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Review

Unraveling the Role of K_2P Channels in Atrial Fibrillation

Gema Mondéjar-Parreño[1,*]

[1]Department of Medicine, Stanford Cardiovascular Institute, Stanford, CA 94304, USA
*Correspondence: gemondej@stanford.edu (Gema Mondéjar-Parreño)

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Abstract

Atrial fibrillation (AF) is a condition in which the electrical signals in the upper heart chambers (atria) are rapid and disorganized, producing an irregular and chaotical heartbeat. The sinus rhythm should be between 60 to 100 bpm at rest, while the heart rhythm in AF patients may be over 140 bpm. Either structural and electro-mechanical remodeling of the atrial tissue underlies the perpetuation and evolution of AF from the paroxysmal to persistent form. Unravelling the different pathological pathways involved in AF that lead to arrhythmogenesis and atrial remodeling is needed to discovery new and effective therapeutic approaches. A variety of drugs are available to convert and maintain the AF patient in a normal sinus rhythm; however, these strategies have limited chances of success or fail with the progression of AF to more persistent/permanent forms. Consequently, it is necessary to find new therapeutic targets for the relief of persistent or chronic AF forms, as well as the development of new and more effective pharmacological tools. The atrial specific two-pore domain K^+ channels (K_2P) constitute the background K^+ current on atrial cardiomyocytes and modulate cell excitability emerging as novel targets in this disease and avoiding ventricle side effects. Moreover, several antiarrhythmic drugs used in AF treatment exert their mechanism of action in part by modulation of K_2P channels. Thus far, TWIK-1, TREK-1, TASK-1, TASK-2 and TASK-3 channel have been identified as responsible for background currents I_{K2P} current in atrial cells; however, it is not excluded that other K_2P_X subunits or subfamilies have physiological roles in atria. To date, a great diversity openers, activators and blockers of K_2P channel have been identified, particularly those targeting TASK and TREK channels. Several studies have demonstrated that the expression of TWIK-1, TREK-1, TASK-1, TASK-2 and TASK-3 are dysregulated in AF and their pharmacology rescue could suppose a novel therapy in AF. The main objective is to examine the regulation of K_2P channels and the current K_2P channels pharmacological modulators for AF treatment.

Keywords: atrial fibrillation; two pore domain K^+ channels; electrophysiological remodeling; pharmacology

1. Atrial Fibrillation: Clinical Relevance, Pathogenesis and Therapy

Atrial fibrillation (AF) is a condition in which the electrical signals in the upper heart chambers (atria) are rapid and disorganized, producing an irregular and chaotical heartbeat. AF is the most common arrhythmia linked to noteworthy mortality and morbidity [1]. The sinus rhythm should be between 60 to 100 bpm at rest, while the heart rhythm in AF patients may be over 140 bpm [2]. The most dramatic cardiovascular outcomes of AF are stroke and heart failure (HF) [3]. AF affects over 33 million people worldwide with increasing prevalence because of aging and obesity population [4]. Men are 1.5 times more likely to develop AF compared with women. In addition to age, race and sex, risk factors for developing AF include intrinsic cardiovascular diseases and modifiable noncardiac risk factors, including smoking, alcohol or drug use, caffeine, lack of physical activity, overweight, diabetes, high blood pressure or obstructive sleep apnea (OSA) [5]. The symptoms of AF include rapid and irregular pulse, palpitations, weakness, fatigue, chest pain, dizziness and shortness of breath, considerably affecting the quality of life [6]. However, for many people AF may have no symptoms. AF is classified based on aetiology or degree of persistence. In terms of aetiology, AF can be classified as environmental factor induced-, congenital or genetic [3]. A strong genetic component underlies the disease, since variants in 160 genes associated with AF have been detected. Cardiac ion channel gene variants are a underlying risk factor to AF development [7]. In terms of persistence, AF can be paroxysmal, persistent (over 7 days), long-standing persistent (over 1 year) or permanent.

The pathophysiology of AF is complex as described Fig. 1. Either structural and electro-mechanical remodeling of the atrial tissue underlies the perpetuation and evolution of AF from the paroxysmal to permanent forms [8]. AF genesis initiates with well-established ectopic firings that initiate reentrant wave propagation under a vulnerable atrial substrate [9]. Both trigger factors and a vulnerable atrial substrate are critical for AF onset [9]. An important substrate for FA may be conduction and refractoriness abnormalities, an inflammatory or fibrotic background. Ectopic atrial foci are thought caused by an enhanced automaticity, delayed afterdepolarizations (DADs) and/or early afterdepolarizations (EADs) [10]. There is no doubt that the autonomic nervous system (ANS) also cooperates in the triggers, substrate and perpetuators of AF [11].

Electrical remodeling is caused by a dysfunction of the atrial ion channels that essentially increasing outward

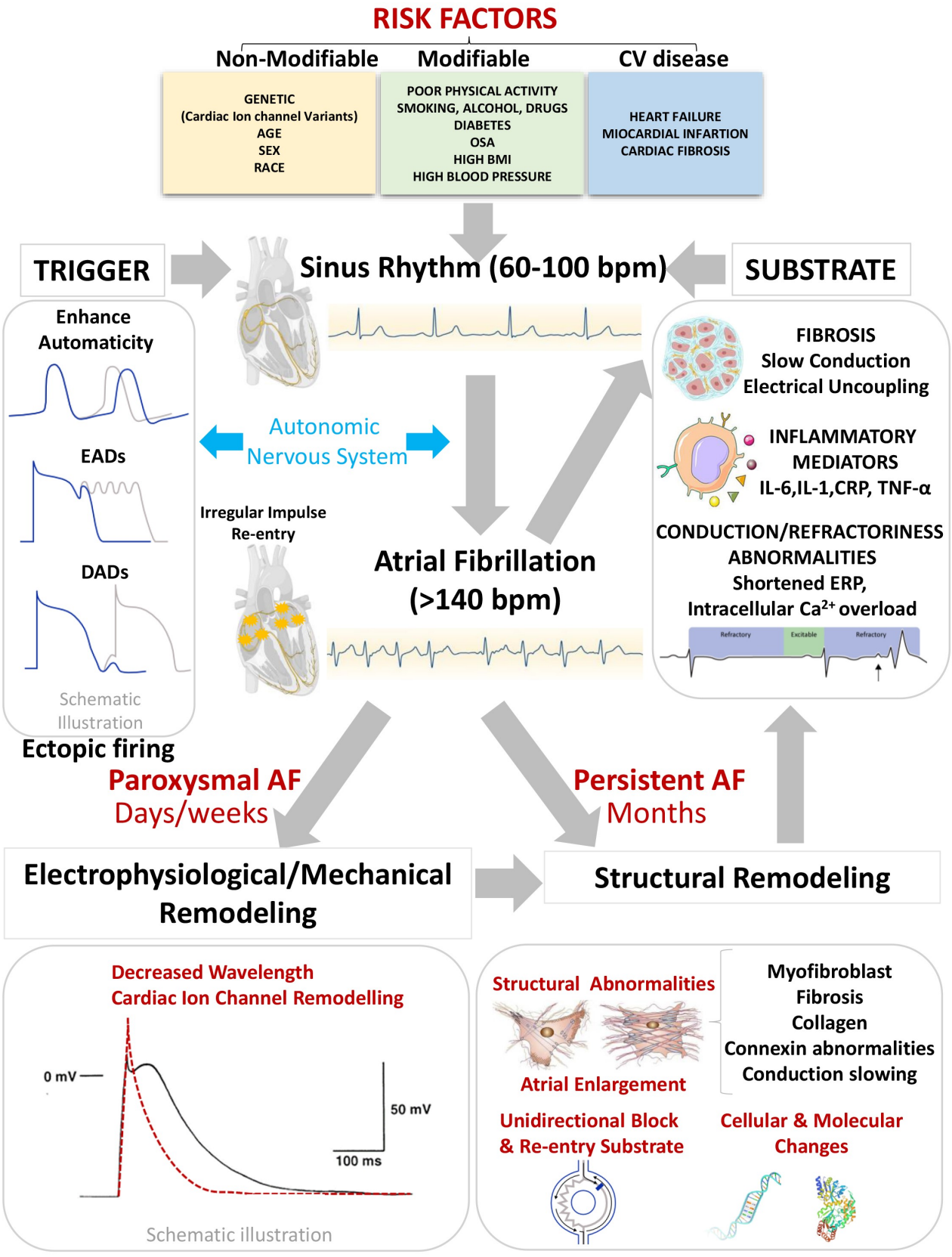

Fig. 1. Pathophysiology of Atrial Fibrillation. AF, Atrial Fibrillation; OSA, Obstructive Sleep Apnea; BMI, Body Mass Index; bpm, Beats per minute; ERP, Effective Refractory Period; EAD, Early afterdepolarizations; DAD, Delayed afterdepolarizations.

K^+ currents and/or decreasing inward L-type Ca^{2+} current, accelerating repolarization which accelerates atrial repolarization lead to a short atrial action potential (AP) duration and refractoriness, and thus favoring reentry [12]. All these changes have a strong impact not only on the atria electrophysiology but also on atria structure [13]. The disruption of Ca^{2+} handling, secondary to electrical remodeling, cause the alteration of sarcomere proteins promoting the contractile remodeling which induce atrium dilatation and blood clot formation perpetuating AF [9]. The structural remodeling particularly atrial enlargement, fibrosis and cellular/molecular changes causing localized conduction slowing and enhance re-entry [14]. Electrophysiological, structural, and mechanical irregularities also encourage AF perpetuation by stabilizing unidirectional block and re-entry [12]. Brief refractoriness, slow conduction and conduction barriers favor the induction and maintenance of reentry [15].

