EDITORIAL

# $K^+$ channels and cardiac electrophysiology

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This special issue of *The Journal of Physiology* includes two reviews (or white papers), seven original research papers, and corresponding perspectives, and focuses on the theme of cardiac $K^+$ channels and cardiacc electrophysiology. Heart diseases including arrhythmias and heart failure (HF) are major cause of mortality and morbidity for both men and women in the developed world. In the heart, $K^+$ channels are largely responsible for stabilizing the resting membrane potential and repolarization of the action potential (AP). A variety of $K^+$ channel types with differential voltage-gating and regulation characteristics work in concert to fine-tune the normal AP. Abnormalities in $K^+$ currents can alter AP duration and profile (i.e. long QT, short QT, early afterdepolariztion), leading to cardiac arrhythmias. Therefore, understanding the detailed inner workings of these $K^+$ channels is critically important for developing both a solid quantitative understanding of cardiac electrophysiology and more effective therapies to prevent and treat heart diseases.

## Conference and white papers on cardiac $K^+$ channels

Recognizing the need to combine experimental investigation and mathematical modelling in studying $K^+$ channels, we held an interdisciplinary conference focusing on the theme of cardiac $K^+$ channels and regulation in March 2016, at the University of California, Davis, USA (https://basicscience.ucdmc.ucdavis.edu/UCDavis-CardiovascularSymposia/index.html). This was the fourth conference in our biennial series entitled *Systems Approach to Understanding Cardiac Excitation–Contraction Coupling and Arrhythmias*. The series started in 2010 with workshop-like discussions of contemperary research isues in this field, including leaders in both experimental and computational modelling approaches. Subsequent meetings drilled down to more narrow topic areas that need quantitative insights. The 2012 topic was *$Ca^{2+}$ channels and SR $Ca^{2+}$ release*. The 2014 topic was *$Na^+$ channel and $Na^+$ transport* and produced three white papers (Chen-Izu *et al.* 2015; Clancy *et al.* 2015; Shattock *et al.* 2015). The 2016 topic was *$K^+$ channels and regulation*. Together these conferences aim to gain in-depth quantitative understanding of each topic area, and also have a long-term goal of overall integration that is essential for understanding heart disease mechanisms.

The 2016 conference on $K^+$ channels covered the following topics in eight sessions: (1) $K^+$ channel dysfunction and arrhythmia: from cell to the heart, (2) Voltage-gated $K^+$ channel structure and function, (3-4) $K^+$ channel regulation I & II, (5) $K^+$ channels regulated by $Ca^{2+}$, (6) Ligand-gated $K^+$ channels, (7) Trafficking and sequestration of $K^+$ channels, and (8) Cardiac $K^+$ channels as therapeutic targets.

The presentations and extensive panel discussions are summarized in two white papers in this special issue. The first (Grandi *et al.* 2017) covers presentations and discussions on voltage-gated $K^+$ channel structure and function, $K^+$ channel expression, trafficking and localization, and regulation. The second (Chiamvimonvat *et al.* 2017) covers the functional roles of $K^+$ channels in health and disease, as well as $K^+$ channels as therapeutic targets. The overall design of the conference and white papers endeavours to combine experimental and modelling studies, and to integrate knowledge at multiple scales from single channels to cells to whole organ and animal levels. These two reviews, written jointly by groups of meeting participants, also summarize consensus, controversies and studies needed to fill gaps in our current knowledge. This special issue also contains original research papers and corresponding perspectives written by conference attendees and other researchers focusing on the theme of cardiac $K^+$ channels and regulation, as summarized below.

## $Ca^{2+}$-regulated $K^+$ channels

Bartos *et al.* (2017) studied the slowly activating delayed rectifier $K^+$ current ($I_{Ks}$) in rabbit ventricular myocytes, combining experimental with modelling methods. They studied the regulation of $I_{Ks}$ by intracellular $[Ca^{2+}]$ ($[Ca^{2+}]_i$) and $\beta$-adrenergic receptor ($\beta$-AR) stimulation. They systematically measured $I_{Ks}$ magnitude and kinetics at known physiological $[Ca^{2+}]_i$ (100–600 nM) with or without isoproterenol. In whole-cell voltage-clamp experiments, both high $[Ca^{2+}]_i$ and $\beta$-AR activation increased $I_{Ks}$ amplitude, shifted the voltage-depend activation towards negative voltages, and slowed deactivation kinetics. These $[Ca^{2+}]_i$ and $\beta$-AR effects were comparable in extent and were additive. They used this experimental data to improve and update their well-established mathematical model, and simulated $I_{Ks}$ during normal cardiac APs. Finally, they validated their findings with physiological AP-clamp and $Ca^{2+}$ transient experiments, showing that normal $Ca^{2+}$ transients are likely to suffice to fully $[Ca^{2+}]_i$-activate $I_{Ks}$ during the AP. This paper demonstrates the power of combining experimental investigation with mathematical modelling (Hill, 2017).

