Two-Pore-Domain Potassium (K_{2P}) Channels: Cardiac Expression Patterns and Disease-Specific Remodelling Processes

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Abstract: Two-pore-domain potassium (K_{2P}) channels conduct outward K^+ currents that maintain the resting membrane potential and modulate action potential repolarization. Members of the K_{2P} channel family are widely expressed among different human cell types and organs where they were shown to regulate important physiological processes. Their functional activity is controlled by a broad variety of different stimuli, like pH level, temperature, and mechanical stress but also by the presence of lipids or pharmacological agents. In patients suffering from cardiovascular diseases, alterations in K_{2P}-channel expression and function have been observed, suggesting functional significance and a potential therapeutic role of these ion channels. For example, upregulation of atrial specific K_{2P}-3.1 (TASK-1) currents in atrial fibrillation (AF) patients was shown to contribute to atrial action potential duration shortening, a key feature of AF-associated atrial electrical remodelling. Therefore, targeting K_{2P}-3.1 (TASK-1) channels might constitute an intriguing strategy for AF treatment. Further, mechanooactive K_{2P}-2.1 (TREK-1) currents have been implicated in the development of cardiac hypertrophy, cardiac fibrosis and heart failure. Cardiovascular expression of other K_{2P} channels has been described, functional evidence in cardiac tissue however remains sparse. In the present review, expression, function, and regulation of cardiovascular K_{2P} channels are summarized and compared among different species. Remodelling patterns, observed in disease models are discussed and compared to findings from clinical patients to assess the therapeutic potential of K_{2P} channels.

Keywords: K_{2P}-channel; TASK-1; TREK-1; two-pore-domain potassium channel

1. Introduction

Two-pore-domain potassium (K_{2P}) channels are expressed throughout the human body and contribute to background potassium conductance in many different cell types [1,2]. In the human genome 15 K_{2P} channels have been described which differ from classical potassium channels by the fact that each subunit carries two pore-forming domains, and the channels thus assemble as dimers instead of tetramers (Figure 1). K_{2P} channels give rise to background or “leak” potassium currents which control a multitude of physiological processes [1]. Initially, K_{2P} currents were described as outward rectifying “leakage currents” but recent work has shown that several members of the K_{2P} family can also be voltage activated [3].

K_{2P} currents show a high degree of similarity to the potassium plateau currents I_{KP}, described in guinea-pig cardiomyocytes and the steady-state potassium current I_{KSS}, characterized in murine cardiomyocytes and the arachidonic acid-sensitive potassium current I_{KAA} from rat ventricular cardiomyocytes [4–7]. Cardiac mRNA abundance was described for several members of the K_{2P} family (Figure 2) In the present review, expression,
function, and regulation of cardiovascular $K_{2P}$ channels are summarized and compared among different species. Remodelling patterns, observed in disease models are discussed and compared to findings from clinical patients to assess the therapeutic potential of $K_{2P}$ channels (Figure 3).

**Figure 1.** Membrane topology and structure of $K_{2P}$ channels. $K_{2P}$ channel monomers (left), consisting of 4 transmembrane domains (M1–4) and 2 pore forming loops (P1–2) assemble as homo- or heterodimers. (right).

**Figure 2.** Cardiac mRNA levels of $K_{2P}$ channels in the human heart (whole tissue). Expression of two-pore-domain potassium ($K_{2P}$) channel mRNA level in human right atrial ($n = 10$) and left ventricular ($n = 5$) tissue samples. Data are given as mean ± SEM relative to the housekeeping gene importin 8 (IPO8). * indicate $p < 0.05$ from Student’s t-tests. Data from Schmidt et al. 2015, Circulation [8].
Figure 3. Potential translational implications of cardiac K2P channel expression. AF, atrial fibrillation; OSAS, obstructive sleep apnea; PAH, pulmonary arterial hypertension; RVOT, right ventricular outflow tract; VF, ventricular fibrillation.

2. Structural Assembly and Nomenclature of K2P Channels

The 15 channel subunits of the K2P family each consists of around 300 and 550 amino acids. The sequence differences between the individual subunits of the K2P channel can sometimes be as large as to other potassium channel families. K2P18.1 (TRESK) channel subunits, for example share only 19% amino acid sequence identity with the other K2P family members. But the common feature that links them is the eponymous structural motif of two pore-forming domains per subunit, which distinguishes them from all other potassium channel groups. As shown in Figure 1, the four alphahelical transmembrane domains (M1–M4) flank two pore-forming loops (P1 and P2), each containing the potassium selective filter motif (GLG, GFG, or GYG). M1 and P1 are connected by a long extracellular loop, forming an overhead cap structure. The short amino terminus and a much longer carboxy terminus, which contains a variety of regulatory phosphorylation and protein interaction motifs, are localized intracellularly. Whereas most potassium channels form tetramers with one pore-forming loop per subunit, a functional two-pore domain potassium channel is composed of two alpha subunits (Figure 1). In addition to homodimerization, certain K2P channel subunits can also assemble as heterodimers. This is mainly described within the same subfamilies (i.e., TASK-1/TASK-3, TREK-1/TRAAK, THIK-1/THIK-2), but can also occur between TWIK-1 and TREK or TASK-1, and between TASK-1/TALK-2 subunits. Physiological relevance in the perception of hypoxia has been described for TASK-1/TASK-3 heterodimers and TWIK-1/TREK-1 heterodimers have been detected in astrocytes. Apart from the TASK-1 and TALK-1 subfamilies, all K2P channel subunits possess a conserved Cys-amino acid residue of the overhead domain that is thought to play a major, although not yet conclusively elucidated, role in dimerization. The predicted membrane topology and tertiary structure have already been confirmed by X-ray structural analysis for several K2P-channels (Table 1).
| Gene Name | IUPHAR K₂P Nomenclature | Functional Name | Other Names | Crystal Structure |
|-----------|-------------------------|----------------|-------------|------------------|
| KCNK1     | K₂P1.1                  | TWIK-1         | hOHO, DPK, KCNO1 | ![Crystal Structure](image1.jpg) |
| KCNK2     | K₂P2.1                  | TREK-1         | TPKC1       | ![Crystal Structure](image2.jpg) |
| KCNK3     | K₂P3.1                  | TASK-1         | TBAK-1, OAT-1, PPH4 | ![Crystal Structure](image3.jpg) |
| KCNK4     | K₂P4.1                  | TRAAK          | FHEIG       | ![Crystal Structure](image4.jpg) |
| KCNK5     | K₂P5.1                  | TASK-2         |            | ![Crystal Structure](image5.jpg) |
| KCNK6     | K₂P6.1                  | TWIK-2         | TOSS        | -                |
| KCNK7     | K₂P7.1                  | TWIK-3         |            | -                |

The name *kcnk8* was initially given to a murine K₂P gene which was later identified as an ortholog of the human KCNK7 gene and therefore renamed to *kcnk7*.

| Gene Name | IUPHAR K₂P Nomenclature | Functional Name | Other Names | Crystal Structure |
|-----------|-------------------------|----------------|-------------|------------------|
| KCNK9     | K₂P9.1                  | TASK-3         | KT3.2, BIBARS, TASK32 | -                |
| Gene Name | IUPHAR K_{2P} Nomenclature | Functional Name | Other Names | Crystal Structure |
|-----------|-----------------------------|-----------------|-------------|------------------|
| KCNK10    | K_{2P}10.1                  | TREK-2          | PPP1R97     |                  |
| KCNK12    | K_{2P}12.1                  | THIK-2          | -           |                  |
| KCNK13    | K_{2P}13.1                  | THIK-1          | -           |                  |

*KCNK11 was withdrawn due to nomenclature duplications with KCNK15*

| Gene Name | IUPHAR K_{2P} Nomenclature | Functional Name | Other Names | Crystal Structure |
|-----------|-----------------------------|-----------------|-------------|------------------|
| KCNK15    | K_{2P}15.1                  | TASK-5          | KT3.3, dJ781B1.1 |                  |
| KCNK16    | K_{2P}16.1                  | TALK-1          | -           |                  |
| KCNK17    | K_{2P}17.1                  | TALK-2          | TASK-4      |                  |
| KCNK18    | K_{2P}18.1                  | TRESK           | MGR13, TRIK, TRESK2 |                  |

*KCNK14 was withdrawn due to nomenclature duplications with KCNK15*

Upon their discovery, the individual K_{2P}-channels received trivial names reflecting their respective structural and regulatory properties: TWIK: “Tandem of P domains in a weak inward rectifying K\(^+\) channel”, TREK: “TWIK-related K\(^+\) channel”, TASK: “TWIK-related acid-sensitive K\(^+\) channel”, TRAAK: “TWIK-related arachidonic acid activated K\(^+\) channel”, TALK “TWIK-related alkaline pH-activated K\(^+\) channel”, THIK “tandem pore domain halothane-inhibited K\(^+\) channel”, and TRESK “TWIK-related spinal cord K\(^+\) channel”. In parallel, the channels are labeled consecutively with the designations K_{2P}1.1 to K_{2P}18.1 according to the Human Genome Organization name of the encoding gene (KCNK1 to KCNK18) (see Figure 2 and Table 1). Each of the 15 subfamilies members (K_{2P}1.1 to K_{2P}18.1) contains only one member. Unfortunately, this led to a confusing nomenclature in which channels with different functional properties such as TASK-1 and TASK-2 have similar names, while other channels are titled with acronyms of factually incorrect names (for example, TWIK-1 is not a weak inward rectifier but an open rectifier). Further, some channels carry a variety of redundant names such as in case of K_{2P}3.1: TBAK1, TASK1 and OAT1. Several KCNKx designators were initially assigned to K_{2P} channel transcripts that later turned out to be orthologs of other human K_{2P} channels. Thus, KCNK8 (the murine transcript designated kcnk8 later proved to be an ortholog of human KCNK7 and was therefore renamed kcnk7), KCNK11, and KCNK14 (both orthologs ...
of KCNK15) do not exist [9]. For better understanding, we will provide the trivial names of the channel subunits in brackets in addition to the International Union of Basic and Clinical Pharmacology IUPHAR (K_{2P}X.1) names. Since they do not show any functional activity in heterologous expression systems, the channels KCNK7, KCNK12 and KCNK15 are referred to as silent K_{2P} channels. It remains unclear whether these K_{2P} channel subunits are truly nonfunctional in vivo or whether they just lack essential cofactors to achieve functionality upon heterologous expression. In fact, the functionality of the K_{2P}16.1 channels could be restored by deletion of an n-terminal ER-retention motif [8].

3. K_{2P}1.1 (TWIK-1)

Robust cardiac mRNA levels were consistently described for KCNK1 [10–15]. In a study from our laboratory, which examined the expression of all K_{2P} channels in the human heart (TaqMan-qPCR; Figure 2), the highest mRNA levels were detected for KCNK1 [10]. Atrial predominant mRNA abundance was shown in patient-derived tissue samples but not in rodents (Table 2) [10,16].

Table 2. Evidence in literature for cardiac expression of K_{2P} channel subunits at mRNA or protein level in different species.

| K_{2P} Channel Subunit | Species | mRNA / mRNA | Observation | Citation |
|------------------------|---------|--------------|-------------|---------|
|                        |         | mRNA (RT-PCR, ISH) | Ubiquitous kcnk1a and kcnk1b ortholog mRNA in embryonic heart | [11] |
| Zebrafish              | Mouse   | mRNA (RT-PCR) | No cardiac mRNA abundance | [17] |
| Mouse                  | Mouse   | mRNA (RT-qPCR, TaqMan) | Moderate cardiac mRNA abundance, V > A | [16] |
|                       | Rat     | mRNA (RT-PCR) | Moderate cardiac mRNA abundance, A > V | [18] |
|                       | Rat     | mRNA (RT-qPCR, TaqMan) | Moderate cardiac mRNA abundance | [15] |
|                       | Rat     | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance mRNA detected in sinoatrial tissue | [19] |
|                       | Human   | mRNA (NB) | Cardiac mRNA abundance | [20] |
|                       | Human   | mRNA (RT-PCR) | Cardiac mRNA abundance, V > A | [21] |
|                       | Human   | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance, A > V | [10] |
|                       | Human   | mRNA (RT-qPCR) | Highest mRNA level among all K_{2P} channels | [25] |
|                       | Human   | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance, A > Purkinje fibers > V | [12] |
|                       | Human   | mRNA (RT-qPCR, TaqMan) | mRNA detected in human ventricular tissue | [22] |
|                       | Human   | mRNA (RT-qPCR) | mRNA detected in iPS-derived cardiomyocytes | [22] |
|                       | Human   | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance | [23] |
|                       | Human   | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance | [14] |
|                       | Mouse   | mRNA (NB) | Cardiac mRNA abundance | [24] |
|                       | Mouse   | mRNA (RT-PCR) | Cardiac mRNA abundance, V > A | [17] |
|                       | Mouse   | mRNA (RT-PCR) | Cardiac mRNA abundance | [25] |
|                       | Mouse   | mRNA (RT-qPCR) and protein (WB) | Cardiac mRNA abundance, V > A | [26] |
Table 2. Cont.

| K2p Channel Subunit | Species | Protein /mRNA | Observation | Citation |
|---------------------|---------|---------------|-------------|----------|
| Mouse               | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA levels, V > A | [16] |
| Mouse               | Protein (IF) | Protein expression in isolated ventricular cardiomyocytes | [27] |
| Rat                 | mRNA (RT-PCR) | mRNA abundance in isolated ventricular cardiomyocytes | [28] |
| Rat                 | mRNA (RT-PCR) | Cardiac mRNA abundance, A and V | [18] |
| Rat                 | mRNA (RT-PCR) | Cardiac mRNA abundance, A and V | [29] |
| Rat                 | mRNA (RT-PCR) | Endocardial mRNA levels > epicardial mRNA expression | [30] |
| Rat                 | mRNA (RT-PCR) | Cardiac mRNA levels, mRNA detected in cardiomyocytes | [15] |
| Rat                 | mRNA (RT-PCR) | Cardiac mRNA abundance | [31] |
| Rat                 | mRNA (RT-qPCR) | Cardiac mRNA abundance, Cardiac mRNA adult heart > fetal heart | [18] |
| Rat                 | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance in sinoatrial tissue | [19] |
| Rat                 | mRNA (RT-PCR) and protein (IF) | Cardiac mRNA abundance, A and V Protein expression in isolated cardiomyocytes | [32] |
| Rat                 | mRNA (RT-PCR) and protein (IF) | mRNA and protein expression in rat cardiomyocytes | [33] |
| Rat                 | mRNA (RT-PCR) and protein (WB, IF) | Cardiac mRNA and protein expression, A and V | [34] |
| Rabbit, mouse       | Protein (WB) | Cardiac protein expression, SAN > A > V | [35] |
| Pig                 | mRNA (RT-qPCR, TaqMan) and protein (WB) | Cardiac mRNA and protein expression, V = A mRNA and protein expression in sinoatrial and atrioventricular node | [36] |
| Pig, human          | mRNA (RT-qPCR, TaqMan) | Atrial mRNA expression in human and pig | [37] |
| Human               | mRNA (RT-PCR) | Cardiac mRNA abundance | [31] |
| Human               | mRNA (RT-PCR) | Low cardiac mRNA abundance | [38] |
| Human               | mRNA (RT-PCR) | Low cardiac mRNA abundance | [39] |
| Human               | mRNA (RT-qPCR) | Cardiac mRNA abundance, V Low mRNA abundance in iPS-derived cardiomyocytes | [22] |
| Human               | mRNA (RT-qPCR) | Cardiac mRNA abundance | [39] |
| Human               | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance, V > A | [10] |
| Human               | mRNA (RT-qPCR, TaqMan) | Low cardiac mRNA abundance | [23] |
| Human               | mRNA (RT-PCR, TaqMan) | Cardiac mRNA levels, V > A | [40] |
| Human, mouse        | mRNA (RT-qPCR, TaqMan) and protein (WB) | Cardiac mRNA and protein expression in human and mice, V > A | [41] |
| Human               | Protein (WB) | Cardiac protein expression | [42] |
| Human               | Protein (WB) | Cardiac protein expression | [43] |
Table 2. Cont.