The main goal of AF treatment is relief of symptoms and prevention of stroke. Pharmacological treatment mainly includes anticoagulation, heart rate or rhythm control, and non-arrhythmic supportive pharmacological therapy. A variety of medicines are available to convert and maintain the patient in a normal sinus rhythm such as atenolol or bisoprolol (beta-blockers) or diltiazem or verapamil (Ca^{2+} channel blockers) could be prescribed. These medications can be combined with digoxin, which helps controlling the heart rate and preventing the rapid ventricular response [16]. Electrical cardioversion and interventional ablation procedures can also help for correcting abnormal heart rhythms. These pharmacological strategies often fail with the progression of AF to the persistent or permanent forms; even ablation procedures have poor success [16]. Consequently, it is necessary to find new therapeutic targets for the relief of persistent or chronic AF forms, as well as the development of new and more effective pharmacological tools.

2. Atrial-Specific Ion Channels

The cardiac PA reflects the integrated conductance of numerous individual ionic currents, largely dominated by the movement of Na^+, Ca^{2+} and K^+ ions, which change the membrane potential (Vm) as a function of time. Cardiac ion channel function is highly regulated and orchestrated, being influenced by multiple factors, such as voltage, ligand binding, second messengers such as cyclic adenosine monophosphate, and post-translational modification. The summarized input and output of all ionic currents expressed in a specific cardiac cell determines the duration and the cardiac AP shape [17]. Consequently pacemaker, atrial, and ventricular cells possess heterogeneous morphology and AP duration due to cardiac ion channel differences which confers distinctive electrophysiological properties [17]. In atrial and ventricular cardiomyocytes, most of the ion channels responsible for determining the AP are essentially the same; however, the expression patterns, biophysical properties, and regulatory pathways may differ. The atrial and ventricular AP are described in 5 main phases (0–4), with different duration and morphology as described Fig. 2.

The ventricular AP exhibits a peak-and-dome morphology with a prominent plateau phase; conversely, the human atrial AP usually has a triangular morphology compared to its ventricular homologue (Fig. 2). Moreover, electrophysiological heterogeneity is included in AP in different zones of the atria. The atrial resting membrane potential (Vrest) varies between -65 and -80 mV and is more depolarized than that in the ventricle mainly due to the differences in the expression density of the inward rectifier K^+ current (Fig. 2) [17,18]. The human atrial AP duration at 90% repolarization (APD90) and the atrial maximum upstroke velocities (Vmax) have been reported between 150–500 ms and $\sim$150 and 300 V/s, respectively; while for ventricular cells the APD90 and Vmax ranging 200–450 ms and 300–400 V/s [17,18]. Atrial APs lose acquire a more triangular shape in AF, the APD is significantly shortened and shows a decreased APD rate with poor adaptation and abrupt changes (Fig. 2) [19]. The atrial AP depends on three prime time- and voltage-dependent currents: I_{Na}, I_K, and I_{Ca}. Alterations in atrial ion currents due to AF pathogenesis have a strong impact on the shape of atrial AP. I_{Na} current density or biophysical properties remain unaltered in patients with chronic AF. I_{CaL} current density is decreased by $\sim$60–75% in chronic AF; whereas it appears to be unaltered in AF. I_{to} and I_{Kur} currents are also downregulated in atrial cardiomyocytes from AF patients. Conversely, the inwardly rectifying potassium current (I_{K1}) and acetylcholine-activated inward rectifier (I_{KACh}), essential currents in the late phase repolarization, are increased in AF. The excessive activity of I_{K1} and I_{KACh} currents could accelerate repolarization shortening the atrial AP and encouraging AF [17,18]. Not much information is available on the role of the rapid (I_{Kr}) and slow (I_{Ks}) components in FA [12,15,18,19].

Some K^+ channels may be distinctively or predominantly expressed in atria compared with ventricles or/and possess distinctive biophysical properties that differentiate them from their counterparts in the ventricles, making them ideal drug targets for AF. So far, the ultrafast activation delayed rectifier voltage-dependent Kv1.5 current (I_{Kur}), the I_{KACh} current, and the TWIK-related acid-sensitive K^+ channel type 1 (TASK1) conducting I_{TASK1} current have been best validated atrial-specific ionic currents [20]. The atrial- and ventricular-K^+-currents could be formed by the participation of several α-subunits as well as β-regulatory subunits as is described in Fig. 2.

Numerous variants in K^+ channel encoding genes are associated with rare forms of genetic AF, such as Kv1.5, Kv4.2, Kv4.3, Kir2.1, Kir3.4, and $K_2P_{3.1}$ (TASK-1) [11], these last two specific to atria cells. So far, many previous studies have demonstrated that the dysregulation of the cardiac ion channel conducting I_{to}, I_{Kur}, I_{CaL}, I_{SK}, I_{K1},

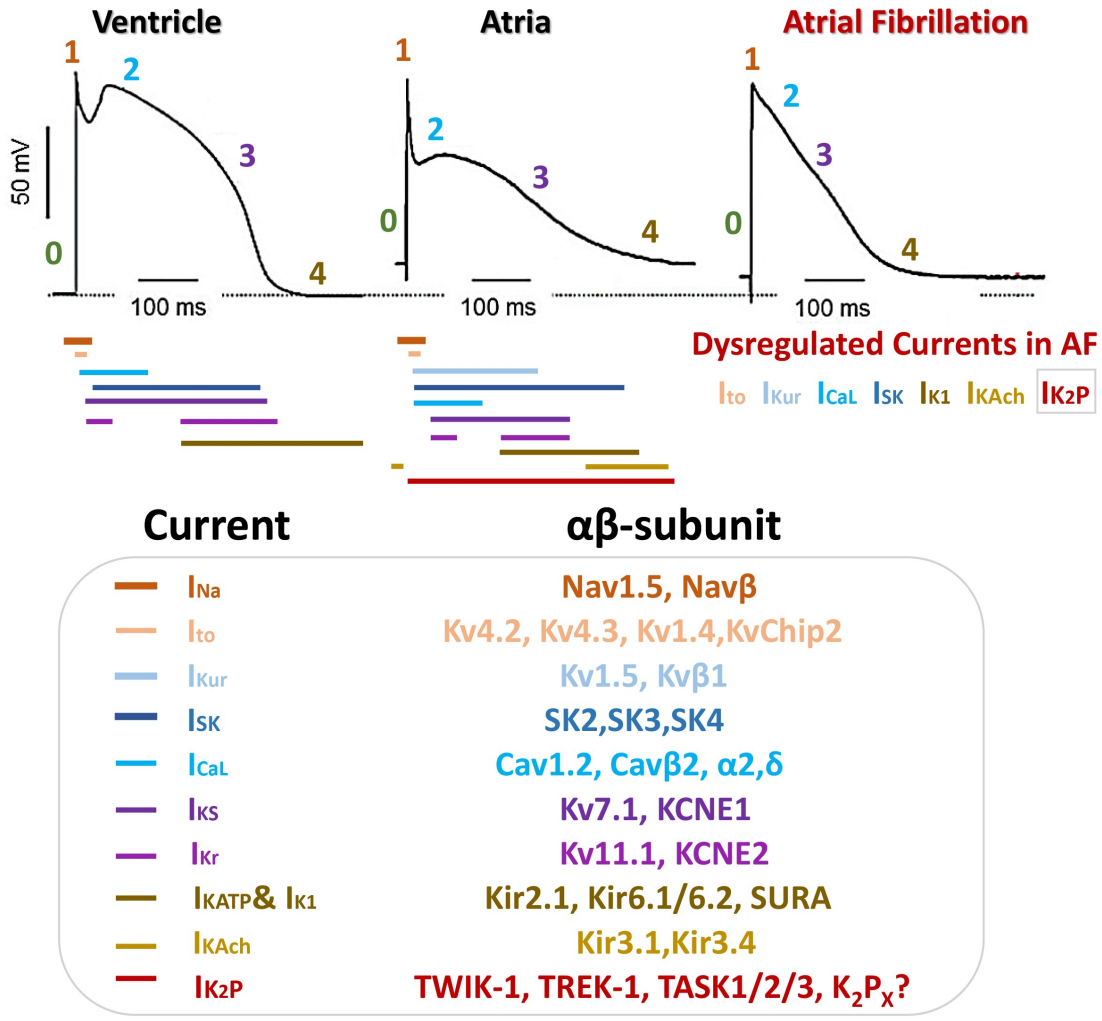

Fig. 2. Schematic illustration of cardiac ion channels, currents and proteins implicated in action potential (AP) morphology of ventricular, atria, and AF-atrial cardiomyocytes.

I_{KACh}, and I_{K2P} currents is critical in the electrophysiological remodeling of AF (Fig. 2). Hence, it has highlighted that targeting these atrial-specific K^+ channel as a promising therapeutic principle for AF. K_2P channels are fascinating ion channel group since are responsible of the leak or conductance voltage-independent K^+ current and appear to have functionality for most of the duration of the atrial AP [21,22]. In addition, knowledge of the regulation and physiological role of K_2P channels is not yet fully understood. Therefore, throughout this review we will mainly emphasize the role of K_2P channels in AF and their therapeutic potential.

