpful to overcome the translational roadblock. Nonspecific channel modulators and serious adverse effects are further problems hampering human application, especially regarding drug development for K_{2P} channels. For instance, the commonly used anesthetic bupivacaine blocks not only TASK1 and TASK3 but also TREK1 [173, 174]. TASK2 inhibition via class III antiarrhythmic drugs is beneficial for cardiovascular disorders but associated with potential adverse effects such as renal failure [175]. Structural studies of K_{2P} channels on the allosteric ligand-binding site might help to identify more specific pharmacological modulators. Also, detailed studies on K_{2P} channel expression and function in different tissues might help to predict adverse events. Besides overcoming current obstacles for human application with the well-studied plasma membrane-localized K_{2P} channel, further research on intracellular K_{2P} channels (e.g., THIK2 in the endoplasmic reticulum, TWIK1 in endosomes, and TWIK2 in lysosomes) [176, 177] might open up new therapeutic avenues due to novel targets in the channel trafficking process. For example, $TWIK2^{-/-}$ mice demonstrated pulmonary hypertension with altered vasocontractiliy [178, 179], and TWIK2 deficient macrophages prevented pulmonary inflammation in mice [180]. Overall, the K_{2P} research field is indispensable and promises a deeper understanding of the pathophysiology of human disorders, allowing us to develop new diagnostic and therapeutic strategies.

Conclusion

Solid evidence suggests that K_{2P} channels are major diagnostic and therapeutic candidates for several human diseases. However, the insights into the underlying molecular processes are only fragmentary. Nevertheless, common pathophysiological mechanisms can be identified as follows (Table 3): (1) aberrant cell proliferation, differentiation, and activation are associated with cancer, neurodevelopmental disease (FHEIG), and autoimmunity; (2) impaired volume regulation is associated with erythrocyte abnormalities in sickle cell disease; (3) dysfunction of endothelial/epithelial barrier integrity in brain and colon is associated with MS and HSCR; (4) altered intracellular and endocrine signaling are found in depression, schizophrenia, and type 2 diabetes; and (5) imbalanced electrochemical activities and dysregulated cellular excitability are associated with neuropathic pain, migraine, epilepsy, and cardiac arrhythmias as well as smooth muscle dysfunction, e.g., in irritable bowel disease and detrusor hyperactivity. However, to warrant further translational research and to develop applications for human diseases, deeper insight into the underlying molecular processes are required.

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Author Contributions

S.M and T.R contributed to the conception and structure of the manuscript discussing the involvement of K_{2P} channels in human diseases. LM. L collected the relevant papers, covering the topic in the field, interpreted, and providing answers and suggestions to the future K_{2P} channel study in human diseases. LM. L drafted the manuscript with supports of critical revising from T.M in oncology section and T.B. for K_{2P} channel physiology. Finally, T.R and S.M provided critical revision of the article and approved the final version to be submitted.

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Disclosure Statement

The authors have no conflicts of interest to declare in this review article.

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