| K2P Channel Subunit | Species | Protein /mRNA | Observation | Citation |
|---------------------|---------|---------------|-------------|----------|
|                     | Chicken embryo | mRNA (ISH) and protein (IF) | Cardiac mRNA and protein expression in chicken embryos | [44] |
|                     | Mouse, human | mRNA (NB) | Human and Mouse: Cardiac mRNA abundance | [45] |
|                     | Mouse | mRNA (RT-PCR) | Cardiac mRNA abundance | [17] |
|                     | Mouse | mRNA (RT-qPCR) | Cardiac mRNA levels, V > A | [26] |
|                     | Mouse | mRNA (RT-PCR) and protein (WB) | Cardiac protein expression | [25] |
|                     | Mouse, human | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA expression | [46] |
|                     | Mouse | mRNA (RT-qPCR, TaqMan) and protein (WB) | Cardiac mRNA and protein expression, A and V | [16] |
|                     | Rat | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance in sinoatrial tissue | [19] |
|                     | Rat | mRNA (NB, RT-PCR) | Cardiac mRNA abundance, A and V | [47] |
|                     | Rat | mRNA (RT-PCR) | Cardiac mRNA abundance, cardiomyocyte mRNA abundance | [15] |
|                     | Rat | mRNA (RT-PCR) | Cardiac mRNA abundance | [48] |
|                     | Rat, guinea pig, human | mRNA (RT-qPCR, TaqMan) | Human: Cardiac mRNA levels, V > A Rat: Cardiac mRNA abundance, A and V Guinea pig: Cardiac mRNA levels, V > A | [49] |
|                     | Dog | Protein (WB) | Atrial protein expression | [50] |
|                     | Pig | mRNA (RT-qPCR, TaqMan) and protein (WB) | Cardiac mRNA and protein expression mRNA abundance in sinoatrial and atrioventricular node | [51] |
|                     | Pig | mRNA (RT-qPCR, TaqMan) and protein (WB) | Cardiac mRNA and protein expression | [52] |
|                     | Human | mRNA (RT-qPCR) | Low cardiac mRNA abundance | [38] |
|                     | Human | mRNA (RT-qPCR) | mRNA abundance in Purkinje fibers | [5] |
|                     | Human | mRNA (RT-qPCR) | Cardiac mRNA abundance | [14] |
|                     | Human | mRNA (RT-qPCR) | Cardiac mRNA levels, A > V | [23] |
|                     | Human | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance | [22] |
|                     | Human | mRNA (RT-qPCR, TaqMan) | Low mRNA abundance in human ventricular tissue mRNA abundance in iPS-derived cardiomyocytes | [22] |
|                     | Human | mRNA (RT-qPCR, TaqMan) | mRNA levels in isolated atrial cardiomyocytes > in isolated atrial fibroblasts | [53] |
|                     | Human | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance | [23] |
|                     | Human | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA levels, A > V | [54] |
|                     | Human | mRNA (Affymetrix chip and RT-qPCR, TaqMan) | Cardiac mRNA abundance, A | [55] |
|                     | Human | mRNA (Affymetrix chip and RT-qPCR, TaqMan) | Cardiac mRNA levels, A > V Expression in Purkinje fibers | [14] |
| K_2P Channel Subunit | Species | Protein /mRNA | Observation | Citation |
|----------------------|---------|---------------|-------------|----------|
|                      | Human   | mRNA (Affymetrix chip and RT-qPCR, TaqMan) | Cardiac mRNA expression, A > V | [12]     |
|                      | Human   | mRNA (RT-qPCR) and protein (IF) | Cardiac mRNA and protein expression | [56]     |
|                      | Human   | mRNA (RT-qPCR, TaqMan) and protein (WB) | Cardiac mRNA levels, A > V Cardiac protein expression, A | [40]     |
|                      | Human   | mRNA (RT-qPCR, TaqMan) and protein (WB) | Cardiac mRNA levels, A > V Cardiac protein expression, A | [10]     |
|                      | Human   | mRNA (bulk RNAseq) | Cardiac mRNA levels, A > V | [57]     |
| Mouse | mRNA (RT-PCR, NB) | Human: no cardiac mRNA detectable | | [58]     |
| Mouse | mRNA (RT-qPCR) | Mouse: Low cardiac mRNA abundance, A > V | | [41]     |
| Mouse | mRNA (qRT-PCR) and protein (WB) | Cardiac mRNA abundance | | [26]     |
| Mouse | mRNA (RT-PCR, TaqMan) | No cardiac mRNA levels detectable | | [16]     |
| Rat | mRNA (RT-PCR) | No cardiac mRNA levels | | [15]     |
| Rat | mRNA (RT-PCR) | Low cardiac mRNA levels, A and V | | [18]     |
| Human | mRNA (RT-qPCR) | mRNA abundance in human ventricular tissue mRNA abundance in iPSC-derived cardiomyocytes | | [22]     |
| Human | mRNA (RT-qPCR) | Low cardiac mRNA levels | | [59]     |
| Human | mRNA (RT-qPCR, TaqMan) | Very low cardiac mRNA levels | | [10]     |
| Human | mRNA (RT-qPCR, TaqMan) | No cardiac mRNA abundance | | [23]     |
| Mouse | mRNA (RT-PCR) | Cardiac mRNA abundance | | [17]     |
| Mouse | mRNA (RT-PCR) | Cardiac mRNA levels, A and V | | [26]     |
| Mouse | mRNA (RT-qPCR) | Low cardiac mRNA abundance | | [25]     |
| Mouse | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA levels, A > V | | [16]     |
| Rat | mRNA (NB) | No cardiac mRNA abundance | | [60]     |
| Rat | mRNA (RT-PCR) | Low cardiac mRNA levels, A and V | | [18]     |
| Rat | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance in sinoatrial tissue | | [19]     |
| Human | mRNA (RT-PCR) | Cardiac mRNA abundance | | [61]     |
| Human | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance | | [23]     |
| Human | mRNA (RT-qPCR) | mRNA abundance in human ventricular tissue mRNA abundance in iPSC-derived cardiomyocytes | | [22]     |
| Human | mRNA (RT-qPCR) | Cardiac mRNA abundance | | [56]     |
| Human | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA levels, A > V | | [10]     |
| $K_{2p}$ Channel Subunit | Species                     | Protein /mRNA                          | Observation                                                                 | Citation |
|--------------------------|----------------------------|----------------------------------------|----------------------------------------------------------------------------|----------|
| $K_{2p6.1}$ (TWIK-2)     | Human                      | mRNA (Affymetrix chip and RT-qPCR, TaqMan) | Cardiac mRNA levels, A > V mRNA abundance in Purkinje fibers              | [14]     |
|                          | Human                      | mRNA (RT-qPCR) and protein (WB)        | Very low cardiac mRNA levels Detectable protein levels                    | [38]     |
|                          | Mouse                      | mRNA (RT-qPCR, TaqMan)                 | Moderate cardiac mRNA abundance, A and V                                  | [16]     |
|                          | Mouse                      | mRNA (RT-qPCR) and protein (WB)        | Low cardiac mRNA abundance, A and V Cardiac protein expression            | [26]     |
|                          | Rat                        | mRNA (RT-PCR)                          | Cardiac mRNA abundance                                                   | [18]     |
|                          | Rat                        | mRNA (RT-PCR)                          | Cardiac mRNA abundance                                                   | [62]     |
|                          | Rat                        | mRNA (RT-PCR)                          | Moderate cardiac mRNA abundance                                          | [15]     |
|                          | Rat                        | mRNA (RT-qPCR, TaqMan)                 | Cardiac mRNA abundance in sinoatrial tissue                             | [19]     |
|                          | Human                      | mRNA (NB)                              | No cardiac mRNA abundance                                               | [17]     |
|                          | Human                      | mRNA (Hybridization array)             | Cardiac mRNA levels, V > A                                              | [62]     |
|                          | Human                      | mRNA (RT-qPCR)                         | mRNA abundance in human ventricular tissue mRNA abundance in iPS-derived cardiomyocytes | [22]     |
|                          | Human                      | mRNA (RT-qPCR, TaqMan)                 | Low cardiac mRNA abundance                                               | [23]     |
|                          | Human                      | mRNA (RT-qPCR, TaqMan)                 | Cardiac mRNA levels, V > A                                              | [10]     |
| $K_{2p7.1}$ (TWIK-3)     | Mouse                      | mRNA (RT-qPCR, TaqMan)                 | No cardiac mRNA abundance detectable                                     | [16]     |
|                          | Human                      | mRNA (RT-qPCR)                         | Cardiac mRNA abundance                                                   | [63]     |
|                          | Human                      | mRNA (RT-qPCR, TaqMan)                 | Cardiac mRNA abundance                                                   | [23]     |
|                          | Human                      | mRNA (RT-qPCR, TaqMan)                 | Very low cardiac mRNA levels, A > V                                      | [10]     |
| $K_{2p9.1}$ (TASK-3)     | Mouse                      | mRNA (RT-qPCR, TaqMan)                 | No cardiac mRNA abundance detectable                                     | [16]     |
|                          | Mouse                      | mRNA (RT-qPCR)                         | Low cardiac mRNA abundance                                               | [26]     |
|                          | Mouse                      | mRNA (RT-PCR)                          | Low cardiac mRNA abundance                                               | [25]     |
|                          | Rat                        | mRNA (RT-PCR)                          | Low cardiac mRNA abundance, A and V                                      | [18]     |
|                          | Rat                        | mRNA (RT-PCR)                          | Cardiac mRNA abundance                                                   | [48]     |
|                          | Rat                        | mRNA (RT-PCR)                          | Cardiac mRNA abundance, cardiomyocyte mRNA expression                   | [15]     |
|                          | Rat, guinea pig, human     | mRNA (RT-qPCR, TaqMan)                 | Human: very low cardiac mRNA abundance                                   | [49]     |
|                          |                             |                                        | Rat: no cardiac mRNA abundance                                          |          |
|                          |                             |                                        | Guinea pig: low cardiac mRNA abundance, V > A                           |          |
|                          | Guinea pig                 | mRNA (RT-PCR)                          | No cardiac mRNA abundance                                               | [64]     |
| \(K_{2p}\) Channel Subunit | Species | Protein /mRNA | Observation | Citation |
|----------------------------|---------|---------------|-------------|---------|
|                            | Human   | mRNA (RT-qPCR) | Moderate mRNA abundance in human ventricular tissue mRNA abundance in iPS-derived cardiomyocytes | [22] |
|                            | Human   | mRNA (RT-qPCR, TaqMan) | Very low cardiac mRNA levels, A > V | [10] |
|                            | Human   | mRNA (RT-qPCR, TaqMan) | Cardiac mRNA abundance | [23] |
|                            | Human   | mRNA (RT-qPCR) an protein (IF) | Strong cardiac mRNA and protein expression | [56] |
| \(K_{2p10.1}\) (TREK-2)  | Mouse   | mRNA (RT-qPCR, TaqMan) | No cardiac mRNA abundance detectable | [16] |
|                            | Rat     | mRNA (RT-PCR) | Cardiac mRNA levels, A > V | [18] |
|                            | Rat     | mRNA (RT-PCR) | Moderate cardiac abundance | [15] |
|                            | Rat     | mRNA (RT-PCR, NB) | No cardiac mRNA abundance | [65] |
|                            | Human   | mRNA (RT-qPCR) | mRNA abundance in human ventricular tissue mRNA abundance in iPS-derived cardiomyocytes | [22] |
|                            | Human   | mRNA (RT-qPCR, TaqMan) | Mild cardiac mRNA abundance, A > V | [41] |
|                            | Human   | mRNA (RT-qPCR, TaqMan) | Low cardiac mRNA abundance | [23] |
|                            | Human   | mRNA (RT-qPCR, TaqMan) | Low cardiac mRNA levels, A > V | [10] |
| \(K_{2p12.1}\) (THIK-2)  | Mouse   | mRNA (RT-PCR) | Very low cardiac mRNA abundance | [15] |
|                            | Mouse   | mRNA (RT-qPCR, TaqMan) | No cardiac mRNA levels detectable | [16] |
|                            | Rat     | mRNA (RT-PCR) | No cardiac mRNA abundance | [66] |
|                            | Human   | mRNA (NB) | Cardiac mRNA abundance | [67] |
|                            | Human   | mRNA (RT-qPCR, TaqMan) | Very low cardiac mRNA abundance, A and V | [10] |
| \(K_{2p13.1}\) (THIK-1)  | Zebrafish | mRNA (RT-PCR) | Cardiac mRNA abundance | [68] |
|                            | Mouse   | mRNA (RT-PCR) | Cardiac mRNA abundance | [15] |
|                            | Mouse   | mRNA (RT-qPCR) | Cardiac mRNA abundance | [26] |
|                            | Mouse   | mRNA (RT-qPCR, TaqMan) | Very low cardiac mRNA abundance | [16] |
|                            | Rat     | mRNA (RT-PCR) | Cardiac mRNA abundance | [66] |
|                            | Human   | mRNA (RT-qPCR) | mRNA abundance in human ventricular tissue mRNA abundance in iPS-derived cardiomyocytes | [22] |
|                            | Human   | mRNA (RT-qPCR, TaqMan) | Low cardiac mRNA abundance | [23] |
|                            | Human   | mRNA (RT-qPCR, TaqMan) | Low cardiac mRNA abundance, A > V | [10] |
| \(K_{2p15.1}\) (TASK-5)  | Mouse   | mRNA (RT-qPCR) | Cardiac mRNA abundance | [26] |
|                            | Mouse   | mRNA (RT-qPCR, TaqMan) | Very low cardiac mRNA abundance | [16] |
|                            | Rat     | mRNA (RT-PCR) | No cardiac mRNA abundance | [48] |
Table 2. Cont.

| $K_2P$ Channel Subunit | Species       | Protein/mRNA                  | Observation                                                                 | Citation |
|------------------------|---------------|------------------------------|----------------------------------------------------------------------------|----------|
|                        | Rat           | mRNA (RT-PCR)                | Moderate cardiac abundance                                                  | [15]     |
|                        | Human         | mRNA (RT-PCR)                | Cardiac mRNA abundance                                                     | [69]     |
|                        | Human         | mRNA (RT-PCR, NB)            | No cardiac mRNA abundance                                                  | [70]     |
|                        | Human         | mRNA (RT-qPCR, TaqMan)       | Low cardiac mRNA abundance, A and V                                        | [10]     |
| $K_{2p}16.1$ (TALK-1)  | Rat           | mRNA (NB)                    | No cardiac mRNA abundance                                                  | [60]     |
|                        | Rat           | mRNA (RT-PCR)                | Moderate cardiac abundance                                                  | [15]     |
|                        | Human         | mRNA (NB)                    | No cardiac mRNA abundance                                                  | [67]     |
|                        | Human         | mRNA (RT-PCR, NB)            | No cardiac mRNA abundance                                                  | [71]     |
|                        | Human         | mRNA (RT-qPCR, TaqMan)       | Very low cardiac mRNA abundance, A and V                                   | [10]     |
|                        | Zebrafish     | mRNA (RT-PCR)                | No cardiac abundance                                                       | [72]     |
|                        | Rat           | mRNA (NB)                    | Cardiac mRNA abundance                                                     | [60]     |
|                        | Human         | mRNA (NB)                    | Cardiac mRNA abundance                                                     | [67]     |
|                        | Human         | mRNA (RT-PCR)                | Cardiac mRNA levels, A > V                                                 | [73]     |
|                        | Human         | mRNA (RT-qPCR)               | mRNA abundance in human ventricular tissue                                 | [22]     |
|                        | Human         | mRNA (RT-qPCR)               | Cardiac mRNA abundance                                                     | [56]     |
|                        | Human         | mRNA (RT-qPCR)               | Cardiac mRNA abundance                                                     | [5]      |
|                        | Human         | mRNA (RT-qPCR, TaqMan)       | mRNA abundance in sinoatrial and atrioventricular node Purkinje fibers > A > V | [5]      |
| $K_{2p}17.1$ (TALK-2)  | Human         | mRNA (RT-qPCR)               | Cardiac mRNA and protein abundance                                         | [74]     |
|                        | Human         | mRNA (RT-qPCR, TaqMan)       | Cardiac mRNA levels, A > V                                                 | [10]     |
|                        | Human         | mRNA (RT-qPCR, TaqMan) and protein (WB) | Cardiac mRNA and protein expression                                     | [40]     |
|                        | Human         | Protein (WB)                 | Cardiac protein expression, A                                              | [75]     |
|                        | Zebrafish     | mRNA (ISH)                   | No cardiac abundance                                                       | [76]     |
|                        | Mouse         | mRNA (RT-qPCR, TaqMan)       | Very low cardiac mRNA abundance                                            | [77]     |
|                        | Mouse         | mRNA (RT-qPCR, TaqMan)       | Very low cardiac mRNA abundance                                            | [16]     |
|                        | Human         | mRNA (RT-PCR)                | No cardiac mRNA abundance                                                  | [61]     |
|                        | Human         | mRNA (RT-PCR)                | No cardiac mRNA abundance                                                  | [78]     |
|                        | Human         | mRNA (RT-qPCR, TaqMan)       | Very low cardiac mRNA abundance                                            | [10]     |