3. Outlook K_2P Channels in Atrial Fibrillation: K_2P Channels Druggability

K_2P channels are formed by a structure of two pore-forming loop domains in each alpha subunit; two of these alpha subunits assemble into a dimer to form the channel [23]. I_{K2P} currents are involved in background K^+ conductance, stabilizing the Vrest and the repolarization in atrial cells. K_2P channels have been considered voltage-independent ion channels, since there is no voltage-sensing domain (VSD) in their structure, where their strong outward rectification arises from the asymmetric K^+ gradient across the membrane following the Goldman-Hodgkin-Katz equation. K_2P channels produce basically instantaneous and non-inactivatable currents an extensive range of the membrane potential (Vm) [24].

Due to these characteristic biophysical properties K_2P channels are also known as background or "leak" K^+ channels with important implications in stabilizing Vrest and contributing to repolarization. Whereas the TASK1 currents conform to the Goldman-Hodgkin-Katz equation, other K_2P channels may exhibit variations: i.e., TREK1 have a slight outward; TWIK1/TWIK2 channels have inward rectification; there is a slow inactivation component that represents for approximately 50% of TWIK2 current; and TRESK shows asymmetric gating behavior [24–

26]. Interestingly a noteworthy voltage-dependent activation has been found in some K_2P channels, nevertheless the exact mechanism remains uncertain due to the lack of a canonical voltage-sensing domain in channel structure [27].

Then, the modulation of K_2P currents provides a mechanism for regulating cellular excitability [27]. K_2P channels can be modulated by several physiological and chemical factors such as temperature, pH, lipids, stretch, kinases, neurotransmitters, unsaturated fatty acids, antidepressants and anesthetics [28]. The K_2P channels is categorized into six groups: Two pore-domain weakly inward rectifying K^+ channel (TWIK), TWIK-related alkaline-sensitive K^+ channel (TALK), TWIK-related acid-sensitive K^+ channel (TASK), TWIK-related spinal cord K^+ channel (TRESK), TWIK-related K^+ channel (TREK) and tandem pore domain halothane-inhibited K^+ channel (THIK) [25]. To date, only TWIK-1, TREK-1, TASK-1, TASK-2 and TASK-3 channel have been identified as responsible for background I_{K2P} current in atrial cells [21,22]. The I_{K2P} current persists throughout all phases of the atrial AP, stabilizing the membrane potential toward Vrest (Fig. 2), prevent EADs, and could be involved in adjusting the availability of the Na^+ channel for depolarization (phase 0) [29]. Patch clamp recordings have indicated that alteration in I_{K2P} current can alter the shape and the duration of action potentials in human atrial cells [30]. Then, the alteration of I_{K2P} current either by changes in channel expression, trafficking or activity, can contribute to changes that can affects the processes involved in the generation of pro-arrhythmic phenomena as development of EADs or DADs and enhancing the automaticity, constituting a trigger for the development and maintenance of AF.

However, it is not excluded that other K_2P_X subunits or subfamilies have physiological roles in atria. New research in this area may improve our knowledge about K_2P channel function. K_2P channel family is really fascinating since several studies have demonstrated that the expression of TWIK-1, TREK-1, TASK-1, TASK-2 and TASK-3 are dysregulated in AF [6,11,23,24,31–33]. Moreover, the loss of function (LoF) mutations on TASK1-enconding gene have been reported in patients with familiar AF [34].

K_2P channel modulators could have enormous therapeutic potential in AF and, luckily, they are known to be very good "druggable" targets [28]. As most studies have focused on elucidating the physiological role of these channels in cardiomyocytes, the pharmacological profiles developed so far have not been very satisfactory. Many studies have shown that several of the medications used to control heart rate and heart rhythm in AF exert their mechanism of action in part by modulation of K_2P channels. To date, many marketed and non-marketed compounds capable of targeting K_2P channels direct or indirectly have been identified. However, many of these drugs are not selective for a unique K^+ channel subfamily or subtype, but rather target several ion channels. Although the exact pharmacology of TWIK channels is not yet known, many potent activators/blockers for TASK and TREK have been identified. Our recent advances in the physiology and pharmacology of K_2P channels have helped us to better understand many of the intricate mechanisms that can modulate the K_2P activity or expression.

Here we will review the information on K_2P channels expressed in atria and review available drugs to modulate potentially the activity of specific K_2P channels and their possible use for AF treatment.

3.1 TWIK-1

TWIK-1 or $K_2P_{1.1}$ channels are encoded by *KCNK1* gene and expressed robustly in atria; however, is still a matter of ongoing debate its physiological significance. The TWIK-1 channel appears to have a well-conserved role in cardiac function. A study in zebrafish embryos demonstrated TWIK-1 channel is needed for a normal atrial morphology and heart rate. The TWIK-1 knockdown results in bradycardia and atrial dilatation [28]. However, despite its functional importance in atria, genetic variation in *KCNK1* has not been revealed to be a common direct cause of AF. Gaborit N and colleagues [35] also showed that TWIK-1 is upregulated in AF associated to valvular heart disease. Therefore, TWIK-1 inhibitors may be useful for AF treatment. Another study also demonstrated that the TWIK-1 channel could change its permeability to Na^+ by promoting membrane depolarization under conditions of hypokalemia and acidosis. The changes in TWIK-1 ion selectivity could increase excitability of atrial cardiomyocytes resulting in enhanced automaticity under these conditions predisposing to tachycardia and AF development [24]. In this case, where the selectivity of K^+ is replaced by Na^+ will be also effective TWIK-1 blockers to preventing AF.

As stated above, the TWIK channels-related pharmacology is still very lacking. To date, it has not been identified any TWIK-1 channels activators or enhancers and any TWIK-1 inhibitor/blockers reported are not useful in the submicromolar range. Bupivacaine, a local anesthetic, showed a low potency block effect on TWIK subfamily [36]. Antiarrhythmic such as quinidine, useful for controlling heart rhythm in AF, and Ibutilide, useful for the cardioversion of recent AF or flutter, have a blocker effect on TWIK-1 channels [37–39]. Quinine, a antimalaria treatment, also have been demonstrated that can inhibit these channels [37] (Fig. 3). It should be noted that TWIK-1 is also expressed in brain, kidney, and pancreatic cells; therefore, drugs targeting these channels for the treatment of AF could have side effects on these tissues. In brain, TWIK-1 channels contribute to the regulation of AP firing and excitability in dentate gyrus granule cells. TWIK-1 channel also participates in the ion and water transport in kidney and in the regulation of Vrest on pancreatic beta cells [25,28,40].

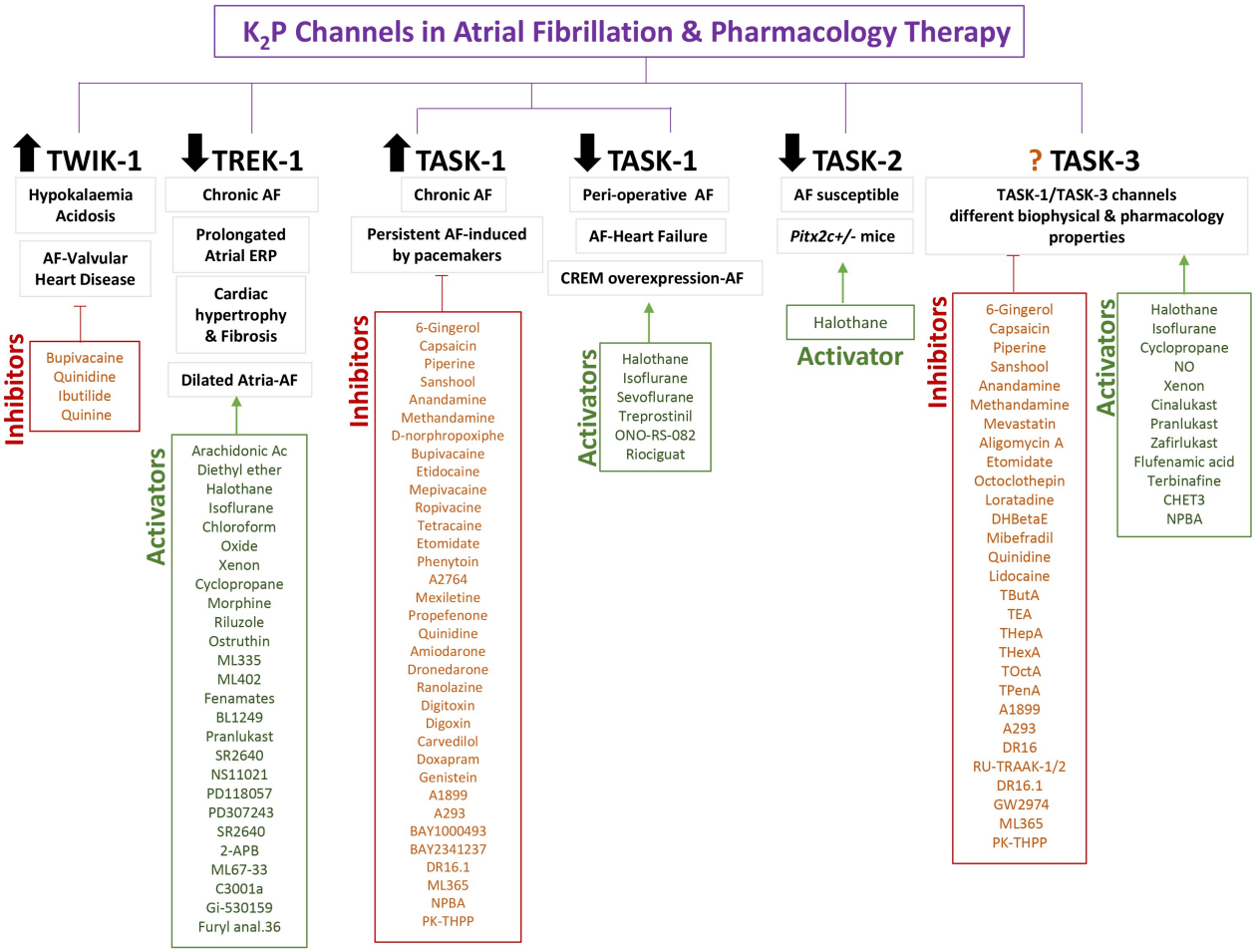

Fig. 3. K_2P channels in the pathogenesis of atrial fibrillation and available drug therapy.