Zhang *et al.* (2017) studied $Ca^{2+}$-activated small conductance $K^+$ channels (SK2) in human atrial myocytes, which they had previously shown to influence arrhythmogenesis and atrial fibrillation. In this paper, they discovered that SK2 channel trafficking depends on distinct roles of the two cytoskeletal proteins, actinin2 and filamin A (by regulating cycling of SK2 channels from endosomes). While actinin2 facilitates recycling of SK2 channels from both early and recycling endosomes, filamin A aids recycling of SK2 channels from the latter. Trafficking of SK2 channels to the right membrane locations in close proximity to $Ca^{2+}$ sources is important for the function of this $Ca^{2+}$-activated $K^+$ channel.

Kennedy *et al.* (2017) conducted detailed mathematical modelling studies to assess how dynamic $Ca^{2+}$-sensitive $K^+$ channels (both SK2 and the $I_{Ks}$) affect membrane voltage and $Ca^{2+}$ alternans during the cardiac AP. They found that with normal $I_{Ks}$ and SK2 currents at baseline levels, the coupling between membrane voltage and $Ca^{2+}$ transient gives rise to concordant alternans (the larger $Ca^{2+}$ transient gives rise to a longer AP at the same beat), and this holds true for both $Ca^{2+}$-driven and voltage-driven alternans. However, in the case of $Ca^{2+}$-driven alternans, increased $I_{Ks}$ and SK2 currents promote discordant


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alternans (the large $Ca^{2+}$ transient gives rise to a shorter AP in the same beat). Their findings help to disentangle the coupling of non-linear dynamic systems, and elucidate the mechanisms underlying cardiac alternans caused by changes in $Ca^{2+}$-sensitive $K^+$ channels under pathological conditions. Their work has also been put into a larger perspective by Huang *et al.* (2017).

### Contribution of $I_{Ks}$ and $I_{Kr}$ to AP repolarization

Devenyi *et al.* (2017) developed a powerful dynamic-clamp approach to study the two major $K^+$ channels – $I_{Ks}$ and $I_{Kr}$ – that are responsible for AP repolarization. These $K^+$ channels have different gating characteristics and time courses during the cardiac AP, and the AP profile feeds back on voltage-gated channels to dynamically reshape their currents. Devenyi *et al.* built a cell-computer interface to carry out model and experimental testing in real time. They used parameter sensitivity analysis to predict how various changes in the biophysical parameters of $I_{Ks}$ and $I_{Kr}$ models may alter AP morphology, which is experimentally tested in live cardiac myocytes by current injection. Mismatch between the model prediction and experiment reveal model inaccuracies, and the models are then optimized, with validation by experimental data. Subsequent simulations using their newly improved model generated an important prediction that $I_{Ks}$ is more influential than $I_{Kr}$ in stabilizing the action potential and suppressing pro-arrhythmic activities. Their findings are further elaborated in the perspective by Grandi (2017).

### Slo2 $K^+$ channel

Giese *et al.* (2017) addressed the fundamental structure–function relationship underlying the gating of the large conductance $K^+$-selective Slo2 channels. Slo2 channels are in a closed state unless activated by elevated intracellular $Na^+$. Two potential mechanisms for stabilization of Slo2 channels in a closed state were investigated. They probed deep into the ion permeation pathway and discovered that (1) hydrophobic interactions between leucine residues in the upper region of the S6 segments contribute to stabilizing the inner pore to a non-conducting state; and (2) ion permeation is not predominantly gated by the S6 bundle crossing. Their findings add to an emerging view on diverse structural mechanisms underlying the gating and permeability of $K^+$ channels, which are nicely brought into larger context in the perspective by Rothberg (2017).

In addition, two other papers are included in this special issue. Ahn *et al.* (2017) describe how inwardly rectifying $K^+$ channels are involved in regulating blood flow in resistance arteries. And Fabbri *et al.* (2017) also present new computational modeling of human sino-atrial node pacemaker cell, including several human ion channel mutations of clinical significance.

### Conclusion

In addition, two other papers are included in this special issue. Ahn *et al.* (2017) describe how inwardly rectifying $K^+$ channels are involved in regulating blood flow in resistance arteries. And Fabbri *et al.* (2017) also present new computational modeling of human sino-atrial node pacemaker cell, including several human ion channel mutations of clinical significance.

The heart is a dynamic organ. Most heart diseases including arrhythmias, ischaemia and heart failure are caused not by a single molecular defect, but by a constellation of changes at the molecular, cellular and whole organ levels. Even in monogenic diseases such as long-QT syndrome the mutation in one molecule often interacts with other channels, modifiers and compensatory changes culminating in advancing disease stages. Therefore, it is critically important to decipher the interactions of different channels and modulation factors, and to integrate their effects in order to understand heart disease mechanisms. Besides the large number of individual factors, additional complexity also comes from heart function being controlled by complex dynamic systems – electrical, $Ca^{2+}$ signalling, contractile and energetic. Each system involves many molecules and interacting regulation that is nonlinear with multiple feedback loops. Hence, combining experimental investigation and quantitative modelling is important for testing our mechanistic insight in deciphering these complex systems, understanding physiological functions, and predicting pathological changes in heart diseases. We think that this special issue, providing collective insights on these timely topics of cardiac $K^+$ channels, will be of interest to readers.