A, expression in atrial tissue; IF, immunofluorescence; iPS, induced pluripotent stem cell; ISH, in situ hybridization; LA, left atrium; NB, Northern blot; RT-PCR, reverse transcriptase PCR; RT-qPCR, reverse transcriptase quantitative PCR; RA, right atrium; TAC, transverse aortic constriction; TaqMan, reverse transcriptase quantitative PCR employing TaqMan® hydrolyse probes to increase specificity; V, expression in ventricular tissue; WB, Western blot.
The zebrafish possess two orthologues of the human KCNK1 gene, kcnk1a and kcnk1b which, most likely as the result of an ancient genome duplication, both encode functional TWIK-1 channels. Knockdown of kcnk1a or kcnk1b in zebrafish embryos resulted in a phenotype atrial dilatation and bradycardia, suggesting a role of K2P1.1 (TWIK-1) in regulation of sinus node function and structural heart development [11]. Further, downregulation of cardiac Kcnk1 mRNA levels was reported in a diabetic rat model, displaying again a phenotype of sinus bradycardia [19]. The presence of single nucleotide polymorphisms in the KCNK1 gene might be correlated with the prevalence of coronary artery disease [79]. Christensen et al. reported the identification of three non-synonymous KCNK1 gene variants (p.R171H, p.I98M, and p.G236S) in a cohort of 373 atrial fibrillation (AF) patients. Although these variants are localized in highly conserved domains, no effect on potassium current, reversal potential, or subcellular localization was detected in heterologous expression systems [11]. Pharmacological modulation of homodimeric K2P1.1 (TWIK-1) channels by quinine and quinidine was described (Table 3) [20]. In our own studies, AF and heart failure patients showed unchanged cardiac KCNK1 mRNA levels [10,40], while others reported upregulation of KCNK1 mRNA patients with atrial dilatation [11] or Brugada syndrome [80], downregulation of KCNK1 mRNA in AF [12] or mitral valve disease [81].

| K2P Channel | Drug/Compound | Effect (Organism) | EC50/IC50 (Organism) | Citation |
|-------------|---------------|------------------|----------------------|----------|
| **K2P1.1** (TWIK-1) | Quinine | Inhibition (XO) | 50 µM (XO) | [20] |
| | Quinidine | Inhibition (XO) | 95 µM (XO) | [20] |
| | Barium | Inhibition (XO) | 100 µM (XO) | [20] |
| | Charybdotoxin | < 10% inhibition at 3 nM (XO) | n.m. | [20] |
| | Dendrotoxin | < 10% inhibition at 100 nM (XO) | n.m. | [20] |
| | Apamin | < 10% inhibition at 300 nM (XO) | n.m. | [20] |
| | Clofilium | < 10% inhibition at 30 µM (XO) | n.m. | [20] |
| | Gilbenclamid | < 10% inhibition at 30 µM (XO) | n.m. | [20] |
| | Cromakalim | No effect at 100 µM (XO) | n.m. | [20] |
| | Tedisamil | 30% inhibition at 100 µM (XO) | n.m. | [20] |
| | Dronedarone | No significant effect at 100 µM (XO) | n.m. | [82] |
| | Amiodarone | < 10% inhibition at 100 µM (XO) | n.m. | [20] |
| | Pinacidil | No effect at 100 µM (XO) | n.m. | [20] |
| | Vernakalant | No significant effect at 100 µM (XO) | n.m. | [83] |
| | Flecaïnide | No significant effect at 100 µM (XO) | n.m. | [84] |
| | Genistein | No significant effect at 100 µM (XO) | n.m. | [85] |
| | 4-AP | < 10% inhibition at 1 mM (XO) | n.m. | [20] |
| | TEA | 30% inhibition at 10 mM (XO) | n.m. | [20] |
| | GI-530159 | High affinity K2P2.1 activator (MC) | 890 nM (MC) | [86] |
| | Copper | Activation (MC) | 3 µM (MC) | [87] |
| | Ostruthin | Activator (MC) | 5.3 µM (MC) | [88] |
| | BL-1249 | High affinity TREK-1/2 activator (XO) | 5.5 µM (XO) | [89] |
| | ML402 | High affinity TREK-1/2 activator (XO) | 13.7 µM (XO) | [90] |
| | ML335 | High affinity TREK-1/2 activator (XO) | 14.3 µM (XO) | [90] |
| | ML67-33 | High affinity TREK-1/2 activator (XO) | 36.3 µM (XO); 9.7 µM (MC) | [91] |
| | Pranlukast | 66.4% activation at 3 µM (MC) | n.m. | [92] |
| | DCPiB | ~3-fold activation at 10 µM (MC) | n.m. | [93] |
| K<sub>2P</sub> Channel | Drug/Compound | Effect (Organism) | EC<sub>50</sub> / IC<sub>50</sub> (Organism) | Citation |
|----------------------|---------------|------------------|--------------------------------------|----------|
| Morphine             | ~2-fold activation at 10 µM (MC) | n.m.             | [94]                                 |
| Flufenamic acid      | ~4-fold activation at 100 µM (MC) | n.m.             | [95]                                 |
| Niflumic acid        | ~2.5-fold activation at 100 µM (MC) | n.m.             | [95]                                 |
| Mefenamic acid       | ~2-fold activation at 100 µM (MC) | n.m.             | [95]                                 |
| Carbamazepine        | 42% activation at 100 µM (MC) | n.m.             | [96]                                 |
| Valproate            | 28% activation at 100 µM (MC) | n.m.             | [96]                                 |
| Gabapentin           | 25% activation at 100 µM (MC) | n.m.             | [96]                                 |
| Diethyl ether        | ~1.75-fold activation at 600 µM (MC) | n.m.             | [97]                                 |
| Chloroform           | ~3.5-fold activation at 800 µM (MC) | n.m.             | [97]                                 |
| Lithium              | 31% activation at 1 mM (MC) | n.m.             | [96]                                 |
| Rubidium             | 27% activation at 1 mM (MC) | n.m.             | [96]                                 |
| Halothane            | ~1.4-fold activation at 1 mM (MC) | n.m.             | [97]                                 |
| Isoflurane           | ~1.5-fold activation at 2 mM (MC) | n.m.             | [97]                                 |
| Cyclopropane         | ~30% activation at 10% (MC) | n.m.             | [98]                                 |
| Xenon                | ~30% activation at 80% (MC) | n.m.             | [98]                                 |
| Nitrous oxide        | ~30% activation at 80% (MC) | n.m.             | [98]                                 |
| Spadin               | High affinity K<sub>2P</sub>2.1 inhibitor (MC) | 40 nM (MC) | [99]                                 |
| Amlodipine           | Inhibition (MC)              | 430 nM (MC)      | [100]                                |
| Nigludipine          | Inhibition (MC)              | 750 nM (MC)      | [100]                                |
| Pimozide             | Inhibition (MC)              | 1.8 µM (MC)      | [101]                                |
| Fluphenthixol        | Inhibition (MC)              | 2.0 µM (MC)      | [101]                                |
| Chlorpromazine       | Inhibition (MC)              | 2.7 µM (MC)      | [96,101]                             |
| Sipatrigine          | 73.3% inhibition at 10 µM (MC) | 4 µM             | [59]                                 |
| Fluphenazine         | Inhibition (MC)              | 4.7 µM (MC)      | [101]                                |
| Haloperidol          | Inhibition (MC)              | 5.5 µM (MC)      | [101]                                |
| Norfluoxetine        | Inhibition (MC)              | 9 µM (MC)        | [102]                                |
| Vernakalant          | Inhibition (MC)              | 13.3 µM (MC)     | [84]                                 |
| Losapine             | Inhibition (MC)              | 19.7 µM (MC)     | [101]                                |
| Fluoxetine           | Inhibition (MC)              | 19–37.9 µM (MC)  | [96,102]                             |
| Carvedilol           | Inhibition (XO, MC)          | 20.3 µM (XO); 1.6 µM (MC) | [42]                  |
| A1899 (High affinity K<sub>2P</sub>3.1 inhibitor) | Inhibition (XO) | 23.8 µM (XO) | [103]                                |
| Dronedarone          | Inhibition (XO, MC)          | 26.7 µM (XO); 6.1 µM (MC) | [82]                       |
| Propafenone          | Inhibition (XO, MC)          | 51.0 µM (XO); 7.9 µM (MC) | [104]                          |
| Levobupivacaine      | Inhibition (MC)              | 126 µM (MC)      | [105]                                |
| Diltiazem            | Inhibitor (MC)               | 180 µM (MC)      | [95]                                 |
| Lidocaine            | Inhibition (MC)              | 207 µM (MC)      | [106]                                |
| Bupivacaine          | Inhibition (MC)              | 370 µM (MC)      | [107]                                |
| Caffeine             | Inhibition (MC)              | 377 µM (MC)      | [108]                                |
| Ropivacaine          | Inhibition (MC)              | 402 µM (MC)      | [105]                                |
| Theophylline         | Inhibition (MC)              | 486 µM (MC)      | [108]                                |
| Zinc                 | Inhibition (MC)              | 659 µM (MC)      | [87]                                 |
| Mexiletine           | Inhibition (XO, MC)          | 1.3 mM (XO); 182 µM (MC); | [104]                  |
| Tetramethylammonium  | 63% inhibition (MC)          | n.m.             | [24]                                 |
| Lamotrigine          | ~10% inhibition at 10 µM (MC) | n.m.             | [59]                                 |
| K<sub>2P</sub> Channel | Drug/Compound | Effect (Organism) | EC<sub>50</sub> /IC<sub>50</sub> (Organism) | Citation |
|---------------------|---------------|------------------|---------------------------------|----------|
| Metoprolol         | ~20% inhibition at 100 µM (XO) | n.m.             | [42]                            |
| Propranolol        | ~30% inhibition at 100 µM (XO) | n.m.             | [42]                            |
| Citalopram         | 59% inhibition at 100 µM (MC)  | n.m.             | [96]                            |
| Barium             | 50% inhibition at 300 µM (XO)  | n.m.             | [24]                            |
| Ranolazine         | 7.35% inhibition at 300 µM (XO) | n.m.             | [109]                           |
| Clozapine          | Inhibition (MC)                 | n.m.             | [101]                           |
| Sulpiride          | No significant effect at 10 µM (MC) | n.m.             | [101]                           |
| Tiapride           | No significant effect at 10 µM (MC) | n.m.             | [101]                           |
| Glibenclamide      | No significant effect at 10 µM (XO) | n.m.             | [24]                            |
| Cesium             | No significant effect at 100 µM (XO) | n.m.             | [24]                            |
| Gadolineum         | No significant effect at 100 µM (XO) | n.m.             | [24]                            |
| TEA                | No significant effect at 100 µM (XO) | n.m.             | [24]                            |
| Quinine            | No significant effect at 100 µM (XO) | n.m.             | [24]                            |
| Quinidine          | No significant effect at 100 µM (XO) | n.m.             | [24]                            |
| Tedisamil          | No significant effect at 100 µM (XO) | n.m.             | [24]                            |
| Genistein          | No significant effect at 100 µM (XO) | n.m.             | [85]                            |
| Flecainide         | No significant effect at 100 µM (XO, MC) | n.m.             | [84]                            |
| Amiodarone         | No significant effect (XO)       | n.m.             | [110]                           |
| Sotalol            | No significant effect (XO)       | n.m.             | [82]                            |
| Digoxin            | No significant effect (XO)       | n.m.             | [111]                           |
| Digitoxin          | No significant effect (XO)       | n.m.             | [111]                           |
| A293               | No significant effect (XO)       | n.m.             | [10]                            |
| Ajmaline           | No significant effect (MC)       | n.m.             | [104]                           |
| GSMTx4             | No significant effect (MC)       | n.m.             | [112]                           |
| Magnesium          | No significant effect (XO)       | n.m.             | [24]                            |
| Halothane          | Activation (XO, MC)              | 300–1000 µM (XO) | [97,113,114]                    |
| Sevoflurane        | ~40% activation at 1 mM          | n.m.             | [114]                           |
| Isoflurane         | ~15% activation at 1 mM (XO)    | 20% activation at 2 mM (MC) | n.m. | [97,113] |
| BAY2341237         | High affinity K<sub>2P</sub>3.1 inhibitor | 7.6 nM (XO)  | [115]                           |
| BAY1000493         | High affinity K<sub>2P</sub>3.1 inhibitor | 9.5 nM (XO)  | [115]                           |
| ML365              | High affinity K<sub>2P</sub>3.1 inhibitor | 16 nM (MC)  | [116]                           |
| A1899 (S20951)     | High affinity K<sub>2P</sub>3.1 inhibitor | 35 nM (XO); 7 nM (MC)  | [103,115]                      |
| S9947 (K<sub>V</sub>1.5 blocker) | Inhibition (XO)                  | 200 nM (XO)     | [103,117]                      |
| A293 (AVE1231)     | High affinity K<sub>2P</sub>3.1 inhibitor | 222 nM (XO)  | [10,15]                         |
| PK-THPP            | Inhibition (XO)                  | 243 nM          | [118]                          |
| MSD-D (K<sub>V</sub>1.5 blocker) | Inhibition (XO) | 350 nM (XO)  | [117]                          |
| Amiodarone         | Inhibition (XO)                  | 400 nM (XO)     | [82,110]                      |
| Doxapram           | Inhibition (XO, MC)              | 410 nM (XO)     | [119]                          |
| AVE01118 (K<sub>V</sub>1.5 blocker) | Inhibition (XO) | 600 nM (XO)  | [117]                          |
| Methanandamide     | Inhibition (XO)                  | 700 nM (MC)     | [120]                          |
| Digoxin            | Inhibition (XO)                  | 900 nM (XO)     | [111]                          |
Table 3. Cont.