3.2 TREK-1

TREK-1 or $K_2P_{2.1}$ channels, encoded by the *KCNK2* gene, are stretch-sensitive contributing to mechanoelectrical feedback, AP regulation and atrial electrophysiology. It was identified with a time-dependent reduction of TREK-1 protein expression in the right atrium by 70% at 7 days and 80% at 21 days of induced-AF in a porcine model; however, TREK-1 channel expression in the left atrium, AV node, and ventricles was not affected [26]. Lugenbiel P *et al.* [41], also demonstrated that atrial TREK-1 mRNA levels were reduced by 82% (left atrium) and 81% (right atrium) in patients with chronic AF and HF which was associated with prolongation of atrial effective refractory periods (ERP). The authors propose that functional correction of the TREK-1 channel by gene therapy could represent a new paradigm for the AF treatment [41]. Schmidt C *et al.* [42], study also recapitulated in CREM transgenic mice the development of AF-associated with TREK-1 mRNA/protein downregulation suggesting a mechanistic contribution of this channel to cardiac arrhythmogenesis. The dysregulation of TREK-1 channel has also been implicated in cardiac fibrosis and hypertrophy as well as heart failure due to their mechano-active properties [24].

Only downregulation of the TREK-1 channel has been reported in the pathogenesis of AF, therefore specific activators or enhancers of this channel could be a pharmacological therapy for the disease (Fig. 3). A distinctive feature of TREK channels with respect to other K_2P channels is the activation through the *C-terminal* region by polyunsaturated fatty acids (arachidonic acid) or lysophospholipids [43]. As other K_2P channels, TREK channels can be activated at clinically concentration by many general anesthetics (cyclopropane, nitrous trichloroethanol, xenon and oxide) and volatile compounds (chloroform, halothane, isoflurane and diethyl ether) [44,45]. Opioids such as morphine can induce an opioid receptor-independent TREK-1 channel activation by binding directly to TREK-1 structure [46]. Many fenamates (diclofenac, flufenamic acid, mefenamic acid and niflumic acid), fenamate-like compound (BL1249, Pranlukast) and other negatively charged activators [NCAs] (SR2640 NS11021, PD118057, PD307243, and SR2640) are activate TREK-1 through direct unlocking and stabilizing the selectivity filter gate [47–49].

2-aminoethoxydiphenyl borate (2-APB) also activates TREK-1 channels through *C-terminal* region [50]. Riluzole, a drug used for amyotrophic lateral sclerosis treat-

ment, exhibits a dual effect on TREK-1 channels. Riluzole can transiently activate TREK-1 followed by a longer lasting inhibitory effect attributed to increased intracellular cAMP and protein kinase A (PKA)-dependent inhibition [51]. Then, Tolbutamide, cAMP inhibitor, has the contrary to riluzole's long term-effect of on TREK-1 channels. A plant extract named aristolochic acid used in pain treatment, and caffeic acid esters such as CAPE and CDC also are TREK-1 channels enhancers [52,53]. Joseph A *et al.* [54], showed that ostruthin may exert its anxiolytic and antidepressive effects in part through TREK-1 channel activation. Recently, two small molecular activators (ML335 and ML402) capable of binding near the selectivity filter of the TREK-1 channel have been identified [55]. Other small molecules as ML67-33, C3001a and gi-530159 have been also identified as activators of this channels [56–58]. However, many of these TREK-1 activator compounds described here are no selective for TREK1 channel presenting other side effects on other potassium subunits, which does not make them good candidates [59]. One study identified a furyl analogue 36 as one of the first promising selective TREK-1 agonist (Fig. 3) [60]. Several studies have demonstrated the functionality of this channel in neurons, endothelial, vascular smooth muscle cells, and in gastrointestinal tract cells. TREK-1 is targeted for general anesthesia by volatile and gaseous agents playing a role in ischemic and epileptic neuroprotection, pain sensing and depression [61].

3.3 TASK-1

TASK1 or $K_2P_{3.1}$ channels, encoded by *KCNK3* gene, exhibited predominantly atrial expression which is conserved in different species including human, pigs, dogs, chicken, mice, rats, and zebrafish [23]. Importantly, TASK-1 current is considered the major component of background conductance in human atrial cardiomyocytes which is inhibited by α1A-adrenergic receptor stimulation and extracellular acidosis [30]. These specific properties are shared by the sustained cardiac outward K^+ current, indicating that TASK1 channels largely conduct the cardiac plateau K^+ current known as I_{K2P} [23]. Its functional significance in atria has been strongly supported by several studies suggesting TASK-1 channel dysregulation has a huge impact on atrial electrical activity and morphology supposing an arrhythmogenic substrate for AF [30].

It has been evidenced that atrial TASK1 mRNA/protein levels are upregulated in a human chronic AF cohort (5-11) compared with people in sinus rhythm; while, TASK1 expression was not affected in paroxysmal AF patients [23]. TASK1 channel upregulation causes a shortened AP duration in the right atrium which is restored using pharmacological TASK1 inhibitors [62]. Animals studies in pigs, have also demonstrated that TASK1 channel expression is upregulated in persistent AF-induced by atrial burst stimulation via implanted pacemakers. The TASK1 current upregulation as well as the shortening of the APD is prevented by the intravenously treatment of a TASK1 specific blocker, A293, administered one per day during 14 days [63]. Constanze Schmidt, Felix Wiedmann and colleagues [64] also demonstrated that TASK1 genetic ablation using Anti-TASK-1 adeno-associated virus suppresses AF and corrects the electrical remodeling in a pig AF animal model. For instance, TASK channel inhibition seems to be a promising therapeutic approach for the treatment of AF (Fig. 3). Many plant extracts (6-Gingerol, capsaicin, piperine, sanshool) [50,65], cannabinoids (anandamine and methandamine) [66], and the opioid D-norphropoxiphe [67] can inhibit TASK1 channels. A large group of anesthetics such as bupivacaine, etidocaine, mepivacaine, ropivacine, tetracaine, etomidate has been demonstrated to block TASK1 channels [38,68]. The anticonvulsant phenytoin, the antipsychotics fluoxetine and a cloxiquin analogs (A2764) also showed to exert a TASK1 blocker effect on several studies [67–69]. The therapeutic effect of several drugs used and commercialized for targeting different cardiac diseases among them AF could be mediated by the TASK1 inhibition such as antiarrhythmics (mexiletine, propefenone, quinidine, amiodarone, dronedarone, ranolazine), cardiac glycosides (digitoxin and digoxin), and the $\alpha\beta$ blocker carvedilol [32,69–74]. Doxapram, a ventilatory stimulant, and genistein, TK inhibitor, also inhibit TASK1 channel; however, these two drugs also act indiscriminately on TASK3 channels [75]. A new potent TASK-1 inhibitor, doxapram, is being investigated under DOCTOS clinical trial. This study will reveal in the near future whether doxapram is a good option for the acute conversion of paroxysmal/persistent AF to sinus rhythm [76]. Selective Kv1.5 channel blockers (A1899 and A293) designed as antiarrhythmic drugs for AF treatment, have showed interestingly to be much about 70-fold more potent on TASK-1 channels than Kv1.5 channels, making them TASK selective at low doses [77]. Furthermore, A293 treatment significantly reduced AF burden in a persistent AF animal model. A limitation of this study was an increase in pulmonary arterial pressure after acute TASK-1 inhibition. However, no adverse effects on the central nervous system were observed [63]. Other small molecules have been developed to exert a blocker effect on TASK1 currents such as BAY1000493, BAY2341237, DR16.1, ML365, NPBA and PK-THPP [68,78–82].