## References

Ahn SJ, Fancher IS, Bian JT, Zhang CX, Schwab S, Gaffin R, Phillips SA & Levitan I (2017). Inwardly rectifying $K^+$ channels are major contributors to flow-induced vasodilatation in resistance arteries. *J Physiol* **595**, 2339–2364.

Bartos DC, Morotti S, Ginsburg KS, Grandi E & Bers DM (2017). Quantitative analysis of the $Ca^{2+}$-dependent regulation of delayed rectifier $K^+$ current $I_{Ks}$ in rabbit ventricular myocytes. *J Physiol* **595**, 2253–2268.

Chen-Izu Y, Shaw RM, Pitt GS, Yarov-Yarovoy V, Sack JT, Abriel H, Aldrich RW, Belardinelli L, Cannell MB, Catterall WA, Chazin WJ, Chiamvimonvat N, Deschenes I, Grandi E, Hund TJ, Izu LT, Maier LS, Maltsev VA, Marionneau C, Mohler PJ, Rajamani S, Rasmusson RL, Sobie EA, Clancy CE & Bers DM (2015). $Na^+$ channel function, regulation, structure, trafficking and sequestration. *J Physiol* **593**, 1347–1360.

Chiamvimonvat N, Chen-Izu Y, Clancy CE, Deschenes I, Dobrev D, Heijman J, Izu L, Qu Z, Ripplinger CM, Vandenberg JI, Weiss JN, Koren G, Banyasz T, Grandi E, Sanguinetti MC, Bers DM & Nerbonne JM (2017). Potassium currents in the heart: functional roles in repolarization, arrhythmia and therapeutics. *J Physiol* **595**, 2229–2252.

Clancy CE, Chen-Izu Y, Bers DM, Belardinelli L, Boyden PA, Csernoch L, Despa S, Fermini B, Hool LC, Izu L, Kass RS, Lederer WJ, Louch WE, Maack C, Matiazzi A, Qu Z, Rajamani S, Rippinger CM, Sejersted OM, O'Rourke B, Weiss JN, Varro A & Zaza A (2015). Deranged sodium to sudden death. *J Physiol* **593**, 1331–1345.

Devenyi RA, Ortega FA, Groenendaal W, Krogh-Madsen T, Christini DJ & Sobie EA (2017). Differential roles of two delayed rectifier potassium currents in regulation of ventricular action potential duration and arrhythmia susceptibility. *J Physiol* **595**, 2301–2317.

Fabbri A, Fantini M, Wilders R & Severi S (2017). Computational analysis of the human sinus node action potential: model development and effects of mutations. *J Physiol* **595**, 2365–2396.

Giese MH, Gardner A, Hansen A & Sanguinetti MC (2017). Molecular mechanisms of Slo2 $K^+$ channel closure. *J Physiol* **595**, 2321–2336.

Grandi E (2017). Size matters, proportion too: coupling of experiments and theory reveals relative roles of $K^+$ channels in action potential stability. *J Physiol* **595**, 2319–2320.

Grandi E, Sanguinetti MC, Bartos DC, Bers DM, Chen-Izu Y, Chiamvimonvat N, Colecraft HM, Delisle BP, Heijman J, Navedo MF, Noskov S, Proenza C, Vandenberg JI & Yarov-Yarovoy V (2017). Potassium channels in the heart: structure, function and regulation. *J Physiol* **595**, 2209–2228.

Hill AP (2017). Boosting the reserves: additive regulation of cardiac repolarisation. *J Physiol* **595**, 2269–2270.

Huang CL (2017). From channels to systems: $Ca^{2+}$-sensitive $K^+$ currents, alternans and cardiac arrhythmia. *J Physiol* **595**, 2299–2300.

Kennedy M, Bers DM, Chiamvimonvat N & Sato D (2017). Dynamical effects of calcium-sensitive potassium currents on voltage and calcium alternans. *J Physiol* **595**, 2285–2297.

Rothberg B (2017). A Slick, Slack pathway through the pore. *J Physiol* **595**, 2337–2338.

Shattock MJ, Ottolia M, Bers DM, Blaustein MP, Boguslavskyi A, Bossuyt J, Bridge JH, Chen-Izu Y, Clancy CE, Edwards A, Goldhaber J, Kaplan J, Lingrel JB, Pavlovic D, Philipson K, Sipido KR & Xie ZJ (2015). $Na^+/Ca^{2+}$ exchange and $Na^+/K^+$-ATPase in the heart. *J Physiol* **593**, 1361–1382.

Zhang Z, Ledford HA, Park S, Wang W, Rafizadeh S, Kim HJ, Xu W, Lu L, Lau VC, Knowlton AA, Zhang XD, Yamoah EN & Chiamvimonvat N (2017). Distinct subcellular mechanisms for the enhancement of the surface membrane expression of SK2 channel by its interacting proteins, $\alpha$-actinin2 and filamin A. *J Physiol* **595**, 2271–2284.

## Additional information

### Competing interests

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