| K<sub>2P</sub> Channel | Drug/Compound | Effect (Organism) | EC<sub>50</sub> / IC<sub>50</sub> (Organism) | Citation |
|------------------------|---------------|-------------------|-------------------------------------------|----------|
| ICAGEN-4 (K<sub>v</sub>1.5 blocker) | Inhibition (XO) | 1.05 µM (XO) | [117] |
| ML308 (High affinity K<sub>2P</sub>9.1 inhibitor) | Inhibition (MC) | 3.2 µM (MC) | [121] |
| Carvedilol | Inhibition (XO, MC) | 3.8 µM (XO); 0.83 µM (MC) | [42] |
| Dicitoxin | Inhibition (XO) | 7.4 µM (XO) | [111] |
| Genistein | 81.1% inhibition at 100 µM (XO) | 12.3 µM (MC) | [85] |
| Dronedarone | Inhibition (XO, MC) | 18.7 µM (XO); 5.2 µM (MC) | [82] |
| Propafenone | Inhibition (XO, MC) | 18.1 µM (XO); 5.1 µM (MC); | [104] |
| Etidocaine | Inhibition (XO) | 39 µM (XO) | [122] |
| Ostruthin | Inhibition (MC) | 41 µM (MC) | [88] |
| R-Ropivacaine | Inhibition (XO) | 51 µM (XO) | [122] |
| S-Ropivacaine | Inhibition (XO) | 53 µM (XO) | [122] |
| Bupivacaine | Inhibition (XO) | 68 µM (XO) | [123] |
| Etomidate | Inhibition (XO) | 119 µM (XO) | [113] |
| Zinc | Inhibition (XO) | 175 µM (XO) | [123] |
| Ranolazine | Inhibition (XO, MC) | 198.4 µM (XO); 30.6 µM (MC) | [109] |
| Lidocain | Inhibition (XO) | 222 µM (XO) | [122] |
| Mexiletine | Inhibition (XO, MC) | 405 µM (XO); 97.3 µM (MC) | [104] |
| Tetracaine | Inhibition (XO) | 668 µM | [122] |
| Mepivacaine | Inhibition (XO) | 709 µM (XO) | [122] |
| Agitoxin | <15% inhibition at 1 nM (XO) | n.m. | [123] |
| Margatoxin | <15% inhibition at 10 nM (XO) | n.m. | [123] |
| Dendrotoxin | <15% inhibition at 100 nM (XO) | n.m. | [123] |
| Charybdotoxin | <15% inhibition at 200 nM (XO) | n.m. | [123] |
| Anandamide | ~90% inhibition at 3 µM (MC) | n.m. | [120] |
| CP35940 (CB1/CB2agonist) | ~50% inhibition at 10 µM (MC) | n.m. | [120] |
| Sipatrigine | 37% inhibition at 10 µM (MC) | n.m. | [59] |
| Cilbenclamide | <15% inhibition at 30 µM (XO) | n.m. | [123] |
| Propranolol | ~60% inhibition at 100 µM (XO) | n.m. | [42] |
| Cesium | 31% inhibition at 100 µM (XO) | n.m. | [45] |
| Quinidine | <20–71% inhibition at 100 µM (XO) | n.m. | [45,123] |
| Quinine | <20% inhibition at 100 µM (XO) | n.m. | [45] |
| Quinacrine | <20% inhibition at 100 µM (XO) | n.m. | [45] |
| Barium | ~19% inhibition at 100 µM (XO) | n.m. | [45] |
| Daidzein | 18.2% inhibition at 100 µM (XO) | n.m. | [85] |
| Cromakalim | <15% inhibition at 100 µM (XO) | n.m. | [123] |
| Metoprolol | ~10% inhibition at 100 µM (XO) | n.m. | [42] |
| Phenytoin | ~50% inhibition at 200 µM (XO) | n.m. | [123] |
| Diethyl ether | ~45% at 600 µM (MC) | n.m. | [97] |
| Magnesium | ~14% inhibition at 10 mM (XO) | n.m. | [123] |
| 4-AP | <15% inhibition at 10 mM (XO) | n.m. | [45,123] |
| Flecainide | No significant effect at 100 µM (XO, MC) | n.m. | [84] |
| Ouabain | No significant effect at 100 µM (XO) | n.m. | [111] |
| \(K_{2P}\) Channel | Drug/Compound | Effect (Organism) | \(EC_{50}/IC_{50}\) (Organism) | Citation |
|------------------|---------------|-------------------|-----------------|---------|
| Vernakalant      | No significant effect at 100 \(\mu\)M (XO, MC) | n.m. | [84] |
| Sotalol          | No significant effect at 100 \(\mu\)M (XO) | n.m. | [82] |
| Genistin         | No significant effect at 100 \(\mu\)M (XO) | n.m. | [85] |
| Propofol         | No significant effect at 200 \(\mu\)M (XO) | n.m. | [113] |
| Chloroform       | No significant effect at 800 \(\mu\)M (MC) | n.m. | [97] |
| TEA              | No significant effect at 1 mM (XO) | n.m. | [45] |
| Sipatrigine      | 45% inhibition at 10 \(\mu\)M (MC) | 10 \(\mu\)M | [59] |
| ML67-33          | Activation (XO, MC) | 27.3 \(\mu\)M (XO); 1.8 \(\mu\)M (MC) | [91] |
| BL-1249          | Activation (XO) | 48 \(\mu\)M (XO) | [89] |
| A1899            | Inhibition (XO) | >20 \(\mu\)M (XO) | [103] |
| Docosahexaenoate | −12-fold activation at 10 \(\mu\)M (MC) | n.m. | [58] |
| Eicosapentaenoate| −8-fold activation at 10 \(\mu\)M (MC) | n.m. | [58] |
| Arachidonic acid | −5-fold activation at 10 \(\mu\)M (MC) | n.m. | [58] |
| Oleate           | −1.5-fold activation at 10 \(\mu\)M (MC) | n.m. | [58] |
| Linoleate        | −1.5-fold activation at 10 \(\mu\)M (MC) | n.m. | [58] |
| Riluzole         | 3.9-fold activation at 100 \(\mu\)M (MC) | n.m. | [58] |
| Flufenamic acid  | −2-fold activation at 100 \(\mu\)M (MC) | n.m. | [95] |
| Niflumic acid    | −2-fold activation at 100 \(\mu\)M (MC) | n.m. | [95] |
| Mefenamic acid   | −1.6-fold activation at 100 \(\mu\)M (MC) | n.m. | [95] |
| Lamotrigine      | −10% inhibition at 10 \(\mu\)M (MC) | n.m. | [59] |
| Vernakalant      | 17.1% inhibition at 100 \(\mu\)M (XO) | n.m. | [83] |
| Barium           | 56.7% inhibition at 1 mM (XO) | n.m. | [56] |
| Charybdotoxin    | No significant effect at 20 nM (XO) | n.m. | [58] |
| Dendrotoxin      | No significant effect at 100 nM (XO) | n.m. | [58] |
| Tetrodotoxin     | No significant effect at 1 \(\mu\)M (XO) | n.m. | [58] |
| Tedisamil        | No significant effect at 10 \(\mu\)M (XO) | n.m. | [58] |
| Palmitate        | No significant effect at 10 \(\mu\)M (MC) | n.m. | [58] |
| Stearate         | No significant effect at 10 \(\mu\)M (MC) | n.m. | [58] |
| Arachidate       | No significant effect at 10 \(\mu\)M (MC) | n.m. | [58] |
| Fluphenazine     | No significant effect at 10 \(\mu\)M (MC) | n.m. | [101] |
| Chlorpromazine   | No significant effect at 10 \(\mu\)M (MC) | n.m. | [101] |
| Haloperidol      | No significant effect at 10 \(\mu\)M (MC) | n.m. | [101] |
| Flupenthixol     | No significant effect at 10 \(\mu\)M (MC) | n.m. | [101] |
| Loxapine         | No significant effect at 10 \(\mu\)M (MC) | n.m. | [101] |
| Pimozide         | No significant effect at 10 \(\mu\)M (MC) | n.m. | [101] |
| Clozapine        | No significant effect at 10 \(\mu\)M (MC) | n.m. | [101] |
| Sulpiride        | No significant effect at 10 \(\mu\)M (MC) | n.m. | [101] |
| Tiapride         | No significant effect at 10 \(\mu\)M (MC) | n.m. | [101] |
| Tolbutamide      | No significant effect at 100 \(\mu\)M (XO) | n.m. | [58] |
| Pinacidil        | No significant effect at 100 \(\mu\)M (XO) | n.m. | [58] |
| P1060            | No significant effect at 100 \(\mu\)M (XO) | n.m. | [58] |
Table 3. Cont.

| K<sub>2P</sub> Channel | Drug/Compound | Effect (Organism) | EC<sub>50</sub> /IC<sub>50</sub> (Organism) | Citation |
|------------------------|---------------|-------------------|------------------------------------------|----------|
|                        | Glibenclamide | No significant effect at 200 µM (XO) | n.m. | [58] |
|                        | Cobalt        | No significant effect at 500 µM (XO) | n.m. | [58] |
|                        | Dronedarone   | No significant effect at 100 µM (XO) | n.m. | [82] |
|                        | Flecaïnide    | No significant effect at 100 µM (XO) | n.m. | [84] |
|                        | Genistein     | No significant effect at 100 µM (XO) | n.m. | [85] |
|                        | Ranolazine    | 3.32 % inhibition at 300 µM (XO) | n.m. | [109] |
|                        | Diethyl ether | No significant effect at 600 µM (MC) | n.m. | [97] |
|                        | Chloroform    | No significant effect at 800 µM (MC) | n.m. | [97] |
|                        | Halothane     | No significant effect at 1 mM (MC) | n.m. | [97] |
|                        | Diltiazem     | No significant effect at 1 mM (MC) | n.m. | [95] |
|                        | TEA           | No significant effect at 1 mM (XO) | n.m. | [58] |
|                        | 4-AP          | No significant effect at 1 mM (XO) | n.m. | [58] |
|                        | Caesium       | No significant effect at 1 mM (XO) | n.m. | [58] |
|                        | Isoflurane    | No significant effect at 2 mM (MC) | n.m. | [97] |
|                        | Digoxin       | No significant effect (XO) | n.m. | [111] |
|                        | Digitoxin     | No significant effect (XO) | n.m. | [111] |
| K<sub>2P.5.1</sub> (TASK-2) | A293 (High affinity K<sub>2P</sub>3.1 inhibitor) | Inhibition (XO) | 8.1 nM (XO) | [10,15] |
|                        | A1899 (High affinity K<sub>2P</sub>3.1 inhibitor) | Inhibition (XO) | 12 µM (XO) | [103] |
|                        | Quinine       | Inhibition (XO) | 22.4 µM (XO) | [17] |
|                        | Quinidine     | 65% inhibition at 100 µM (XO) | n.m. | [17] |
|                        | Zinc          | 15.3% inhibition at 100 µM (XO) | n.m. | [17] |
|                        | Ranolazine    | 30.02% inhibition at 300 µM (XO) | n.m. | [17] |
|                        | Barium        | 16.9% inhibition at 1 mM (XO) | n.m. | [17] |
|                        | Lidocaine     | 60.4% inhibition at 10 mM (XO) | n.m. | [17] |
|                        | Bupivacaine   | 80.9% inhibition at 10 mM (XO) | n.m. | [17] |
|                        | Arachidonic acid | No significant effect at 10 µM (XO) | n.m. | [17] |
|                        | 4-AP          | No significant effect at 100 µM (XO) | n.m. | [17] |
|                        | Dronedarone   | No significant effect at 100 µM (XO) | n.m. | [82] |
|                        | Flecaïnide    | No significant effect at 100 µM (XO) | n.m. | [84] |
|                        | Genistein     | No significant effect at 100 µM (XO) | n.m. | [85] |
|                        | Vernakalant   | No significant effect at 100 µM (XO) | n.m. | [83] |
|                        | Digoxin       | No significant effect (XO) | n.m. | [111] |
|                        | Digitoxin     | No significant effect (XO) | n.m. | [111] |
|                        | TEA           | No significant effect at 1 mM (XO) | n.m. | [17] |
|                        | Cesium        | No effect at 1 mM (XO) | n.m. | [17] |
| K<sub>2P.6.1</sub> (TWIK-2) | Barium | Inhibition (MC) | ~100 µM (MC) | [124] |
|                        | Quinidine     | 73% inhibition at 100 µM (XO) | n.m. | [124] |
|                        | Quinine       | 73% inhibition at 100 µM (XO) | n.m. | [124] |
|                        | Genistein     | ~30% inhibition at 100 µM (XO) | n.m. | [85] |
|                        | Dronedarone   | 10.7% inhibition at 100 µM (XO) | n.m. | [82] |
|                        | Chloroform    | 32% inhibition at 300 µM (XO) | n.m. | [124] |
|                        | Halothane     | 27% inhibition at 750 µM (XO) | n.m. | [124] |
Table 3. Cont.

| K<sub>2P</sub> Channel | Drug/Compound | Effect (Organism) | EC<sub>50</sub>/IC<sub>50</sub> (Organism) | Citation |
|----------------------|--------------|-------------------|---------------------------------|----------|
| Cesium               | 92% inhibition of inward current at 10 mM (XO) | n.m.                           | [124]   |
| TEA                  | No significant effect at 5 mM (XO) | n.m.                           | [124]   |
| 4-AP                 | No significant effect at 3 mM (XO) | n.m.                           | [124]   |
| Glibenclamide        | No significant effect at 10 µM (XO) | n.m.                           | [124]   |
| Vernakalant          | No significant effect at 100 µM (XO) | n.m.                           | [83]    |
| Flecaïnide           | No significant effect at 100 µM (XO) | n.m.                           | [84]    |
| **K<sub>2P</sub>7.1** (TWIK-3) | Non-functional channel |                          |          |
| DCPIB                | −3-fold activation at 10 µM (MC) | n.m.                           | [93]    |
| Halothane            | 65.6% activation at 1 mM (XO) | n.m.                           | [125]   |
| BAY2341237           | Inhibition (XO) | 2.3 nM (XO) | [115]   |
| BAY1000493           | Inhibition (XO) | 15.1 nM (XO) | [115]   |
| A1899                | Inhibition (XO, MC) | 318 nM (XO); 70 nM (MC) | [103]   |
| **ML308**            | High affinity K<sub>2P</sub>9.1 inhibitor | 413 nM (MC) | [121]   |
| A293                 | Inhibition (XO) | 950 nM (XO) | [10,15] |
| ML365                | Inhibition (MC) | 990 nM (MC) | [116]   |
| Copper               | Inhibition (MC) | 2.7 µM (MC) | [87]    |
| Zinc                 | Inhibition (MC) | 12.7 µM (MC) | [87]    |
| Mibefradil           | Inhibition (MC) | 24.6 µM (MC) | [126]   |
| Doxapram             | Inhibition (XO) | 37 µM (XO) | [119]   |
| L-703,606 oxalate    | Inhibition (MC) | 45.5 µM (MC) | [126]   |
| Oligomycin A         | Inhibition (MC) | 47.7 µM (MC) | [126]   |
| GW2974               | Inhibition (MC) | 50.1 µM (MC) | [126]   |
| Loratadine           | Inhibition (MC) | 63.4 µM (MC) | [126]   |
| Dihydro-β-erythroidine hydrobromide | Inhibition (MC) | 73.8 µM (MC) | [126]   |
| (±)-Octolothepin maleate | Inhibition (MC) | 73.8 µM (MC) | [126]   |
| Ruthenium red        | Inhibitor (XO) | 114 µM | [127]   |
| Etomidate            | Inhibition (XO) | 128 µM (XO) | [113]   |
| Mevastatin           | Inhibition (MC) | 159 µM (MC) | [126]   |
| Ostruthin            | Inhibition (MC) | 227 µM (MC) | [88]    |
| Barium               | 11% inhibition at 100 µM (XO) | 290 µM (XO) | [64]    |
| Arachidonic acid     | 4.81% inhibition at 10 µM (XO) | n.m.                           | [125]   |
| Genistein            | −60% inhibition at 100 µM (XO) | n.m.                           | [85]    |
| Bupivacaine          | 50.2–56% inhibition at 100 µM (XO, MC) | n.m.                           | [70,125]|
| Alphaxolone          | 49.2% inhibition at 100 µM (XO) | n.m.                           | [125]   |
| Quinidine            | 42.2% inhibition at 100 µM (XO) | n.m.                           | [125]   |
Table 3. Cont.

| $K_{2P}$ Channel | Drug/Compound | Effect (Organism) | $EC_{50}$/IC$_{50}$ (Organism) | Citation |
|------------------|---------------|-------------------|-------------------------------|----------|
|                  | Quinine       | 36.9% inhibition at 100 µM (XO) | n.m. | [125] |
|                  | Dronedarone   | 31.7% inhibition at 100 µM (XO) | n.m. | [82] |
|                  | Fluoxetine    | 31% inhibition at 100 µM (MC) | n.m. | [102] |
|                  | Ketamine      | 7.3% inhibition at 100 µM (XO) | n.m. | [125] |
|                  | Pentobarbital | 4.3% inhibition at 100 µM (XO) | n.m. | [125] |
|                  | Glibenclamide | 3.6% inhibition at 100 µM (XO) | n.m. | [125] |
|                  | Ranolazine    | 28.28% inhibition at 300 µM (XO) | n.m. | [109] |
|                  | TEA           | 6% inhibition at 1 mM (XO) | n.m. | [125] |
|                  | Xenon         | No significant effect at 80% (MC) | n.m. | [98] |
|                  | Nitrous oxide | No significant effect at 80% (MC) | n.m. | [98] |
|                  | Cyclopropane  | No significant effect at 10% (MC) | n.m. | [98] |
|                  | Propofol      | No significant effect at 200 µM (XO) | n.m. | [113] |
|                  | Vernakalant   | No significant effect at 100 µM (XO) | n.m. | [83] |
|                  | Flecaïnide    | No significant effect at 100 µM (XO) | n.m. | [84] |
|                  | Digoxin       | No significant effect (XO) | n.m. | [111] |
|                  | Digitoxin     | No significant effect (XO) | n.m. | [111] |
|                  | Cesium        | 8–12% inhibition at 10 mM (XO) | n.m. | [64,125] |
|                  | Ostruthin     | Activator (MC) 3.7 µM (MC) | [86] |
|                  | ML335         | High affinity TREK-1/2 activator 5.2 µM (XO) | [90] |
|                  | ML402         | High affinity TREK-1/2 activator 5.9 µM (XO) | [90] |
|                  | Arachidonic acid | Activation (MC) 7.3 µM (MC) | [65] |
|                  | BL-1249       | High affinity TREK-1/2 activator 8.0 µM (XO) | [69] |
|                  | ML67-33       | High affinity TREK-1/2 activator 30.2 µM (XO); 1.6 µM (MC) | [91] |
| $K_{2P10.1}$ (TREK-2) | 11-deoxyprostaglandin F2α | ~5-fold activation at 2 µM (MC) | n.m. | [128] |
|                  | Pranlukast    | 228% activation at 3 µM (MC) | n.m. | [92] |
|                  | Ocosahexaenoic acid | ~5-fold activation at 20 µM (MC) | n.m. | [65] |
|                  | Linolenic acid | ~6-fold activation at 20 µM (MC) | n.m. | [65] |
|                  | Eicosapentaenoic acid | ~8-fold activation at 20 µM (MC) | n.m. | [65] |
|                  | Linoleic acid | ~8-fold activation at 20 µM (MC) | n.m. | [65] |
|                  | Flufenamic acid | ~4-fold activation at 100 µM (MC) | n.m. | [95] |
|                  | Niflumic acid | ~2.5-fold activation at 100 µM (MC) | n.m. | [95] |
|                  | Mefenamic acid | ~2-fold activation at 100 µM (MC) | n.m. | [95] |
|                  | Ruthenium red | Inhibition (XO) 230 nM (XO) | [127] |
|                  | A1899         | Inhibition (XO) 8.4 µM (XO) | [103] |
|                  | Carvedilol    | Inhibition (XO, MC) 24 µM (XO); 7.6 (MC) | [43] |
|                  | Fluoxetine    | 68% inhibition at 10 µM (MC) 28.7 µM (MC) | [96] |
|                  | Diltiazem     | Inhibition (MC) 330 µM (MC) | [95] |
|                  | Fluphenthixol | ~80% inhibition at 10 µM (MC) | n.m. | [101] |
|                  | Pimozide      | ~80% inhibition at 10 µM (MC) | n.m. | [101] |
|                  | Fluphenazine  | ~70% inhibition at 10 µM (MC) | n.m. | [101] |
|                  | Clozapine     | ~50% inhibition at 10 µM (MC) | n.m. | [101] |
|                  | Loxapine      | ~50% inhibition at 10 µM (MC) | n.m. | [101] |
Table 3. Cont.