On the other hand, many other studies had supported the downregulation of the TASK1 channel or the absence of TASK1 current in peri-operative AF (peri-op AF), which is common complication after thoracic surgery; and in AF associated to heart failure (AF-HF) which is increasingly encountered in patients with HF (Fig. 3). In 2013, Harleton and colleagues [83] investigated that canine perioperative AF was associated with loss of TASK-1 current function due to an increased phosphorylation at threonine 383 in the *C-terminus* of TASK-1 channel. In 2015, the same

group found TASK-1 current was present in human and canine atrial myocytes with regular sinus rhythm, but was absent in humans with AF undergoing cardiac surgery and in canine atrial myocytes after induction of AF by chronic tachypacing [84]. In this study, phosphatase treatment rescued TASK-1 current in atrial myocytes with AF, indicating that inhibition in TASK-1 current is phosphorylation-dependent; however, the specific phosphorylation site in the channel remains unidentified [84]. Other study in pigs also showed TASK1 channel down-regulation in pacing-induced AF with HF [31]. Wiedmann F *et al.* [85], also found atrial TASK-1 channel expression was pointedly reduced in HF murine model where the cardiac dysfunction was induced by transverse aortic constriction. The same group also assessed the TASK1 channel modulation in *(CREM)-IbΔC-X* transgenic mice since human AF susceptibility has been associated with CREB/CREM transcription factors target genes downregulation [85]. Myocardial overexpression of the transcriptional repressor CREM-IbΔC-X in these transgenic mice (CREM-AF) results in downregulation of target genes, among them TASK-1 channels, showing a phenotype of atrial ectopy and AF [85]. Then in peri-op AF, AF-HF and CREM-AF cases, TASK1 channels activators would be also of therapeutic interest in AF. Nevertheless, few TASK-1 or TASK-3 channel activators are known so far. Volatile anesthetics (halothane, isoflurane and sevoflurane) have been identified as TASK1 activators probably through the anesthetic binding pocket, between M4 and M3 segment [59,68]. A prostacyclin analog (potent pulmonary vasodilator) named treprostinil activates the TASK-1 channel at clinically relevant concentrations. Activation is mediated via cyclic AMP (cAMP)–dependent phosphorylation of the channel induced by protein kinase A (PKA) [86]. The loss of TASK-1 current function can be reversed by application of the phospholipase inhibitor ONO-RS-08288 [87]. A recent drug licensed for the pulmonary arterial hypertension treatment, riociguat, a soluble guanylate cyclase (sGC) stimulator, activates protein kinase G (PKG) and stimulates the production of cGMP which can enhance TASK1 current [88]. Drugs targeting TASK1 channel could have side effect in neurons, vascular smooth muscle, and endocrine cells. Loss-of-function mutations at multiple sites in the TASK1 encoding gene are one of the causes of pulmonary arterial hypertension [89].

Taking together all these findings, TASK1 ion channel is a strong regulator of the atrial repolarizing phase of the atrial AP and drugs targeting this atrial-specific ion channel could provide a treatment for AF patients. The full understanding of its role in atria will help to develop better therapeutic approaches.

3.4 TASK-2

TASK-2 or $K_2P_{5.1}$ channel, encoded by *KCNK5* gene, is expressed uniquely in left atria and its function is still uncertain [90]. The transcription factor homeodomain-2 (*PITX2*) may regulate gene expression and electrical function in the adult left atrium. Mice with low levels of atrial Pitx2 expression have a shortened atrial AP and are more susceptible to AF. *Pitx2c+/-* mice also showed atria Vrest more depolarized related to a TASK-2 gene and protein expression downregulation (Fig. 3) [91]. In this case, TASK-2 activators could prevent this phenotype; however, there are no selective activators or inhibitors for this channel currently. Volatile anesthetics appear to activate TASK-2, especially halothane [92]. To consider possible side effects of treatment with TASK-2 activators, it is important to know TASK-2 is also involved in breathing regulation by brainstem retrotrapezoid nucleus chemosensory neurons and pH homeostasis by kidney proximal tubule cells [93].

3.5 TASK-3

TASK-3 or $K_2P_{9.1}$ channel, encoded by *KCNK9* gene, is also expressed consistently in right human auricles. TASK-3 channel is the closest relative of TASK-1 sharing many similarities. It has been demonstrated that TASK-3 forms heteromeric TASK-1/TASK-3 channels at the surface membrane of atria cardiomyocytes with a lower affinity for TASK-1 blockers [94]. Therefore, the design of drugs against AF should consider the possible expression of heteromers at the atrial level and antagonism could be useful for AF treatment (Fig. 3). To date, it is uncertain whether TASK-3 channel is up- or down-regulated in AF, but since it can form heteromers with TASK-1 subunits it should be considered as a possible pharmacological target. In addition to activating TASK-1 channels, halothane and isoflurane also activate TASK-3 channels [94]. Other gaseous anesthetics such as cyclopropane, NO and xenon showed TASK3-enhancer properties [45].

Leukotriene receptor antagonists (LTRA) drugs used for asthma treatment such as cinalukast, pranlukast and zafirlukast could activate TASK-3 current among other potassium channel [48]. TASK-3 is also activated by flufenamic acid [47], the antifungal terbinafine [48], the biguanide derivate CHET3 [95] or the small molecule NPBA [82].

Many plant extracts (6-Gingerol, capsaicin, piperine, sanshool) [50,65], cannabinoids (anandamine and methandamine) [66], antibiotics (mevastatin, aligomycin A) [96] and the general anesthtetic etomidate [68] have been identified as TASK-3 channel inhibitors. Some neurotransmitters antagonists as octoclothepin (D2), loratadine (H1) and DHBetaE (nAChR) also can inhibit TASK-3 channels [96]. We can use Ca^{2+} channel blockers such as mibefradil and the antiarrhythmics quinidine and lidocaine to inhibit these channels [96,97]. Different quaternary ammonium (QA) ions (TButA, TEA, THepA, THexA, TOctA, and TPenA) are binded to the interior of the TASK-3 pore with high-affinity leading to inhibition of the I_{TASK3} current [98].

Other small molecules such as A1899, A293, DR16, DR16.1, GW2974, ML365, PK-THPP, RU-TRAAK-1/2

designed and modified to strongly inhibit TASK channels has a blocker effect on TASK-3 channels, but share affinity for TASK-1 channels as well [77].

TASK-3 gene is also imprinted in the brain and can participates in cognition, sleep/wake control, and epilepsy [82]. On the other hand, several types of cancer cells overexpress TASK-3 channel at the level mRNA and protein, suggesting that upregulation of the TASK-3 channel may play a role in oncogenesis [99]. In addition, mutations in *KCNK9* gene are associated with Birk-Barel dymosphyrm syndrome which is an inherited disease characterized by intellectual disability, hyperactivity, hypotonia and unusual facial features [100].

4. Conclusion, Limitations and New Challenges

Remarkable efforts over several years have been made to define and improve the molecular, structural and electrophysiological processes underlying the induction and perpetuation of AF. Our mechanistic and biological understanding of AF is incomplete and current therapeutic options have limited efficacy and are often fraught with risk and side effects. There is a primordial need to explore and propose new therapeutic approaches. Understanding the pathological mechanisms involved in atrial tissue remodeling and arrhythmogenesis in AF is essential for developing targeted approaches. Understanding the pathological pathways linked to atrial arrhythmogenesis and remodeling in AF is crucial for developing new targeted approaches. Atrial-specific K_2P channels constitute the background current in atrial cardiomyocytes and modulate cell excitability emerging as novel targets in this disease. This family was one of the last K^+ channels to be cloned, which makes them relatively unknown compared to other channels. By advancing crystal structures, *in silico* experiments with molecular dynamics simulations, mathematical models, docking studies and electrophysiological studies have greatly helped to reveal the physiological role of these channels and improve the drug design [101–104]. Molecular dynamics simulations provide information at molecular level that can be contrasted with functional studies [101–104]. These simulations are used for the study of conductance, ion selectivity and ion channel opening where the channel is usually embedded in a membrane patch model that allows following ion movements with a high spatial-temporal resolution [30,105]. Knowing in more detail the ion channel structure allows to perform docking studies between the channel and candidate drugs, to investigate the points of highest affinity for modulation and to propose new modulatory structures. For instance, Xin Tan and colleges investigated how Quercetin alleviate AF explored by network pharmacology combined with molecular docking and experimental validation [106]. Limberg SH *et al.* [30], demonstrated that TASK1 channel modulate atrial AP shape and duration and shape of human atrial cells using mathematical modeling and patch-clamp technique.

Given the recent advances related to their physiological importance in different cellular, k2p channels have emerged as relevant pharmacological targets against a wide variety of diseases, including AF. So far, TWIK-1, TREK-1, TASK-1, TASK-2 and TASK-3 channel have been identified as responsible for background currents I_{K2P} current in atrial cells [21,22]. However, it is not excluded that other groups or subunits have physiological roles. To date, a great diversity openers, activators and blockers of K_2P channel have been identified, particularly those targeting TASK and TREK channels. However, a major limitation is that many of these TASK modulators are not selective for TASK-1, TASK-2, or TASK-3 members, but have affinity for all subunits due to their high homology. The main goal of this review is to outline the pathways of K_2P channel modulation in AF and how correct their dysfunction using different pharmacological K_2P modulators. Interestingly, many of heart rate and rhythm controlling medications used as current therapy in AF patients have a multichannel blocking profile, among them K_2P channels. Blockade of K_2P channels in the heart causes AP prolongation and may provide antiarrhythmic action in AF [72]. Here, it has been summarized as several antiarrhythmic drugs exert their mechanism of action in part by modulation of K_2P channels. Despite the multitude of known K_2P channel modulators, more selective and potent compounds with adequate pharmacokinetics are needed to avoid side effects on other tissues. There are two TASK-1 channel blockers under clinical investigation against and AF (DOCTOS Clinical Trial) and OSA (SANDMAN Clinical Trial) [77,107]. The future therapeutic applications of these two compounds for AF are a compelling incentive for further study of the pharmacology of K_2P channels. However, a serious complication of the use of TASK1 blockers for the treatment of AF may be their effect on the pulmonary vasculature. For example, Wiedmann and colleagues [63] found that *in vivo* TASK-1 channel inhibition in pigs with persistent AF was associated with an increase in pulmonary arterial pressure (PAP), confirming that TASK-1 plays a role in the homeostasis of the pulmonary vasculature. One way to overcome this could be to encourage a more cardiac-targeted drug delivery procedure, cardiac cell therapy or regulation of the expression of this ion channel by an upstream component, i.e., using oligonucleotide therapeutics. For example, one study showed that microRNA-34a might regulate the expression of atrial TASK-1 channels and modulation of this miR-34a can help alleviating AF [108]. Up to now, many studies have highlighted the pathological role and pharmacology of TWIK-1, TREK-1, TASK-1, TASK-1, TASK-2 and TASK-3 channels in AF and, undoubtedly, future research study in this field will provide more detailed mechanistic knowledge about K_2P channels allowing the development of new drugs modulation of these channels to alleviate AF.