| K_{2P} Channel | Drug/Compound | Effect (Organism) | EC_{50} /IC_{50} (Organism) | Citation |
|----------------|---------------|-------------------|-----------------------------|----------|
|                | Haloperidol   | ~50% inhibition at 10 µM (MC) | n.m. | [101] |
|                | Paroxetin     | 33% inhibition at 20 µM (MC) | n.m. | [96] |
|                | Citalopram    | 59% inhibition at 100 µM (MC) | n.m. | [96] |
|                | Chlorpromazine| 57% inhibition at 100 µM (MC) | n.m. | [96,101] |
|                | Vernakalant   | 19.8% inhibition at 100 µM (XO) | n.m. | [83] |
|                | Barium        | 36% inhibition at 2 mM (MC) | n.m. | [65] |
|                | Sulpiride     | No significant effect at 10 µM (MC) | n.m. | [101] |
|                | Tiapride      | No significant effect at 10 µM (MC) | n.m. | [101] |
|                | Elaidic acid  | No significant effect at 20 µM (MC) | n.m. | [65] |
|                | Stearic acid  | No significant effect at 100 µM (MC) | n.m. | [65] |
|                | Palmitic acid | No significant effect at 100 µM (MC) | n.m. | [65] |
|                | Gabapentin    | No significant effect at 100 µM (MC) | n.m. | [96] |
|                | Valproate     | No significant effect at 100 µM (MC) | n.m. | [96] |
|                | Carbamazepine | No significant effect at 100 µM (MC) | n.m. | [96] |
|                | Flecaïnide    | No significant effect at 100 µM (XO) | n.m. | [84] |
|                | Genistein     | No significant effect at 100 µM (XO) | n.m. | [85] |
|                | Dronedarone   | No significant effect at 100 µM (XO) | n.m. | [82] |
|                | Quinidine     | No significant effect at 100 µM (XO) | n.m. | [65] |
|                | Bupivacaine   | No significant effect at 100 µM (MC) | n.m. | [65] |
|                | Gadolinium    | No significant effect at 100 µM (MC) | n.m. | [65] |
|                | Ranolazine    | No significant effect at 300 µM (XO) | n.m. | [109] |
|                | TEA           | No significant effect at 1 mM (MC) | n.m. | [65] |
|                | Lidocaine     | No significant effect at 1 mM (MC) | n.m. | [65] |
|                | Lithium       | No significant effect at 1 mM (MC) | n.m. | [96] |
|                | Rubidium      | No significant effect at 1 mM (MC) | n.m. | [96] |
|                | Digitoxin     | No significant effect (XO) | n.m. | [111] |
|                | Digoxin       | No significant effect (XO) | n.m. | [111] |

K_{2P12.1}

|                | Quinidine     | Inhibition (XO) 160 µM (XO) | n.m. | [8] |
|                | Halothane     | ~50% inhibition at 5 mM (XO) | n.m. | [8] |
|                | Arachidonic acid | No significant effect at 5 µM (XO) | n.m. | [8] |
|                | Lysophosphatidylcholine | ~20% activation at 10 µM (XO) | n.m. | [66] |
|                | Arachidonic acid | 69.6–85% activation at 5–20 µM (XO) 980 nM (XO) | n.m. | [66,68] |
|                | Dronedarone   | 14.9% activation at 100 µM (XO) | n.m. | [82] |
|                | Quinidine     | 10.9% activation at 100 µM (XO) | n.m. | [129] |
|                | Amiodarone    | 9.3% activation at 100 µM | n.m. | [129] |
|                | Ranolazine    | 4.98% activation at 300 µM (XO) | n.m. | [109] |

K_{2P13.1} (THIK-1)

|                | A1899 (High affinity K_{2P3.1} inhibitor) | Inhibition (XO) 2.2 µM (XO) | n.m. | [103] |
|                | Mexiletine    | 74.6% inhibition at 1.5 mM (XO) 356 µM (XO) | n.m. | [68,129] |
|                | Halothane     | 56% inhibition at 5 mM (XO) 2.8 mM (XO) | n.m. | [66] |
|                | Lidocaine     | 59.2% inhibition at 100 µM (XO) | n.m. | [68] |
|                | Carvedilol    | No significant effect at 100 µM (XO) | n.m. | [129] |
|                | Metoprolol    | No significant effect at 100 µM (XO) | n.m. | [129] |
|                | Vernakalant   | No significant effect at 100 µM (XO) | n.m. | [83] |
|                | Flecaïnide    | No significant effect at 100 µM (XO) | n.m. | [84] |
Table 3. Cont.

| K_{2P} Channel | Drug/Compound | Effect (Organism) | EC_{50} / IC_{50} (Organism) | Citation |
|----------------|---------------|-------------------|-------------------------------|----------|
|                | Verapamil     | No significant effect at 100 µM (XO) | n.m. | [129] |
|                | Propafenone   | 26% inhibition at 100 µM (XO) | n.m. | [129] |
|                | Genistein     | ~20% inhibition at 100 µM (XO) | n.m. | [85] |
|                | Propranolol   | 37.6% inhibition at 200 µM (XO) | n.m. | [129] |
|                | Chloroform    | No significant effect at 1 mM (XO) | n.m. | [66] |
|                | Barium        | 88.7% inhibition at 2 mM (XO) | n.m. | [66,68] |
|                | Digoxin       | No significant effect (XO) | n.m. | [111] |
|                | Digitoxin     | No significant effect (XO) | n.m. | [111] |

K_{2P}15.1 (TASK-5) Non-functional channel

| Drug/Compound | Effect (Organism) | EC_{50} / IC_{50} (Organism) |
|---------------|-------------------|-------------------------------|
| Digitoxin     | ~30% inhibition at 100 µM (XO) | n.m. |
| Ranolazine    | 23.04% inhibition at 300 µM (XO) | n.m. |
| Halothane     | 26.8% inhibition at 800 µM (XO) | n.m. |
| Chloroform    | 21.5% inhibition at 800 µM (XO) | n.m. |
| Barium        | 51.4% inhibition at 1 mM (XO) | n.m. |
| Quinine       | 45.1% inhibition at 1 mM (XO) | n.m. |
| Quinidine     | 36.8% inhibition at 1 mM (XO) | n.m. |
| TEA           | 14.9% inhibition at 1 mM (XO) | n.m. |
| Arachidonic acid | No significant effect at 20 µM (XO) | n.m. |
| 4-AP          | No significant effect at 100 µM (XO) | n.m. |
| Vernakalant   | No significant effect at 100 µM (XO) | n.m. |
| Flecaïnide    | No significant effect at 100 µM (XO) | n.m. |
| Genistein     | No significant effect at 100 µM (XO) | n.m. |
| Dronedarone   | No significant effect at 100 µM (XO) | n.m. |
| Isoflurane    | No significant effect at 800 µM (XO) | n.m. |
| Cesium        | No significant effect at 1 mM (XO) | n.m. |
| Digoxin       | No significant effect (XO) | n.m. |

K_{2P}16.1 (THIK-1)

| Drug/Compound | Effect (Organism) | EC_{50} / IC_{50} (Organism) |
|---------------|-------------------|-------------------------------|
| A1899 (High affinity K_{2P}3.1 inhibitor) | Inhibition (XO) | 8.1 µM (XO) |
| A293 (High affinity K_{2P}3.1 inhibitor) | Inhibition (XO) | 18.1 µM (XO) |

K_{2P}17.1 (THIK-2)

| Drug/Compound | Effect (Organism) | EC_{50} / IC_{50} (Organism) |
|---------------|-------------------|-------------------------------|
| Propafenone   | 296.1% activation at 100 µM (XO, MC) | 75.4 µM (XO) |
| Quinidine     | 57.7% activation at 100 µM (XO) | n.m. |
| Mexiletine    | 20.6% activation at 100 µM (XO) | n.m. |
| Verapamil     | 20.5% inhibition at 100 µM (XO) | n.m. |
| Amiodarone    | 12.5% inhibition at 100 µM (XO) | n.m. |
| Sotalol       | 9.8% inhibition at 100 µM (XO) | n.m. |
| Ranolazine    | 8.3–34.88% inhibition at 100–300 µM (XO) | n.m. |
| Barium        | 81.2–82.8% inhibition at 2 mM (XO) | n.m. |
| Cesium        | No significant effect at 1–2 mM (XO) | n.m. |
| Arachidonic acid | No significant effect at 100 µM (XO) | n.m. |
| Flecaïnide    | No significant effect at 100 µM (XO) | n.m. |
| Genistein     | No significant effect at 100 µM (XO) | n.m. |
| Carvedilol    | No significant effect at 100 µM (XO) | n.m. |
| Amitriptyline | No significant effect at 100 µM (XO) | n.m. |
| $K_{2P}$ Channel | Drug/Compound   | Effect (Organism)                                         | EC_{50} /IC_{50} (Organism) | Citation |
|-----------------|-----------------|----------------------------------------------------------|----------------------------|----------|
|                 | Ajmaline        | No significant effect at 100 µM (XO)                     | n.m.                       | [75]     |
|                 | Vernakalant     | No significant effect at 100 µM (XO)                     | n.m.                       | [83]     |
|                 | Dronedarone     | No significant effect at 100 µM (XO)                     | n.m.                       | [82]     |
|                 | Digoxin         | No significant effect (XO)                              | n.m.                       | [111]    |
|                 | Digitoxin       | No significant effect (XO)                              | n.m.                       | [111]    |
|                 | Metoprolol      | 17.3% activation at 100 µM (XO)                         | n.m.                       | [75]     |
|                 | Propranolol     | 139.2% activation at 100 µM (XO)                        | n.m.                       | [75]     |
|                 | Bupivacaine     | 25.7% inhibition at 1 mM (XO)                           | n.m.                       | [73]     |
|                 | TEA             | 19.9% inhibition at 1 mM (XO)                           | n.m.                       | [67]     |
|                 | Quinidine       | 17.8% inhibition at 1 mM (XO)                           | n.m.                       | [73]     |
|                 | Lidocaine       | 13.1% inhibition at 1 mM (XO)                           | n.m.                       | [73]     |
|                 | 4-AP            | No significant effect at 0.1-2 mM (XO)                   | n.m.                       | [67,73]  |
|                 | Chloroform      | 44.7% inhibition at 800 µM (XO)                         | n.m.                       | [67]     |
|                 | Halothane       | 56.4% inhibition at 800 µM (XO)                         | n.m.                       | [67]     |
|                 | Isoflurane      | 58.4% activation at 800 µM (XO)                         | n.m.                       | [67]     |
|                 | Vernakalant     | Activation (XO, MC)                                     | 40 µM (MC)                 | [83]     |
|                 | Isoflurane      | Activation (XO)                                         | 162 µM (XO)                | [61]     |
|                 | Sevoflurane     | Activation (XO)                                         | 224 µM (XO)                | [61]     |
|                 | Halothane       | Activation (XO)                                         | 300 µM (XO)                | [61]     |
|                 | Desflurane      | Activation (XO)                                         | 658 µM (XO)                | [61]     |
|                 | Dronedarone     | 29% activation at 100 µM (XO)                           | n.m.                       | [82]     |
|                 | Loratadine      | Inhibition (MC)                                         | 490 nM (MC)                | [126]    |
|                 | A1899 (High affinity $K_{2P}3.1$ inhibitor) | Inhibition (XO)                                      | 900 nM (XO)                | [103]    |
|                 | Cloxiquine      | Inhibition (MC)                                         | 3.2 µM (MC)                | [130]    |
| $K_{2P}18.1$ (TRESK) | Zinc           | Inhibition (XO)                                         | 5–10 µM for the murine but not the human ortholog | [131]    |
|                 | Arachidonic acid| 43% inhibition at 20 µM (MC)                            | 6.6 µM (MC)                | [73,78]  |
|                 | Lamotrigine     | Inhibition (MC)                                         | 47 µM (MC)                 | [132]    |
|                 | Bupivacaine     | −75% inhibition at 100 µM (MC)                          | 80.4 µM (XO)               | [61,133] |
|                 | Tetracaine      | Inhibition (XO)                                         | 496 µM (XO)                | [61]     |
|                 | Ropivacaine     | Inhibition (XO)                                         | 610 µM (XO)                | [61]     |
|                 | Chlorprocaine   | Inhibition (XO)                                         | 832 µM (XO)                | [61]     |
|                 | Mepivacaine     | Inhibition (XO)                                         | 1300 µM (XO)               | [61]     |
|                 | Lidocaine       | ~70–75% inhibition at 1 mM (MC)                         | 3.4 mM (MC)                | [61,73,78]|
|                 | Mibefradil      | Inhibition at 3 µM (XO)                                 | n.m.                       | [131]    |
|                 | Quinidine       | 49% inhibition at 10 µM (MC)                            | n.m.                       | [133]    |
|                 | Linoleic acid   | ~35% inhibition at 20 µM (MC)                           | n.m.                       | [78]     |
|                 | Oleic acid      | ~50% inhibition at 20 µM (MC)                           | n.m.                       | [78]     |
|                 | Docosahexaenoic acid | ~60% inhibition at 20 µM (MC) | n.m.                       | [78]     |
|                 | Propafenone     | 95% inhibition at 50 µM (MC)                            | n.m.                       | [78]     |
|                 | Glyburide       | 76% inhibition at 50 µM (MC)                            | n.m.                       | [78]     |
|                 | Quinidine       | 90% inhibition at 100 µM (MC)                           | n.m.                       | [78]     |
|                 | Quinidine       | 41.9–75% inhibition at 100 µM (MC)                      | n.m.                       | [61,78]  |
|                 | Etomidate       | 30.5% inhibition at 100 µM (XO)                         | n.m.                       | [61]     |
|                 | Pentobarbital   | 10.4% inhibition at 100 µM (XO)                         | n.m.                       | [61]     |
### Table 3. Cont.

| K2P Channel | Drug/Compound | Effect (Organism) | EC50 /IC50 (Organism) | Citation |
|-------------|---------------|-------------------|-----------------------|----------|
| Ketamine    | 14.5% inhibition at 100 µM (XO) | n.m. | [61] |
| Alphaxalone | 45.4% inhibition at 100 µM (XO) | n.m. | [61] |
| Gabapentin  | 4.2% inhibition at 100 µM (XO) | n.m. | [61] |
| Barium      | 38% inhibition at 3 mM (MC) | n.m. | [78,133] |
| Ethanol     | –15% inhibition at 150 mM (MC) | n.m. | [61,133] |
| Apamin      | No significant effect at 100 nM (XO) | n.m. | [133] |
| Ruthenium red | No significant effect at 5 µM (MC) | n.m. | [133] |
| Glibenclamide | No significant effect at 10 µM (MC) | n.m. | [133] |
| Stearic acid | No significant effect at 20 µM (MC) | n.m. | [78] |
| Digoxin     | No significant effect at 100 µM (XO) | n.m. | [111] |
| Digitoxin   | No significant effect at 100 µM (XO) | n.m. | [111] |
| Flecainide  | No significant effect at 100 µM (XO) | n.m. | [84] |
| Genistein   | No significant effect at 100 µM (XO) | n.m. | [85] |
| Tolazamide  | No significant effect at 100 µM (MC) | n.m. | [78] |
| Glipizide   | No significant effect at 100 µM (MC) | n.m. | [78] |
| Paxilline   | No significant effect at 100 µM (MC) | n.m. | [78] |
| Penitrem A  | No significant effect at 100 µM (MC) | n.m. | [78] |
| Ranolazine  | No significant effect at 300 µM (XO) | n.m. | [109] |
| Cesium      | No significant effect at 1 mM (MC) | n.m. | [133] |
| 4-AP        | No significant effect at 1 mM (XO) | n.m. | [73,78] |
| TEA         | No significant effect at 1 mM (XO) | n.m. | [61,73,78] |
| Mercury     | Inhibition (XO) | n.m. | [131] |
| Tetraptethyl-ammonium | Inhibition (MC) | n.m. | [130] |

Potency of different drugs or compounds to activate or inhibit heterologously expressed K2P currents. Compounds that are used as experimental high-affinity inhibitors of individual K2P channels are highlighted in bold. Please note, however, that these compounds are by no means completely specific for single members of the K2P family. IC50, mean inhibitory concentration; MC, mammalian cells; n.m., not measured; XO, Xenopus laevis oocytes.

The physiological role of K2P.1.1 (TWIK-1) channel subunits has not been conclusively clarified, mostly due to lack of specific inhibitors and its very low currents in heterologous expression systems [82]. If measurable, heterologously expressed K2P.1.1 (TWIK-1) channel homodimers give rise to potassium currents that are sensitive to acidic pH as well as external K+ concentration [134]. Therefore, it was speculated whether K2P.1.1 (TWIK-1) might contribute to cardiac I_{K1}, I_{KAcH}, I_{KATP}, and I_{TASK} currents [11–14,80,135,136]. Altered ion conductivity under low extracellular potassium concentrations (for example Na+ permeability, which shifts homodimeric K2P.1.1 (TWIK-1) channels from an inhibitory to an excitatory channel) could link K2P.1.1 (TWIK-1) channels to the pathophysiology of hypokalemia-induced rhythm disturbances [137]. Through its ability to heterodimerize with other K2P subunits, K2P.1.1 (TWIK-1) subunits could modulate the pharmacological and functional properties of atrial K2P.3.1 (TASK-1) channel subunits [138–140].

### 4. K2P.2.1 (TREK-1)

Mechanosensitivity is a unique feature of the TREK/TRAALK subfamily, as these K2P channels are activated by membrane stretch and osmotic swelling [141]. Temperature, lipids, extracellular or intracellular pH, anesthetics or other drugs, phosphorylation, glycosylation, G protein-coupled receptors and other protein partners represent further regulators of homodimeric K2P.2.1 (TREK-1) channels [97,124,141–144]. The versatility of this channel is further enhanced by alternative translation initiation (ATI) variants that
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differ in spatiotemporal expression, single-channel conduction, ion selectivity and regarding their pharmacological profile [43,145,146]. Further, K$_{2p}$2.1 (TREK-1) channel subunits are reported to from heterodimers with K$_{2p}$1.1 (TWIK-1), K$_{2p}$4.1 (TRAALK) and K$_{2p}$10.1 (TREK-2) [147,148].

In the rat heart, Kcnk2 mRNA and protein expression has been described in both atrial and ventricular tissue samples (Table 2) [28,29,32,33,149]. However, in the mouse heart, most studies describe ventricular-dominant K$_{2p}$2.1 (TREK-1) expression or mRNA abundance patterns [16,26,41]. Abundant K$_{2p}$2.1 (TREK-1) expression was also detected in the porcine heart, with the highest expression levels in the sinoatrial and atrioventricular nodal tissue [36,37] and in human cardiac tissue samples, where again ventricular dominant K$_{2p}$2.1 (TREK-1) expression could be observed [10,37,40,41]. Interestingly, a transmural gradient of ventricular K$_{2p}$2.1 (TREK-1) expression levels was described with endocardial expression levels 17-fold higher than that in the epicardium, [30,149]. Strikingly, this gradient seems to parallel transmural changes in stretch-activated potassium currents, as mechanical stretch has been shown to cause increased action potential shortening in subendocardial cardiomyocytes compared to the subepicardium [150].

Homodimeric K$_{2p}$2.1 (TREK-1) channels are inhibited by the anticonvulsant drugs valproate, gabapentin and carbamazepine [102] by the antidepressants like fluoxetine, paroxetine, citalopram or escitalopram (Table 3) [96,102], and the antipsychotics haloperidol or clozapine [101]. While some of these interactions would only be relevant at supratherapeutic plasma levels, others already have an impact in the physiological range [141]. It has therefore been speculated whether the blockade of cardiac K$_{2p}$2.1 (TREK-1) channels could contribute to the proarrhythmic potential of these compounds [41,141]. Remarkably, K$_{2p}$2.1 (TREK-1) knockout was shown to cause a phenotype of QT interval prolongation, linking loss of cardiac K$_{2p}$2.1 (TREK-1) to QT prolongation [151]. Likewise, antiarrhythmic drugs were described to block K$_{2p}$2.1 (TREK-1) channels: Vaughan Williams class I compounds lidocaine, mexiletine and propafenone, class III antiarrhythmic drugs dronedarone and vernakalant, the beta-blocker carvedilol and late sodium current inhibitor ranolazine were identified as in vitro K$_{2p}$2.1 (TREK-1) inhibitors (Table 3) [43,82,84,104,106,109]. Since IC$_{50}$ levels are mostly in the supratherapeutic range, it is unclear to what extent inhibition of K$_{2p}$2.1 (TREK-1) contributes to the antiarrhythmic effects of these compounds.

In isolated rat ventricular cardiomyocytes the mechano-, pH-, and arachidonic acid-sensitive potassium current I$_{KAA}$ displays a number of further features like activation by volatile anesthetics, inhibition by cAMP analogues as well as beta-adrenergic receptor agonists, the absence of a relevant voltage dependency, a specific single-channel conductance and burst mode activity, which identify it as a K$_{2p}$2.1 (TREK-1) current (Table 4) [7,28,29,32,33,149,152]. Further, resting membrane potentials of chicken embryo-derived atrial cardiomyocytes are regulated by K$_{2p}$2.1 (TREK-1) [153]. Finally, cardiomyocyte-specific K$_{2p}$2.1 (TREK-1) knockout mice exhibit a phenotype of stress-induced sick sinus syndrome and prolongation of QT intervals that could be reproduced in a transgenic model which employed C-terminal truncation of beta IV spectrin to disrupt its interaction with K$_{2p}$2.1 (TREK-1), thereby impairing intracellular K$_{2p}$2.1 (TREK-1) protein trafficking [27,151]. In a similar fashion, knockout of K$_{2p}$2.1 (TREK-1) channel surface targeting by its protein partners POPDC1 or POPDC2 revealed a phenotype of exercise-induced and age-dependent sick sinus syndrome [154,155], while a double-knockout mouse displayed AV conduction disturbance [156]. Moreover, a familial autosomal recessive POPDC1 mutation has been associated with the phenotype of limb-girdle muscular dystrophy type X2 in combination with AV block [157] and POPDC2 mutations have been shown to cause AV block without a skeletal muscle phenotype [158]. The fact that K$_{2p}$2.1 (TREK-1) channels are activated in acidosis and by mechanical stress has given rise to speculation about a role of this channel in the development of cardiac arrhythmias for more than two decades [28]. Metabolic changes associated with myocardial ischemia lead to a decrease in pH. By activating K$_{2p}$2.1 (TREK-1), this can
cause a dispersion of repolarization and consecutively the development of arrhythmias. Similarly, altered wall tension due to hypertension, valvular vitiation, in the margins of myocardial scars, or AF may activate K$_{\text{2P}}$.1 (TREK-1) [141,158,159]. Recently, a heterozygous missense mutation (I267T) of K$_{\text{2P}}$.1 (TREK-1) was identified in a patient with idiopathic right ventricular outflow tract tachycardia [160]. This mutation results in an amino acid exchange from isoleucine to threonine in close proximity to the selectivity filter of the channel, leading to increased stretch sensitivity and sodium permeability.

Table 4. Functional evidence for K$_{\text{2P}}$ channel expression in the cardiovascular system.

| K$_{\text{2P}}$ Channel Subunit | Species | Population/Model/Methodology | Observation | Citation |
|---------------------------------|---------|------------------------------|-------------|----------|
| **K$_{\text{2P}}$.1 (TWIK-1)** | Zebrafish | Morpholino knockdown mRNA (RT-PCR, ISH) | Knockdown of kcnk1a or kcnk1b in zebrafish embryos resulted in a phenotype atrial dilatation and bradycardia | [11] |
| | Mouse | CREM-transgenic murine AF model mRNA (RT-qPCR, TaqMan) | Moderate cardiac mRNA expression, V > A Ventricular mRNA downregulated in murine AF model | [16] |
| | Rat | Goto-Kakizaki type 2 diabetic rats mRNA (RT-qPCR, TaqMan) | Downregulation of sinoatrial mRNA levels in Goto-Kakizaki type 2 diabetic rats | [19] |
| | Human | Patient-derived tissue samples mRNA (RT-PCR) | Identical mRNA levels in failing and healthy hearts | [21] |
| | Human | Patient-derived tissue samples | Upregulation of atrial mRNA levels in patients with atrial dilatation | [11] |
| | Human | Patient-derived tissue samples | Upregulation of atrial mRNA levels in patients with Brugada syndrome | [80] |
| | Human | Patient-derived tissue samples | Downregulation of atrial mRNA levels in AF | [12] |
| | Human | AF patients | Identification of three non-synonymous KCNK1 gene variants (p.R171H, p.I98M, and p.G236S) in a cohort of 373 atrial fibrillation (AF) patients | [11] |
| | Human | mRNA (RT-qPCR, TaqMan) | No regulation of atrial mRNA levels in AF | [10] |
| **K$_{\text{2P}}$.2.1 (TREK-2)** | Mouse | CREM-transgenic murine AF model Murine TAC model mRNA (RT-qPCR, TaqMan) | Upregulated of atrial and ventricular mRNA in a murine AF model Downregulation of atrial and ventricular mRNA in a murine TAC model | [16] |
| | Rat | Rat model of isoproterenol-induced left ventricular hypertrophy | Increased protein levels upon isoproterenol stimulation | [149] |
| K<sub>2P</sub> Channel Subunit | Species | Population/Model/Methodology | Observation | Citation |
|-------------------------------|---------|------------------------------|-------------|---------|
|                               | Mouse   | Protein (IF)                 | Global K<sub>2P</sub>2.1 (TREK-1) knockout mice showed an exaggerated form of pressure overload-induced concentric ventricular hypertrophy, which could be prohibited only by fibroblast-specific deletion of K<sub>2P</sub>2.1 (TREK-1) whereas the cardiomyocyte-specific knockout of K<sub>2P</sub>2.1 (TREK-1) resulted in cardiac dysfunction under pressure-overload conditions | [161] |
| Human                         | Patient-derives tissue samples mRNA (RT-qPCR, TaqMan) | Downregulation of atrial mRNA in AF | [37] |
| Pig                           | Large animal model of burst pacing-induced AF and heart failure | Downregulation of atrial mRNA and protein | Attenuation of the AF phenotype by KCNK2 gene therapy | [36,37] |
| Rat                           | Goto-Kakizaki type 2 diabetic rats mRNA (RT-qPCR, TaqMan) | Upregulation of sinuatrial mRNA levels in Goto-Kakizaki type 2 diabetic rats | [19] |
| Human                         | Index patient | A heterozygous missense mutation (I267T) of K<sub>2P</sub>2.1 (TREK-1) was identified in a patient with idiopathic right ventricular outflow tract tachycardia | [160] |
| Chicken                       | Isolated atrial cardiomyocytes | Resting membrane potentials of chicken embryo-derived atrial cardiomyocytes are regulated by K<sub>2P</sub>2.1 | [153] |
| Rat                           | Isolated rat ventricular cardiomyocytes | In isolated rat ventricular cardiomyocytes the mechano-, pH-, and arachidonic acid-sensitive potassium current I<sub>KAA</sub> displays a number of characteristics which identify it as a K<sub>2P</sub>2.1 (TREK-1) current | [7,28,29,32,33,149,152] |
| Mouse                         | Kcnk2 knockout mouse | Phenotype of QT interval prolongation and sick sinus syndrome | [35] |
| Rat                           | Isolated rat ventricular cardiomyocytes | K<sub>2P</sub>3.1 (TASK-1) currents were isolated from rat ventricular cardiomyocytes by lowering pH, activation of cardiac α1-adrenergic receptors and by administration of the inhibitor A293 | [15,162,163] |
| Mouse                         | Isolated cardiomyocytes | Patch-clamp measurements of K<sub>2P</sub>3.1 (TASK-1) currents (controlled by knockout mice) | [45] |
| Pig                           | Isolated atrial cardiomyocytes | Patch-clamp measurements of K<sub>2P</sub>3.1 (TASK-1) currents using A293: APD prolongation via K<sub>2P</sub>3.1 (TASK-1) inhibition | [52–54,164] |
Table 4. Cont.

| K<sub>2P</sub> Channel Subunit | Species | Population/Model/Methodology | Observation | Citation |
|--------------------------------|---------|-----------------------------|-------------|---------|
|                                | Human   | Isolated atrial cardiomyocytes | Patch-clamp measurements of K<sub>2P</sub>3.1 (TASK-1) currents using A293: APD prolongation via K<sub>2P</sub>3.1 (TASK-1) inhibition. \(I_{\text{TASK-1}}\) was identified to carry up to 28% of the background potassium current in isolated human atrial cardiomyocytes | [10,39,40,53,56]. |
|                                | Human   | iPSC | Prolongation of APD values by transfection of K<sub>2P</sub>3.1 (TASK-1) siRNA | [22] |
|                                | Zebrafish | Morpholino knockdown | Decreased heart rate was observed after K<sub>2P</sub>3.1 (TASK-1) knockdown | [165]. |
|                                | Mouse   | CREM-transgenic murine AF model, Murine TAC model mRNA (RT-qPCR, TaqMan) and protein (WB) | Downregulation of atrial mRNA and protein level in murine AF model, Downregulation of atrial mRNA and protein level in murine TAC model | [16] |
|                                | Guinea pig | Excised guinea pig hearts | Prolongation of atrial effective refractory periods upon TASK-1 inhibition at pH 7.8 | [49] |
|                                | Mouse   | Kcnk3 knockout mouse | Phenotype of QTc prolongation (around 30%), prolongation of single cell APDs or monophasic action potentials and a broad QRS complex | [47] |
|                                | Rat     | Kcnk3 knockout rat | Phenotype of cardiomyocyte APD prolongation as well as resting membrane depolarization | [15] |
|                                | Dog     | Dog model of postoperative AF | Downregulation of atrial TASK-1 expression in postoperative AF | [50] |
|                                | Pig     | Large animal model of burst pacing-induced AF | Uregulation of atrial TASK-1 expression and currents, Acute cardioversion upon TASK-1 inhibition, Rhythm control of AF upon TASK-1 gene therapy of pharmacological TASK-1 inhibition | [52,141,164] |
|                                | Human   | mRNA (RT-qPCR, TaqMan), protein (WB) | Upregulation of atrial TASK-1 expression and currents in cAF | [10,41,55,57] |
|                                | Human   | AF patient cohort | Three genetic KCNK3 variants which reduce the expression or channel function were found in patients with familial AF | [49] |
|                                | Mouse   | Kcnk3 knockout mouse | Compared to wild-type littermates, Kcnk3 knockout mice showed a preservation of systolic as well as diastolic function and a relative abrogation in concentric left ventricular hypertrophy upon TAC-induced pressure overload | [46] |
Table 4. Cont.

| $\text{K}_2\text{P Channel Subunit}$ | Species | Population/Model/Methodology | Observation | Citation |
|-------------------------------------|---------|-------------------------------|-------------|----------|
| $\text{K}_2\text{P}4.1$ (TRAAK)     | Human   | Patient cohorts               | $\text{KCNK3}$ loss-of-function mutations were found to cause idiopathic pulmonary arterial hypertension | [166] |
|                                    | Human   | Patient-derived tissue samples mRNA (RT-qPCR, TaqMan) and protein (WB) | Upregulation of atrial mRNA and protein in AF Downregulation of atrial mRNA in heart failure | [40] |
|                                    | Mouse   | $\text{Kcnk4}$ knockout mice  | No obvious cardiac phenotype reported | [167,168] |
|                                    | Human   | Patient-derived tissue samples mRNA (RT-qPCR) | Downregulation of ventricular mRNA levels in non-ischemic heart failure | [22] |
|                                    | Human   | Patient-derived tissue samples mRNA (RT-qPCR, TaqMan) | No regulation of atrial mRNA levels in AF patients | [10] |
|                                    | Mouse   | $\text{Kcnk5}$ knockout mice  | Observation of subviable phenotype and sudden unexplained dead but association with arrhythmia or cardiomyopathy remains speculative as no detailed cardiac characterization was reported | [169] |
| $\text{K}_2\text{P}5.1$ (TASK-2)   | Mouse   | CREM-transgenic murine AF model mRNA (RT-qPCR, TaqMan) | No regulation of atrial mRNA in murine AF model | [16] |
|                                    | Rat     | Goto-Kakizaki type 2 diabetic rats mRNA (RT-qPCR, TaqMan) | Downregulation of sinoatrial mRNA levels in Goto-Kakizaki type 2 diabetic rats | [19] |
|                                    | Human   | mRNA (RT-qPCR, TaqMan)       | Trend towards downregulation of atrial mRNA levels in AF | [10] |
|                                    | Mouse   | CREM-transgenic murine AF model Murine TAC model mRNA (RT-qPCR, TaqMan) | No regulation in murine AF model Upregulation of atrial mRNA in murine TAC model | [16] |
| $\text{K}_2\text{P}6.1$ (TWIK-2)   | Rat     | Goto-Kakizaki type 2 diabetic rats mRNA (RT-qPCR, TaqMan) | Downregulation of sinoatrial mRNA levels in Goto-Kakizaki type 2 diabetic rats | [19] |
|                                    | Mouse   | $\text{Kcnk6}$ knockout mouse | $\text{Kcnk6}$ knockout mice are hypertensive and display elevated RV pressure level as well as enhanced vascular contractility | [170–172] |
|                                    | Human   | Patient-derived tissue samples mRNA (RT-qPCR, TaqMan) | No regulation of atrial mRNA in AF patients | [10] |
| $\text{K}_2\text{P}7.1$ (TWIK-3)   | Human, Mouse | mRNA (RT-qPCR, TaqMan) | Most studies showed very low cardiac mRNA levels. Functionality of the channel still under debate. | [16] al. 2015, Wang et al. 2018 |
|                                    | Human   | Patient-derived tissue samples mRNA (RT-qPCR) | Upregulation of atrial mRNA levels in AF | [63] |
Table 4. Cont.