Author Contributions

GMP wrote, edited and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

References

[1] Sagris M, Vardas EP, Theofilis P, Antonopoulos AS, Oikonomou E, Tousoulis D. Atrial Fibrillation: Pathogenesis, Predisposing Factors, and Genetics. International Journal of Molecular Sciences. 2021; 23: 6.

[2] Liu X, Guo N, Zhu W, Zhou Q, Liu M, Chen C, *et al*. Resting Heart Rate and the Risk of Atrial Fibrillation. International Heart Journal. 2019; 60: 805–811.

[3] Baman JR, Passman RS. Atrial Fibrillation. The Journal of the American Medical Association. 2021; 325: 2218.

[4] Roberts JD, Vittinghoff E, Lu AT, Alonso A, Wang B, Sitlani CM, *et al*. Epigenetic Age and the Risk of Incident Atrial Fibrillation. Circulation. 2021; 144: 1899–1911.

[5] Bhatt HV, Fischer GW. Atrial Fibrillation: Pathophysiology and Therapeutic Options. Journal of Cardiothoracic and Vascular Anesthesia. 2015; 29: 1333–1340.

[6] Ravens U, Odening KE. Atrial fibrillation: Therapeutic potential of atrial K+ channel blockers. Pharmacology & Therapeutics. 2017; 176: 13–21.

[7] Andersen JH, Andreasen L, Olesen MS. Atrial fibrillation-a complex polygenetic disease. European Journal of Human Genetics. 2021; 29: 1051–1060.

[8] Vizzardi E, Curnis A, Latini MG, Salghetti F, Rocco E, Lupi L, *et al*. Risk factors for atrial fibrillation recurrence: a literature review. Journal of Cardiovascular Medicine. 2014; 15: 235–253.

[9] Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrillation. Circulation Research. 2017; 120: 1501–1517.

[10] Andrade J, Khairy P, Dobrev D, Nattel S. The Clinical Profile and Pathophysiology of Atrial Fibrillation. Circulation Research. 2014; 114: 1453–1468.

[11] Burg S, Attali B. Targeting of Potassium Channels in Cardiac Arrhythmias. Trends in Pharmacological Sciences. 2021; 42: 491–506.

[12] Iwasaki Y, Nishida K, Kato T, Nattel S. Atrial Fibrillation Pathophysiology. Circulation. 2011; 124: 2264–2274.

[13] Linz D, Elliott AD, Hohl M, Malik V, Schotten U, Dobrev D, *et al*. Role of autonomic nervous system in atrial fibrillation. International Journal of Cardiology. 2019; 287: 181–188.

[14] Miragoli M, Glukhov AV. Atrial Fibrillation and Fibrosis: beyond the Cardiomyocyte Centric View. BioMed Research International. 2015; 2015: 798768.

[15] Al Ghamdi B, Hassan W. Atrial Remodeling And Atrial Fibrillation: Mechanistic Interactions And Clinical Implications. Journal of Atrial Fibrillation. 2009; 2: 125.

[16] Patel C, Salahuddin M, Jones A, Patel A, Yan G, Kowey PR. Atrial Fibrillation: Pharmacological Therapy. Current Problems in Cardiology. 2011; 36: 87–120.

[17] Du DM, Hellen N, Kane C, Terracciano CN. Action Potential Morphology of Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes does not Predict Cardiac Chamber Specificity and is Dependent on Cell Density. Biophysical Journal. 2015; 108: 1–4.

[18] Dawodu AA, Monti F, Iwashiro K, Schiariti M, Chiavarelli R, Puddu PE. The shape of human atrial action potential accounts for different frequency-related changes *in vitro*. International Journal of Cardiology. 1996; 54: 237–249.

[19] Bosch R. Cellular electrophysiology of atrial fibrillation. Cardiovascular Research. 2002; 54: 259–269.

[20] Varró A, Tomek J, Nagy N, Virág L, Passini E, Rodriguez B, *et al*. Cardiac transmembrane ion channels and action potentials: cellular physiology and arrhythmogenic behavior. Physiological Reviews. 2021; 101: 1083–1176.

[21] Ravens U. Atrial-selective K+ channel blockers: potential antiarrhythmic drugs in atrial fibrillation? Canadian Journal of Physiology and Pharmacology. 2017; 95: 1313–1318.

[22] Voigt N, Dobrev D. Atrial-Selective Potassium Channel Blockers. Cardiac Electrophysiology Clinics. 2016; 8: 411–421.

[23] Schmidt C, Wiedmann F, Schweizer PA, Katus HA, Thomas D. Inhibition of cardiac two-pore-domain K+ (K2P) channels – an emerging antiarrhythmic concept. European Journal of Pharmacology. 2014; 738: 250–255.

[24] Wiedmann F, Frey N, Schmidt C. Two-Pore-Domain Potassium (K2P-) Channels: Cardiac Expression Patterns and Disease-Specific Remodelling Processes. Cells. 2021; 10: 2914.

[25] Feliciangeli S, Chatelain FC, Bichet D, Lesage F. The family of K2P channels: salient structural and functional properties. Journal of Physiology. 2015; 593: 2587–2603.

[26] Schmidt C, Wiedmann F, Tristram F, Anand P, Wenzel W, Lugenbiel P, *et al*. Cardiac expression and atrial fibrillation-associated remodeling of K2P2.1 (TREK-1) K+ channels in a porcine model. Life Sciences. 2014; 97: 107–115.

[27] Schewe M, Nematian-Ardestani E, Sun H, Musinszki M, Cordeiro S, Bucci G, *et al*. A Non-canonical Voltage-Sensing Mechanism Controls Gating in K2P K+ Channels. Cell. 2016; 164: 937–949.

[28] Christensen AH, Chatelain FC, Huttner IG, Olesen MS, Soka M, Feliciangeli S, *et al*. The two-pore domain potassium channel, TWIK-1, has a role in the regulation of heart rate and atrial size. Journal of Molecular and Cellular Cardiology. 2016; 97: 24–35.

[29] Jeevaratnam K, Chadda KR, Huang CLH, Camm AJ. Cardiac Potassium Channels: Physiological Insights for Targeted Therapy. Journal of Cardiovascular Pharmacology and Therapeutics. 2018; 23: 119–129.

[30] Limberg SH, Netter MF, Rolfes C, Rinné S, Schlichthörl G, Zuzarte M, *et al*. TASK-1 Channels may Modulate Action Potential Duration of Human Atrial Cardiomyocytes. Cellular Physiology and Biochemistry. 2011; 28: 613–624.

[31] Schmidt C, Wiedmann F, Langer C, Tristram F, Anand P, Wenzel W, *et al*. Cloning, functional characterization, and remodeling of K2P3.1 (TASK-1) potassium channels in a porcine model of atrial fibrillation and heart failure. Heart Rhythm. 2014; 11: 1798–1805.

[32] Ratte A, Wiedmann F, Kraft M, Katus HA, Schmidt C. Antiarrhythmic Properties of Ranolazine: Inhibition of Atrial Fibrillation Associated TASK-1 Potassium Channels. Frontiers in Pharmacology. 2019; 10: 1367.

[33] Herrera-Pérez S, Campos-Ríos A, Rueda-Ruzafa L, Lamas JA. Contribution of K2P Potassium Channels to Cardiac Physiology and Pathophysiology. International Journal of Molecular Sciences. 2021; 22: 6635.