| \(K_{2P}\) Channel Subunit | Species | Population/Model/Methodology | Observation | Citation |
|---------------------------|---------|-------------------------------|-------------|----------|
| \(K_{2P}9.1\) (TASK-3)   | Human   | Patient-derived tissue samples mRNA (RT-qPCR, TaqMan) | No mRNA regulation in AF | [10] |
|                           | Mouse   | \(Kcnk7\) knockout mouse       | No cardiac phenotype of the \(Kcnk7\) knockout mouse has been described | [173] |
|                           | Human   | Genetic disease               | \(KCNK9\) imprinting syndrome linked to obstructive sleep apnea |         |
|                           | Human   | Patient-derived tissue samples mRNA (RT-qPCR) | Downregulation of ventricular mRNA levels in heart failure | [22] |
|                           | Human   | Patient-derived tissue samples mRNA (RT-qPCR, TaqMan) | Trend towards upregulation in AF | [10] |
|                           | Mouse   | \(Kcnk9\) knockout mouse      | Phenotype of concentric left ventricular hypertrophy with preserved ejection fraction | [46] |
|                           | Human   | Single channel patch-clamp measurements on isolated human atrial cardiomyocytes | Evidence for heteromeric \(K_{2P}9.1/3.1\) but not for \(K_{2P}9.1\) homodimers | [56] |
| \(K_{2P}10.1\) (TREK-2)  | Human, mouse | Patient-derived tissue samples, CREM-transgenic murine AF model, Murine TAC model, mRNA (RT-qPCR, TaqMan) | No regulation of atrial mRNA levels in AF patients No regulation of atrial or ventricular mRNA levels in a murine AF model No changes in ventricular mRNA levels in a murine TAC model Upregulation of left and right atrial mRNA in heart failure patients | [41] |
|                           | Mouse   | \(Kcnk10\) knockout mouse     | No cardiac phenotype of the \(Kcnk10\) knockout mouse has been described | [174] |
|                           | Human   | Patient-derived tissue samples mRNA (RT-qPCR, TaqMan) | No regulation of atrial mRNA levels in AF patients | [10] |
| \(K_{2P}12.1\) (THIK-2)  | Human, Rat, Mouse | mRNA (NB, RT-PCR, RT-qPCR, TaqMan) | Most studies show very low cardiac mRNA levels. Functionality of the channel still under debate. | [10,15,16,66,67] |
| \(K_{2P}13.1\) (THIK-1)  | Human   | Patient-derived tissue samples mRNA (RT-qPCR, TaqMan) | Downregulation of atrial mRNA level in cAF patients | [10] |
|                           | Human   | Patient-derived tissue samples mRNA (RT-qPCR, TaqMan) | Trend towards downregulation of atrial mRNA level in heart failure patients | [40] |
|                           | Pig     | Large animal model of burst-pacing induced AF and heart failure | Downregulation of atrial protein expression in combined AF and heart failure | [129] |
| \(K_{2P}15.1\) (TASK-5)  | Human, Rat, Mouse | mRNA (RT-PCR, RT-qPCR) | Most studies show rather low cardiac mRNA levels. Functionality of the channel still under debate. | [10,15,69,70] Wiedemann et al. 2018 |
|                           | Human   | Patient-derived tissue samples mRNA (RT-qPCR, TaqMan) | No regulation of atrial mRNA levels in cAF patients | [10] |
| \(K_{2P}16.1\) (TALK-1)  | Mouse   | CREM-transgenic murine AF model mRNA (RT-qPCR, TaqMan) | Downregulation of atrial mRNA levels in murine AF model | [16] |
|                           | Human, Rat | mRNA (NB, RT-PCR, RT-qPCR, TaqMan) | Most studies show negligible or low cardiac mRNA levels | [10,15,60,67,71] |
| $K_{\text{2}P}$ Channel Subunit | Species | Population/Model/Methodology | Observation | Citation |
|-------------------------------|---------|-----------------------------|-------------|---------|
| $K_{2P17.1}$ (TALK-2)        | Human, Mouse | Index patient HL-1 cells (cultured cardiomyocyte cell line), mRNA (RT-qPCR) | Downregulation of ventricular mRNA levels in non-ischemic heart failure iPSC: KCNK17 knockdown led to APD prolongation | [22] |
|                               | Human   | Patient-derived tissue samples, iPSC mRNA (RT-qPCR) | A patient suffering from progressive and severe cardiac conduction disorder in combination with idiopathic ventricular fibrillation was identified to carry both, a splice site mutation in the sodium channel gene SCN5A as well as a gain-of-function mutation in the KCNK17 gene HL-1 cells: KCNK17 knockdown overexpression led to APD shortening | [5] |
|                               | Human   | Index family Patient derived iPSC | A common KCNK17 gain-of-function variant might be protective for LQTS by promoting APD shortening | [74] |
|                               | Human   | Patient-derived tissue samples, mRNA (RT-qPCR, TaqMan) | Downregulation of right atrial mRNA levels in cAF | [10] |
|                               | Human   | Patient-derived tissue samples, mRNA (RT-qPCR, TaqMan) and protein (WB) | Downregulation of left and right atrial protein and mRNA level in HF | [40] |

| $K_{2P18.1}$ (TRESK) | Zebrafish, Mouse, Human | mRNA (ISH, RT-PCR, RT-qPCR, TaqMan) | Most studies show negligible cardiac mRNA levels | [10,16,61,76–78] |

Evidence in literature for cardiac relevance of $K_{2P}$ channel subunits. A, expression in atrial tissue; AF, atrial fibrillation; HF, heart failure; IF, immunofluorescence; iPSC, induced pluripotent stem cell; ISH, in situ hybridization; LA, left atrium; NB, Northern blot; RT-PCR, reverse transcriptase PCR; RT-qPCR, reverse transcriptase quantitative PCR; RA, right atrium; TAC, transverse aortic constriction; TaqMan, reverse transcriptase quantitative PCR employing TaqMan® hydrolyse probes to increase specificity; V, expression in ventricular tissue; WB, Western blot.

In a murine model of transverse aortic constriction (TAC)-induced pressure overload upregulation of ventricular $Kcnk2$ mRNA expression was described [16]. In a similar fashion, $K_{2P2.1}$ (TREK-1) protein levels were increased in a rat model of isoproterenol-induced left ventricular hypertrophy [149]. Global $K_{2P2.1}$ (TREK-1) knockout mice showed an exaggerated form of pressure overload-induced concentric ventricular hypertrophy, which could be prohibited only by fibroblast-specific deletion of $K_{2P2.1}$, (TREK-1) whereas the cardiomyocyte-specific knockout of $K_{2P2.1}$ (TREK-1) resulted in cardiac dysfunction under pressure-overload conditions [161]. In a murine atrial fibrillation (AF) model of CREM-IbΔC-X transgenic mice, downregulation of atrial $K_{2P2.1}$ (TREK-1) mRNA and protein levels were observed [16,41]. It, however, remains uncertain whether this is also the case for AF patients: while one study described AF-associated downregulation of atrial $K_{2P2.1}$ (TREK-1) [37] others merely describe a trend that does not reach statistical significance [10,40,41]. One possible explanation is the remote regulation of atrial $K_{2P2.1}$ (TREK-1) expression by ventricular heart failure, a mechanism recently described for $K_{2P3.1}$ (TASK-1) [40] and also observed for $K_{2P2.1}$ (TREK-1) in another study [41]. Indeed, in contrast to the other study, the cohort of patients characterized in the former study was performed in patients who all suffered from severe heart failure. In a similar fashion, a strong trend towards downregulation of atrial $Kcnk2$ mRNA could be observed in a murine
model of TAC-induced pressure overload [16]. Furthermore, downregulation of atrial \( K_{\text{2P}2.1} \) (TREK-1) protein expression was described in a porcine model of combined AF and heart failure [36] and gene therapeutic restoration of \( K_{\text{2P}2.1} \) (TREK-1) expression was able to attenuate the AF phenotype [37].

For a more detailed description of the cardiac role of \( K_{\text{2P}2.1} \) (TREK-1), we would like to refer to the following literature [41,141,158].

5. \( K_{\text{2P}3.1} \) (TASK-1)

Among the entire \( K_{\text{2P}} \) family, \( K_{\text{2P}3.1} \) (TASK-1) is the channel with the best characterized cardiac significance. \( K_{\text{2P}3.1} \) (TASK-1) channels are expressed in neuronal tissue, cardiomyocytes, vascular smooth muscle cells, the carotid body glomus, the adrenal gland, brown adipose tissue and immunocytes, where they control important physiological processes [2,113]. \( K_{\text{2P}3.1} \) (TASK-1) channels are regulated by a number of different stimuli, such as pH level, hypoxia, PKA, PKC, or PLC activity, and several drugs like volatile anesthetics [2].

In the murine and the rat heart, \( KCNK3 \) mRNA was detected, both in atrial as well as in ventricular tissue samples (Northern blot, RT-PCR, Taq-Man qPCR; Table 2) [15,16,18,25,26,34,44,45,47]. Humans, however, show an almost atrial-specific \( K_{\text{2P}3.1} \) (TASK-1) expression within the heart with 14- to 16-fold lower expression levels in ventricular tissue (RT-PCR, Taq-Man qPCR, microarray, bulk RNASeq, Western blot) [10,12,14,39,49,54,56,57]. In guinea pigs and domestic swine, atrial-specific \( K_{\text{2P}3.1} \) (TASK-1) expression was also described [49,51–54].

Several clinically relevant antiarrhythmic drugs have been identified to inhibit homodimeric \( K_{\text{2P}3.1} \) (TASK-1) channels at either physiological or subtherapeutic concentrations (Table 3). Among them are the class I antiarrhythmic drugs propafenone, mexiletine, lidocaine, and quinidine [104,122,123], the betablockers propranolol and carvedilol [42], class III antiarrhythmics amiodarone and dronedarone [82,110] as well as cardiac glycosides [111] and ranolazine [109]. The respiratory stimulant doxapram was further identified as a potent blocker of both \( K_{\text{2P}3.1} \) (TASK-1) and \( K_{\text{2P}9.1} \) (TASK-3) channels through which it presumably exerts the main part of its respiratory drive-increasing effect [119,175]. Furthermore, preclinical experimental antiarrhythmic drugs developed as specific inhibitors of the \( K_{\text{V}1.5} \) channel (A239 [AVE1231], A1899 [S20591], AVE0118, S9947, MSD-D, and ICAGEN-4) are potent \( K_{\text{2P}3.1} \) (TASK-1) inhibitors [117]. Although no direct structural similarities of the pore regions of both channels could be detected, these compounds were shown to be 1.4- to 70-fold more potent \( K_{\text{2P}3.1} \) (TASK-1) inhibitors as compared to \( K_{\text{V}1.5} \) [117]. In addition, bisamides represent a new class of high-affinity \( K_{\text{2P}3.1} \) (TASK-1) inhibitors with \( IC_{50} \) values in the single-digit nanomolar range, as in the case of compound ML365 (Table 3) [116].

Availability of high-affinity inhibitors enables functional detection of \( K_{\text{2P}3.1} \) (TASK-1) currents in isolated cardiomyocytes. \( K_{\text{2P}3.1} \) (TASK-1) currents were isolated from rat ventricular cardiomyocytes by lowering pH, activation of cardiac \( \alpha_1 \)-adrenergic receptors and by administration of the inhibitor A293 (Table 4) [15,162,163]. Patch-clamp measurements of murine \( K_{\text{2P}3.1} \) (TASK-1) current could be confirmed by the use of \( Kcnk3 \) knockout mice [25] and likewise, functional detection of \( K_{\text{2P}3.1} \) (TASK-1) currents was achieved by patch-clamp technique in isolated porcine [52–54,164] and human atrial cardiomyocytes, where a significant APD prolongation could be demonstrated [10,39,40,53,56]. Under physiological conditions, \( I_{\text{TASK-1}} \) was identified to carry up to 28% of the background potassium current in isolated human atrial cardiomyocytes [39].

In induced pluripotent stem cell- (iPSC-) derived cardiomyocytes (iPSC), APD values could be prolonged by transfection of \( K_{\text{2P}3.1} \) (TASK-1) siRNA [22]. In a zebrafish model, a decreased heart rate was observed after \( K_{\text{2P}3.1} \) (TASK-1) knockdown, which was accompanied by an increased atrial diameter [165]. In excised guinea pig hearts, APD remained unchanged upon \( K_{\text{2P}3.1} \) (TASK-1) inhibition with A293 or ML365. Switching the pH level from pH 7.4 to 7.8, however, resulted in significant prolongation of atrial effective refractory periods [49]. Global \( Kcnk3 \) knockout mice exhibited a phenotype of QTc prolongation...
(around 30%), prolongation of single cell APDs or monophasic action potentials and a broad QRS complex [25,26]. In transgenic Kcnk3 knockout rats, APD prolongation as well as resting membrane depolarization was described [163].

In a porcine large animal model of AF, atrial K2P3.1 (TASK-1) expression was found to be significantly upregulated (TaqMan qPCR, western blot, patch-clamp electrophysiology) [52,141,164]. These results could also be reproduced on atrial tissue samples from atrial fibrillation patients (TaqMan qPCR, microarray, bulk RNAseq, western blot, patch-clamp electrophysiology) [10,41,55,57]. Considering its atrial-specific expression, its effect on atrial APD, and its upregulation in patients with AF, K2P3.1 (TASK-1) channels combine several properties that make it an ideal molecular target for the treatment of AF.

Inhibition of K2P3.1 (TASK-1) in cardiomyocytes from AF patients has been shown to counteract AF-induced APD shortening [104,154]. After administration of A293 (200 nM), APDs of atrial cardiomyocytes isolated from AF patients could be prolonged around 30% to values observed in sinus rhythm controls [104,154]. After intravenous application of K2P3.1 (TASK-1) inhibitors in healthy control pigs, significant prolongation of both, atrial effective refractory periods and ADP values pointed towards class III antiarrhythmic effects of K2P3.1 (TASK-1) inhibition [53,54]. Furthermore, the inducibility of atrial arrhythmias was significantly reduced by K2P3.1 (TASK-1) inhibitors in different studies [176–178]. In a similar fashion, intravenous administration of K2P3.1 (TASK-1) inhibitors A293 and doxapram led to rapid, safe and successful cardioversion of artificially induced AF episodes in a porcine large animal model [53,54]. These antiarrhythmic effects could further be employed for rhythm control in a porcine model of burst pacing induced “persistent” AF, induced via implanted pacemakers using a biofeedback algorithm [53,164] and reproduced with an AAV-mediated anti-K2P3.1 (TASK-1) gene therapy approach [52]. Based on these encouraging results, the currently ongoing DOCTOS trial (doxapram conversion to sinus rhythm; EudraCT No: 2018-002979-17) was started, which investigates whether the FDA and EMA approved K2P3.1 (TASK-1) inhibitor doxapram can cardiovert AF in patients [2,179].

Interestingly, also reduction of atrial K2P3.1 (TASK-1) expression was linked to AF as in a dog model of postoperative AF, a phosphorylation dependent downregulation of K2P3.1 (TASK-1) was reported [50] and CREM-TG AF mice display atrial downregulation of K2P3.1 (TASK-1) expression, independently from their rhythm state [40]. Finally, three genetic variants (two kozak variants and missense variant K2P3.1 (TASK-1) V123L mutation all of which reduce the expression or channel function) were found in patients with familial AF [49].

In addition to its role in the control of heart rhythm, K2P3.1 (TASK-1) is also discussed as a regulator of cardiac energetics and metabolic function, as Kcnk3 knockout mice were protected from pressure overload-induced cardiomyopathy. Compared to wild-type littermates, Kcnk3 knockout mice showed a preservation of systolic as well as diastolic function and a relative abrogation in concentric left ventricular hypertrophy upon TAC-induced pressure overload [46].

Moreover, K2P3.1 (TASK-1) channels were described to be expressed in in human pulmonary artery smooth muscle cells, where they serve as regulators of the basal membrane potential and consecutively regulate pulmonary vascular tone [180]. Furthermore, KCNK3 loss-of-function mutations were found to cause idiopathic pulmonary arterial hypertension [166] and acute pharmacological K2P3.1 (TASK-1) inhibition in pigs led to a mild but significant increase in invasively measured pulmonary arterial pressure [164]. In the context of adrenal KCNK3 expression, a role of the K2P3.1 (TASK-1) channel in aldosterone secretion and blood pressure control is further discussed. Global Kcnk3 knockout mice display a phenotype of mild hyperaldosteronism [181] and single nucleotide polymorphisms in the KCNK3 gene were associated with plasma aldosterone levels [182]. Accordingly, elevated systolic blood pressure values were described in the Kcnk3 knockout mouse [25]. Finally, K2P3.1 (TASK-1) channels are also discussed to be involved in regulating function
of immune cells and in thermogenesis in brown adipose tissue [183]. Thus, there is a need for further studies that exclude systemic side effects in the use of TASK-1 inhibitors for treatment of AF.

6. K_{2P}4.1 (TRAALK)

Although it was suspected about 20 years ago, that the K_{2P}4.1 (TRAALK) channel, based on northern blot analysis, might be mainly expressed in the human heart there is little evidence to date for a cardiac role of this K_{2P} channel. Several studies reported cardiac KCNK4 mRNA expression, mostly with atrial predominant expression patterns (TaqMan qPCR; Table 2) in human as well as in murine heart tissue samples [10,22,26,41]. Compared with other cardiac ion channels, however, expression levels were relatively low [10,16,41]. A mild inhibitory effect of vernakalant and the late sodium channel blocker ranolazine has also been described for hK_{2P}4.1 (TRAALK) homodimeric channels (Table 3) [83,109].