[34] Liang B, Soka M, Christensen AH, Olesen MS, Larsen AP, Knop FK, *et al*. Genetic variation in the two-pore domain potassium channel, TASK-1, may contribute to an atrial substrate for arrhythmogenesis. Journal of Molecular and Cellular Cardiology. 2014; 67: 69–76.
[35] Gaborit N, Steenman M, Lamirault G, Le Meur N, Le Bouter S, Lande G, *et al*. Human Atrial Ion Channel and Transporter Subunit Gene-Expression Remodeling Associated with Valvular Heart Disease and Atrial Fibrillation. Circulation. 2005; 112: 471–481.
[36] Foster RH, Wilde MI, Markham A. Ibutilide. A review of its pharmacological properties and clinical potential in the acute management of atrial flutter and fibrillation. Drugs. 1997; 54: 312–330.
[37] Lesage F, Guillemare E, Fink M, Duprat F, Lazdunski M, Romey G, *et al*. TWIK-1, a ubiquitous human weakly inward rectifying K+ channel with a novel structure. EMBO Journal. 1996; 15: 1004–1011.
[38] Kindler C, Yost S, Gray A. Local Anesthetic Inhibition of Baseline Potassium Channels with Two Pore Domains in Tandem. Anesthesiology. 1999; 90: 1092–1102.
[39] Doggrell SA, Hancox JC. Ibutilide – recent molecular insights and accumulating evidence for use in atrial flutter and fibrillation. Expert Opinion on Investigational Drugs. 2005; 14: 655–669.
[40] Lesage F, Lazdunski M. Molecular and functional properties of two-pore-domain potassium channels. American Journal of Physiology-Renal Physiology. 2000; 279: F793–F801.
[41] Lugenbiel P, Wenz F, Syren P, Geschwill P, Govorov K, Seyler C, *et al*. TREK-1 (K2P2.1) K+ channels are suppressed in patients with atrial fibrillation and heart failure and provide therapeutic targets for rhythm control. Basic Research in Cardiology. 2017; 112: 8.
[42] Schmidt C, Wiedmann F, Kallenberger SM, Ratte A, Schulte JS, Scholz B, *et al*. Stretch-activated two-pore-domain (K2P) potassium channels in the heart: Focus on atrial fibrillation and heart failure. Progress in Biophysics and Molecular Biology. 2017; 130: 233–243.
[43] Patel AJ. A mammalian two pore domain mechano-gated S-like K+ channel. EMBO Journal. 1998; 17: 4283–4290.
[44] Harinath S, Sikdar SK. Trichloroethanol enhances the activity of recombinant human TREK-1 and TRAAK channels. Neuropharmacology. 2004; 46: 750–760.
[45] Gruss M, Bushell TJ, Bright DP, Lieb WR, Mathie A, Franks NP. Two-pore-domain K+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. Molecular Pharmacology. 2004; 65: 443–452.
[46] Devilliers M, Busserolles J, Lolignier S, Deval E, Pereira V, Alloui A, *et al*. Activation of TREK-1 by morphine results in analgesia without adverse side effects. Nature Communications. 2013; 4: 2941.
[47] Veale EL, Al-Moubarak E, Bajaria N, Omoto K, Cao L, Tucker SJ, *et al*. Influence of the N Terminus on the Biophysical Properties and Pharmacology of TREK1 Potassium Channels. Molecular Pharmacology. 2014; 85: 671–681.
[48] Wright PD, McCoull D, Walsh Y, Large JM, Hadrys BW, Gaurilcikaite E, *et al*. Pranlukast is a novel small molecule activator of the two-pore domain potassium channel TREK2. Biochemical and Biophysical Research Communications. 2019; 520: 35–40.
[49] Schewe M, Sun H, Mert Ü, Mackenzie A, Pike ACW, Schulz F, *et al*. A pharmacological master key mechanism that unlocks the selectivity filter gate in K+ channels. Science. 2019; 363: 875–880.
[50] Beltrán L, Beltrán M, Aguado A, Gisselmann G, Hatt H. 2-Aminoethoxydiphenyl borate activates the mechanically gated human KCNK channels KCNK 2 (TREK-1), KCNK 4 (TRAAK), and KCNK 10 (TREK-2). Frontiers in Pharmacology. 2013; 4: 63.
[51] Duprat F, Lesage F, Patel AJ, Fink M, Romey G, Lazdunski M. The neuroprotective agent riluzole activates the two P domain K(+) channels TREK-1 and TRAAK. Molecular Pharmacology. 2000; 57: 906–912.
[52] Veale EL, Mathie A. Aristolochic acid, a plant extract used in the treatment of pain and linked to Balkan endemic nephropathy, is a regulator of K2P channels. British Journal of Pharmacology. 2016; 173: 1639–1652.
[53] Danthi S, Enyeart JA, Enyeart JJ. Caffeic Acid Esters Activate TREK-1 Potassium Channels and Inhibit Depolarization-Dependent Secretion. Molecular Pharmacology. 2004; 65: 599–610.
[54] Joseph A, Thuy TTT, Thanh LT, Okada M. Antidepressive and anxiolytic effects of ostruthin, a TREK-1 channel activator. PLoS ONE. 2018; 13: e0201092.
[55] Lolicato M, Arrigoni C, Mori T, Sekioka Y, Bryant C, Clark KA, *et al*. K2P2.1 (TREK-1)–activator complexes reveal a cryptic selectivity filter binding site. Nature. 2017; 547: 364–368.
[56] Bagriantsev SN, Ang KH, Gallardo-Godoy A, Clark KA, Arkin MR, Renslo AR, *et al*. A high-throughput functional screen identifies small molecule regulators of temperature- and mechano-sensitive K2P channels. ACS Chemical Biology. 2013; 8: 1841–1851.
[57] Qiu Y, Huang L, Fu J, Han C, Fang J, Liao P, *et al*. TREK Channel Family Activator with a well-Defined Structure–Activation Relationship for Pain and Neurogenic Inflammation. Journal of Medicinal Chemistry. 2020; 63: 3665–3677.
[58] Loucif AJC, Saintot PP, Liu J, Antonio BM, Zellmer SG, Yoger K, *et al*. GI-530159, a novel, selective, mechanosensitive two-pore-domain potassium (K2P) channel opener, reduces rat dorsal root ganglion neuron excitability. British Journal of Pharmacology. 2018; 175: 2272–2283.
[59] Patel AJ, Honoré E, Lesage F, Fink M, Romey G, Lazdunski M. Inhalational anesthetics activate two-pore-domain background K+ channels. Nature Neuroscience. 1999; 2: 422–426.
[60] Vivier D, Soussia IB, Rodrigues N, Lolignier S, Devilliers M, Chatelain FC, *et al*. Development of the First Two-Pore Domain Potassium Channel TWIK-Related K+ Channel 1-Selective Agonist Possessing *in Vivo* Antinociceptive Activity. Journal of Medicinal Chemistry. 2017; 60: 1076–1088.
[61] Dedman A, Sharif-Naeini R, Folgering JHA, Duprat F, Patel A, Honoré E. The mechano-gated K2P channel TREK-1. European Biophysics Journal. 2009; 38: 293–303.
[62] Schmidt C, Wiedmann F, Voigt N, Zhou XB, Heijman J, Lang S, *et al*. Upregulation of K(2P)3.1 K+ Current Causes Action Potential Shortening in Patients With Chronic Atrial Fibrillation. Circulation. 2015; 132: 82–92.
[63] Wiedmann F, Beyersdorf C, Zhou XB, Kraft M, Foerster KI, El-Battrawy I, *et al*. The Experimental TASK-1 Potassium Channel Inhibitor A293 Can Be Employed for Rhythm Control of Persistent Atrial Fibrillation in a Translational Large Animal Model. Frontiers in Physiology. 2021; 11: 629421.
[64] Schmidt C, Wiedmann F, Beyersdorf C, Zhao Z, El-Battrawy I, Lan H, *et al*. Genetic Ablation of TASK-1 (Tandem of P Domains in a Weak Inward Rectifying K+ Channel-Related Acid-Sensitive K+ Channel-1) (K2P3.1) K+ Channels Suppresses Atrial Fibrillation and Prevents Electrical Remodeling. Circulation: Arrhythmia and Electrophysiology. 2019; 12: e007465.
[65] Bautista DM, Sigal YM, Milstein AD, Garrison JL, Zorn JA, Tsuruda PR, *et al*. Pungent agents from Szechuan peppers excite sensory neurons by inhibiting two-pore potassium channels. Nature Neuroscience. 2008; 11: 772–779.
[66] Berg AP. Motoneurons Express Heteromeric TWIK-Related

Acid-Sensitive K+ (TASK) Channels Containing TASK-1 (KCNK3) and TASK-3 (KCNK9) Subunits. Journal of Neuroscience. 2004; 24: 6693–6702.
[67] Hajdu P, Ulens C, Panyi G, Tytgat J. Drug- and mutagenesis-induced changes in the selectivity filter of a cardiac two-pore background K channel. Cardiovascular Research. 2003; 58: 46–54.
[68] Putzke C, Hanley PJ, Schlichthörl G, Preisig-Müller R, Rinné S, Anetseder M, *et al*. Differential effects of volatile and intravenous anesthetics on the activity of human TASK-1. American Journal of Physiology-Cell Physiology. 2007; 293: C1319–C1326.
[69] Leonoudakis D, Gray AT, Winegar BD, Kindler CH, Harada M, Taylor DM, *et al*. An Open Rectifier Potassium Channel with Two Pore Domains in Tandem Cloned from Rat Cerebellum. Journal of Neuroscience. 1998; 18: 868–877.
[70] Staudacher K, Staudacher I, Ficker E, Seyler C, Gierten J, Kisselbach J, *et al*. Carvedilol targets human K2P 3.1 (TASK1) K+ leak channels. British Journal of Pharmacology. 2011; 163: 1099–1110.
[71] Schmidt C, Wiedmann F, Schweizer PA, Becker R, Katus HA, Thomas D. Novel electrophysiological properties of dronedarone: inhibition of human cardiac two-pore-domain potassium (K2P) channels. Naunyn-Schmiedeberg's Archives of Pharmacology. 2012; 385: 1003–1016.
[72] Schmidt C, Wiedmann F, Schweizer PA, Becker R, Katus HA, Thomas D. Class I antiarrhythmic drugs inhibit human cardiac two-pore-domain K+ (K2P) channels. European Journal of Pharmacology. 2013; 721: 237–248.
[73] Schmidt C, Wiedmann F, Gaubatz AR, Ratte A, Katus HA, Thomas D. New Targets for Old Drugs: Cardiac Glycosides Inhibit Atrial-Specific K2P3.1 (TASK-1) Channels. Journal of Pharmacology and Experimental Therapeutics. 2018; 365: 614–623.
[74] Gierten J, Ficker E, Bloehs R, Schweizer PA, Zitron E, Scholz E, *et al*. The human cardiac K2P3.1 (TASK-1) potassium leak channel is a molecular target for the class III antiarrhythmic drug amiodarone. Naunyn-Schmiedeberg's Archives of Pharmacology. 2010; 381: 261–270.
[75] Cotten JF, Keshavaprasad B, Laster MJ, Eger EI, Yost CS. The Ventilatory Stimulant Doxapram Inhibits TASK Tandem Pore (K2P) Potassium Channel Function but does not Affect Minimum Alveolar Anesthetic Concentration. Anesthesia & Analgesia. 2006; 102: 779–785.
[76] Kraft M, Büscher A, Wiedmann F, L'hoste Y, Haefeli WE, Frey N, *et al*. Current Drug Treatment Strategies for Atrial Fibrillation and TASK-1 Inhibition as an Emerging Novel Therapy Option. Frontiers in Pharmacology. 2021; 12: 638445.
[77] Decher N, Rinné S, Bedoya M, Gonzalez W, Kiper AK. Molecular Pharmacology of K2P Potassium Channels | Cell Physiol Biochem. Cellular Physiology & Biochemistry. 2021; 55: 87–107.
[78] Streit AK, Netter MF, Kempf F, Walecki M, Rinné S, Bollepalli MK, *et al*. A Specific Two-pore Domain Potassium Channel Blocker Defines the Structure of the TASK-1 Open Pore. Journal of Biological Chemistry. 2011; 286: 13977–13984.
[79] Rödström KEJ, Kiper AK, Zhang W, Rinné S, Pike ACW, Goldstein M, *et al*. A lower X-gate in TASK channels traps inhibitors within the vestibule. Nature. 2020; 582: 443–447.
[80] Ramírez D, Concha G, Arévalo B, Prent-Peñaloza L, Zúñiga L, Kiper AK, *et al*. Discovery of Novel TASK-3 Channel Blockers Using a Pharmacophore-Based Virtual Screening. International Journal of Molecular Sciences. 2019; 20: 4014.
[81] Flaherty DP, Simpson DS, Miller M, Maki BE, Zou B, Shi J, *et al*. Potent and selective inhibitors of the TASK-1 potassium channel through chemical optimization of a bis-amide scaffold. Bioorganic & Medicinal Chemistry Letters. 2014; 24: 3968–3973.
[82] Tian F, Qiu Y, Lan X, Li M, Yang H, Gao Z. A Small-Molecule Compound Selectively Activates K2P Channel TASK-3 by Acting at Two Distant Clusters of Residues. Molecular Pharmacology. 2019; 96: 26–35.
[83] Harleton E, Besana A, Chandra P, Danilo P, Rosen TS, Rosen MR, *et al*. TASK-1 current is inhibited by phosphorylation during human and canine chronic atrial fibrillation. American Journal of Physiology-Heart and Circulatory Physiology. 2015; 308: H126–H134.
[84] Harleton E, Besana A, Comas GM, Danilo P, Rosen TS, Argenziano M, *et al*. Ability to Induce Atrial Fibrillation in the Perioperative Period is Associated with Phosphorylation-dependent Inhibition of TWIK Protein-related Acid-sensitive Potassium Channel 1 (TASK-1). Journal of Biological Chemistry. 2013; 288: 2829–2838.
[85] Wiedmann F, Schulte JS, Gomes B, Zafeiriou M, Ratte A, Rathjens F, *et al*. Atrial fibrillation and heart failure-associated remodeling of two-pore-domain potassium (K2P) channels in murine disease models: focus on TASK-1. Basic Research in Cardiology. 2018; 113: 27.
[86] Olschewski A, Li Y, Tang B, Hanze J, Eul B, Bohle RM, *et al*. Impact of TASK-1 in Human Pulmonary Artery Smooth Muscle Cells. Circulation Research. 2006; 98: 1072–1080.
[87] Ma L, Roman-Campos D, Austin ED, Eyries M, Sampson KS, Soubrier F, *et al*. A Novel Channelopathy in Pulmonary Arterial Hypertension. New England Journal of Medicine. 2013; 369: 351–361.
[88] Cunningham KP, Holden RG, Escribano-Subias PM, Cogolludo A, Veale EL, Mathie A. Characterization and regulation of wild-type and mutant TASK-1 two pore domain potassium channels indicated in pulmonary arterial hypertension. Journal of Physiology. 2019; 597: 1087–1101.
[89] Inoue M, Matsuoka H, Harada K, Mugishima G, Kameyama M. TASK channels: channelopathies, trafficking, and receptor-mediated inhibition. PflüGers Archiv - European Journal of Physiology. 2020; 472: 911–922.
[90] Liu W, Saint D. Heterogeneous Expression of Tandem-Pore K+ Channel Genes in Adult and Embryonic Rat Heart Quantified by Real-Time Polymerase Chain Reaction. Clinical and Experimental Pharmacology and Physiology. 2004; 31: 174–178.
[91] Syeda F, Holmes AP, Yu TY, Tull S, Kuhlmann SM, Pavlovic D, *et al*. PITX2 Modulates Atrial Membrane Potential and the Antiarrhythmic Effects of Sodium-Channel Blockers. Journal of the American College of Cardiology. 2016; 68: 1881–1894.
[92] Gray A, Zhao B, Kindler C, Winegar B, Mazurek M, Xu J, *et al*. Volatile Anesthetics Activate the Human Tandem Pore Domain Baseline K+Channel KCNK5. Anesthesiology. 2000; 92: 1722–1730.
[93] Cid LP, Roa-Rojas HA, Niemeyer MI, González W, Araki M, Araki K, *et al*. TASK-2: a K2P K(+) channel with complex regulation and diverse physiological functions. Frontiers in Physiology. 2013; 4: 198.
[94] Rinné S, Kiper AK, Schlichthörl G, Dittmann S, Netter MF, Limberg SH, *et al*. TASK-1 and TASK-3 may form heterodimers in human atrial cardiomyocytes. Journal of Molecular and Cellular Cardiology. 2015; 81: 71–80.
[95] Liao P, Qiu Y, Mo Y, Fu J, Song Z, Huang L, *et al*. Selective activation of TWIK-related acid-sensitive K+ 3 subunit-containing channels is analgesic in rodent models. Science Translational Medicine. 2019; 11: eaaw8434.
[96] Bruner JK, Zou B, Zhang H, Zhang Y, Schmidt K, Li M. Identification of novel small molecule modulators of K2P18.1 two-pore potassium channel. European Journal of Pharmacology. 2014; 740: 603–610.

[97] Kim Y, Bang H, Kim D. TASK-3, a New Member of the Tandem Pore K+ Channel Family. Journal of Biological Chemistry. 2000; 275: 9340–9347.
[98] Piechotta PL, Rapedius M, Stansfeld PJ, Bollepalli MK, Erhlich G, Andres-Enguix I, *et al*. The pore structure and gating mechanism of K2P channels. EMBO Journal. 2011; 30: 3607–3619.
[99] Pei L, Wiser O, Slavin A, Mu D, Powers S, Jan LY, *et al*. Oncogenic potential of TASK3 (Kcnk9) depends on K+ channel function. Proceedings of the National Academy of Sciences of the United States of America. 2003; 100: 7803–7807.
[100] Šedivá M, Laššuthová P, Zámečník J, Sedláčková L, Seeman P, Haberlová J. Novel variant in the KCNK9 gene in a girl with Birk Barel syndrome. European Journal of Medical Genetics. 2020; 63: 103619.
[101] Aguilar-Shardonofsky M, Vigmond E, Nattel S, Comtois P. In Silico Optimization of Atrial Fibrillation-Selective Sodium Channel Blocker Pharmacodynamics. Biophysical Journal. 2012; 102: 951–960.
[102] Bai J, Lo A, Gladding PA, Stiles MK, Fedorov VV, Zhao J. In silico investigation of the mechanisms underlying atrial fibrillation due to impaired Pitx2. PLOS Computational Biology. 2020; 16: e1007678.
[103] Ellinwood N, Dobrev D, Morotti S, Grandi E. In Silico Assessment of Efficacy and Safety of IKur Inhibitors in Chronic Atrial Fibrillation: Role of Kinetics and State-Dependence of Drug Binding. Frontiers in Pharmacology. 2017; 8: 799.
[104] Kutzner C, Köpfer DA, Machtens J, de Groot BL, Song C, Zachariae U. Insights into the function of ion channels by computational electrophysiology simulations. Biochimica et Biophysica Acta (BBA) - Biomembranes. 2016; 1858: 1741–1752.
[105] Trayanova NA, Chang KC. How computer simulations of the human heart can improve anti-arrhythmia therapy. Journal of Physiology. 2016; 594: 2483–2502.
[106] Tan X, Xian W, Li X, Chen Y, Geng J, Wang Q, *et al*. Mechanisms of Quercetin against atrial fibrillation explored by network pharmacology combined with molecular docking and experimental validation. Scientific Reports. 2022; 12: 9777.
[107] Gaisl T, Turnbull CD, Weimann G, Unger S, Finger R, Xing C, *et al*. BAY 2253651 for the treatment of obstructive sleep apnoea: a multicentre, double-blind, randomised controlled trial (SANDMAN). European Respiratory Journal. 2021; 58: 2101937.
[108] Wiedmann F, Kraft M, Kallenberger S, Büscher A, Paasche A, Blochberger PL, *et al*. MicroRNAs Regulate TASK-1 and Are Linked to Myocardial Dilatation in Atrial Fibrillation. Journal of the American Heart Association. 2022; 11: e023472.