Kcnk4 knockout mice were reported to display smaller ischemic areas upon cerebral infarction. No obvious phenotype of heart rhythm disorder or heart failure was described, and the mice were reported as viably and healthy [167,168]. We are, however, not aware of any studies that explicitly study the cardiac phenotype of these transgenic mice (Table 4).

7. K_{2P}5.1 (TASK-2)

Shortly after the first description of the KCNK5 gene, RT-PCR experiments had already indicated robust cardiac abundance of KCNK5 mRNA [184], while other studies (RT-PCR) considered the cardiac mRNA levels to be rather low (Table 2) [22,23,26,38]. Our own studies indicated atrial predominant KCNK5 mRNA abundance within the human and murine heart [10,16]. Further, a trend towards downregulation of atrial KCNK5 mRNA in patients, suffering from chronic AF was noted that did not reach statistical significance [10]. K_{2P}5.1 (TASK-2) homodimers are a molecular target on volatile and amide type local anesthetics (Table 3) [185,186] and inhibited by supratherapeutic concentrations of ranolazine [109]. siRNA transfection experiments pointed towards a functional role of K_{2P}5.1 (TASK-2) in setting the membrane potential of pulmonary artery myocytes [187]. In the diabetic rat model with sinus bradycardia, mentioned above, downregulation of cardiac Kcnk5 mRNA expression was reported (Table 4) [19]. Finally, genome-wide association studies could identify a risk locus, associated with the development of coronary artery disease and migraine within the KCNK5 gene [188].

Breeding of global Kcnk5 knockout mice resulted in a small number of female homozygous offspring, pointing towards a phenotype which might cause antenatal mortality [169]. Further, Gerstin et al. reported that one homozygote female animal was found dead in the cage at 12 days of age [169]. However, whether this was associated with cardiomyopathy or arrhythmia remains speculative.

8. K_{2P}6.1 (TWIK-2)

Robust cardiac expressions patterns of KCNK6 mRNA, derived from RT-PCR were described [10,18,22], while others report mild to moderate cardiac expression of this channel (RT-PCR, WB; Table 2) [15,23,26]. Interestingly, mRNA levels were reported to be significantly higher in the adult as compared to the neonatal rat heart [18]. Furthermore, abundant Kcnk6 mRNA levels were found in rat saphenous arteries [189]. Upon TAC-induced pressure overload, an upregulation of murine ventricular Kcnk6 mRNA could be observed (Table 4) [16]. Kcnk6 deficient mice are hypertensive and display elevated RV pressure level as well as enhanced vascular contractility which was linked to enhanced rho kinase activity [170–172]. The physiological relevance of K_{2P}6.1 (TWIK-2) is under debate because these channels conduct only low currents in the heterologous expression system [82]. It further was recently reported that K_{2P}6.1 (TWIK-2) channel subunits give rise to functional K_{2P} currents in endolysosomes, where they affect the size and number of lysosomes [190] so it remains unclear whether the cell membrane is indeed the actual site of action of these channels.
9. \( \text{K}_{2\text{P}}7.1 \) (TWIK-3)

The mainly neuronally detected \( \text{K}_{2\text{P}}7.1 \) (TWIK-3) channel is a silent \( \text{K}_{2\text{P}} \) channel without proven potassium conductance in heterologous expression systems [191]. Only very low cardiac expression levels have been described for \( \text{KCNK7} \) (RT-qPCR, TaqMan qPCR; Table 2) [10,23]. It was, however, speculated whether its mRNA expression might be up-regulated in atrial tissue samples, derived from AF patients [63]. Although not explicitly cardiac characterized, a global \( \text{Kcnk7} \) knockout mouse showed no obvious cardiac phenotype. Homozygous transgenic mice and wild-type littermates did not differ significantly in general appearance, gross anatomy, locomotion, or overt behavior (Table 4) [173].

10. \( \text{K}_{2\text{P}}9.1 \) (TASK-3)

The cardiac relevance of \( \text{K}_{2\text{P}}9.1 \) (TASK-3) channel subunits which are primarily known for their role in apoptosis, aldosterone secretion and tumor genesis remains controversial. Whereas most studies detected only relatively low mRNA levels in the human heart (qPCR, TaqMan qPCR; Table 2) [10,22,26,49], others showed high atrial expression, almost comparable to \( \text{K}_{2\text{P}}3.1 \) (TASK-1) (RT qPCR, IF) [56]. In the rodent heart, low \( \text{Kcnk9} \) (TASK-3) mRNA abundance been described [15,16,18,25,26,48].

Echocardiographic characterization of \( \text{Kcnk9} \) knockout mice revealed a phenotype of concentric left ventricular hypertrophy with preserved ejection fraction (Table 4) [46]. In contrast to \( \text{Kcnk3} \) knockout mice, however, these animals are not TAC resistant, and heart failure symptoms are more likely to occur at a later time point [46]. Downregulation of ventricular \( \text{KCNK9} \) mRNA expression (TaqMan qPCR) in heart failure patients might point towards a pathophysiological role of this channel [22].

Single channel patch-clamp measurements, performed in isolated human atrial cardiomyocytes were able to detect a channel with characteristics corresponding to a heteromer of \( \text{K}_{2\text{P}}3.1 \) (TASK-1) and \( \text{K}_{2\text{P}}9.1 \) (TASK-3) [56]. However, besides this heteromeric and homodimeric \( \text{K}_{2\text{P}}3.1 \) (TASK-1) channels, no current corresponding to a homodimeric \( \text{K}_{2\text{P}}9.1 \) (TASK-3) channels could be detected. Functional studies in motoneurons or in rat carotid body glomus cells indicate that the \( \text{K}_{2\text{P}}3.1 \) (TASK-1)/ \( \text{K}_{2\text{P}}9.1 \) (TASK-3) heterodimer portion was about 52–75% and thus only a minority of \( \text{K}_{2\text{P}}3.1 \) (TASK-1) channels are expressed as monomer at the cell surface [192,193]. Since the pharmacological properties of homodimeric and heterodimeric channels differ, heterodimerization has to be taken into account when targeting the \( \text{K}_{2\text{P}}3.1 \) (TASK-1) channel in the treatment of cardiac arrhythmias.

A rare genetic disease, \( \text{KCNK9} \) imprinting syndrome, also known as Birk-Barel Syndrome is inherited in an autosomal dominant, maternally imprinted manner and associated with congenital central hypotonia, severe feeding difficulties, delayed development, and dysmorphic manifestations [194]. While no direct cardiac manifestation has been described to date, affected individuals may develop obstructive sleep apnea syndrome, which is particularly interesting because it again links the \( \text{K}_{2\text{P}} \) channels of the TASK subfamily to this disease entity.

Together with \( \text{K}_{2\text{P}}3.1 \) (TASK-1), \( \text{K}_{2\text{P}}9.1 \) (TASK-3) contributes to peripheral and central respiratory regulation [195]. Therefore, these \( \text{K}_{2\text{P}} \)-channels are likely to constitute a molecular target of the respiratory stimulant doxapram [53]. \( \text{K}_{2\text{P}}9.1 \) (TASK-3) homodimers are further inhibited by the class III antiarrhythmic drug dronedarone [82] and the antianginal drug ranolazine [109].

Hopefully, the recently available high-affinity \( \text{K}_{2\text{P}}9.1 \) (TASK-3) inhibitors and activators will help to answer the question of the functional relevance of \( \text{K}_{2\text{P}}9.1 \) (TASK-3) channels in cardiomyocytes.

11. \( \text{K}_{2\text{P}}10.1 \) (TREK-2)

The role of \( \text{K}_{2\text{P}}10.1 \) (TREK-2) channel subunits has so far been characterized mainly in the central nervous system (CNS), where this channel shows ubiquitous expression. However, a \( \text{KCNK10} \) knockout mouse showed remarkably few neurobehavioral phenotypes besides discrete abnormalities in anxiety-related behavior [174]. A cardiac phenotype
of this mouse has not been described yet. Pharmacological in vitro measurements revealed vernakalant and carvedilol as inhibitors of K<sub>2P</sub>10.1 (TREK-2) homodimer channels (Table 3) [43,83]. Low cardiac mRNA abundance was described by our group and others (RT-PCR, TaqMan qPCR; Table 2) [10,15,22,40]. However, the expression patterns appeared atrial-predominant both in murine and patient-derived samples [10,41]. No relevant changes of K<sub>2P</sub>10.1 (TREK-2) expression could be detected in murine disease models of TAC-induced pressure overload or CREM-TG AF (Table 4) [16]. However, in right and left atrial patient-derived tissue samples, significant mRNA upregulation was demonstrated upon systolic heart failure [41].

12. K<sub>2P</sub>12.1 (THIK-2)

K<sub>2P</sub>12.1 (THIK-2) is referred to as a silent K<sub>2P</sub>-channel. This is likely due to both, a N-terminal retention signal and a low endogenous open probability [196]. While cardiac K<sub>2P</sub>12.1 (THIK-2) mRNA levels (RT-PCR, TaqMan qPCR) were described to be rather low (Table 2) [10,15,16,67], K<sub>2P</sub>12.1 (THIK-2) expression was detected in rat saphenous arteries [189] and might therefore be of relevance in control of vascular tone.

13. K<sub>2P</sub>13.1 (THIK-1)

K<sub>2P</sub>13.1 (THIK-1) mRNA was described in the CNS, arterial smooth muscle cells, the kidney and myocardial tissue samples via RT-PCR [15,22,26,66,68]. In patient-derived myocardial tissue samples, KCNK13 mRNA abundance (TaqMan qPCR) could be demonstrated with atrial predominance (Table 2) [10]. Heterologously expressed K<sub>2P</sub>13.1 (THIK-1) channel homodimers were inhibited by the antiarrhythmic drugs lidocaine, mexiletine, propafenone and propranolol, while administration of quinidine, amiodarone, dronedarone or ranolazine resulted in a mild channel activation (Table 3) [82,109,129].

The observation of reduced KCNK13 mRNA levels in patients with chronic AF or heart failure, which could also be recapitulated in a porcine large animal model of combined AF and heart failure might point towards a physiological role of K<sub>2P</sub>13.1 (THIK-1) currents in regulating atrial electrophysiology [10,40,129]. Finally, ventricular expression levels of KCNK13 mRNA, were described as unchanged in heart failure patients (Table 4) [22].

14. K<sub>2P</sub>15.1 (TALK-5)

Data on cardiac expression of K<sub>2P</sub>15 (TASK-5) remain sparse. While some work has shown evidence of KCNK15 mRNA abundance in rodent hearts (RT-PCR), very low levels of mRNA at best have been detected in human (northern blot, RT-PCR, TaqMan qPCR; Table 2) [10,26,48,69,70] or rodent (RT-PCR, TaqMan-qPCR) [15,16,26] heart samples by other groups. Downregulation of atrial KCNK15 mRNA was reported in a murine CREM-TG model of AF (Table 4) [16]. Finally, functionality of K<sub>2P</sub>15 (TASK-5) channel subunits is still controversial, as recombinantly expressed K<sub>2P</sub>15 (TASK-5) homodimers do not give rise to potassium currents [8].

15. K<sub>2P</sub>16.1 (TALK-1)

K<sub>2P</sub>16.1 (TALK-1) is primarily expressed in pancreatic beta cells, where it is supposed to regulate insulin secretion. Recently, a gain of function mutation in KCNK16 was identified to cause maturity-onset diabetes of the young [197]. Five studies showed low to negligible abundance of KCNK16 mRNA in human or rat cardiac tissue samples (Table 2) [10,15,60,67,71]. Upon heterologous expression in <i>Xenopus laevis</i> oocytes, homodimeric K<sub>2P</sub>16.1 (TALK-1) channels are inhibited by ranolazine (Table 3) [109].

16. K<sub>2P</sub>17.1 (TALK-2)

K<sub>2P</sub>17.1 (TALK-2) channel subunits are expressed in the human heart (northern blot, RT-PCR, Taq-Man qPCR, western blot) [5,10,22,40,67,73,75] and in patient-derived iPSC (RT-PCR, qPCR, IF) [22,74]. Cardiac mRNA levels of KCNK17 were described as atrial predominant with highest abundance in purkinje fibers (qPCR, Taq-Man qPCR; Table 2) [5,10].
Reports of reduced KCNK17 mRNA levels in atrial fibrillation [10] and heart failure [22,40] suggest a role for K\textsubscript{2P}17.1 (TALK-2) in the pathophysiology of important cardiac pathologies. K\textsubscript{2P}17.1 (TALK-2) channel subunits were described to heterodimerize with atrial K\textsubscript{2P}3.1 (TASK-1), thereby modulating biophysical and pharmacological properties of atrial I\textsubscript{TASK-1} [198]. In heterologous expression systems, K\textsubscript{2P}17.1 (TALK-2) channel homodimers were reported to be activated by propafenone, quinidine, mexiletine, propranolol, vernakalant, and metoprolol [75]. Amiodarone, sotalol, verapamil, and ranolazine were further described to inhibit K\textsubscript{2P}17.1 (TALK-2) homodimers (Table 3) [75,83]. In iPSC, suppression of K\textsubscript{2P}17.1 (TALK-2) expression was shown to prolong APD (Table 4) [22] while overexpression of K\textsubscript{2P}17.1 (TALK-2) shortened APD levels in the cultured, cardiomyocyte derived HL-1 cell line [5]. Recently, a patient suffering from progressive and severe cardiac conduction disorder in combination with idiopathic ventricular fibrillation was identified to carry both, a splice site mutation in the sodium channel gene SCN5A as well as a mutation in the KCNK17 gene [5]. This K\textsubscript{2P}17.1 (TALK-2) G88R mutation, located in the first extracellular pore loop was shown to increase K\textsubscript{2P}17.1 (TALK-2) currents to about three times upon heterologous expression. Overexpression of K\textsubscript{2P}17.1 (TALK-2) G88R in spontaneously beating HL-1 cells was shown to result in a reduction of the beating frequency, hyperpolarization of the membrane potential and a strong slowing of the upstroke velocity [5].

Single nucleotide polymorphisms in the KCNK17 gene which increase K\textsubscript{2P}17.1 (TALK-2) channel subunit expression levels are associated with the occurrence of ischemic stroke in Caucasians but not in a Chinese population [137,199]. This observation links the channel once again to the pathophysiology of atrial fibrillation. KCNK17 was further proposed as a genetic modifier of long QT syndrome type 2 severity, as a common KCNK17 gain-of-function variant was shown to be LQTS protective by promoting APD shortening [74].

The cardiac characterization of the K\textsubscript{2P}17.1 (TALK-2) channel is complicated by the fact that to date no specific inhibitors are available that would allow functional studies (Table 3). Furthermore, no ortholog to the KCNK17 gene could be identified in mice and the porcine K\textsubscript{2P}17.1 (TALK-2) channel subunit does not appear to show functional activity after heterologous expression in *Xenopus laevis* oocytes (unpublished observation of our lab).

**17. K\textsubscript{2P}18.1 (TRESK)**

KCNK18 mRNA, encoding K\textsubscript{2P}18.1 (TRESK) channel subunits was detected in human spinal cord, trigeminal ganglia, and brain but not in the heart (RT-PCR and TaqMan qPCR; Table 2) [10,61,77,78]. Accordingly, K\textsubscript{2P}18.1 (TRESK) channels are supposed to play a key role in pain perception and KCNK18 was identified as a potential susceptibility gene for migraine, while a cardiac role of this channel is rather unlikely [1]. TRESK channels may nevertheless exert indirect effects on the cardiovascular system: For example, high-fat diet-induced vagal afferent dysfunction has been described to be mediated via upregulation of K\textsubscript{2P}18.1 (TRESK) [200]. Heterologously expressed K\textsubscript{2P}18.1 (TRESK) channel homodimers are inhibited by lidocaine, verapamil, quinidine and apamin (Table 3) [76,200].

**18. Conclusions**

Overall, K\textsubscript{2P} channels are an exciting and relevant new potassium channel class with relevance to a wide variety of disease conditions. For several members, reproducible mRNA regulation patterns in atrial fibrillation, heart failure and other cardiac disease could be described. However, the functional consequence remains difficult to assess, especially in cases where no specific channel inhibitors are available (Table 3), since surface expression and current amplitude in cardiomyocytes cannot be directly inferred from mRNA expression [11]. Further, the actual significance of the individual K\textsubscript{2P} subgroups, some of which show only weak expression patterns, merits further investigation. To date, little is also known about the differential expression of K\textsubscript{2P} channels in different cardiac cell populations and the consequence of remodelling in different cell types. In this regard, single cell next generation sequencing technology is expected to provide further evidence...
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soon. Furthermore, computational models of cardiac electrophysiology must consider effects of K<sub>2P</sub> channels. Taken together, emerging evidence suggests that K<sub>2P</sub> channels play an important role in cardiac repolarization and in the development of various cardiac arrhythmias such as atrial fibrillation, conduction disorders, and ventricular proarrhythmia that goes far beyond the role of unspecific leak currents.

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