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EDITORIAL

Sodium and calcium regulation in cardiac myocytes: from molecules to heart failure and arrhythmia

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This special issue, *Sodium and calcium in heart*, brings together three reviews (Clancy *et al.* 2015; Chen-Izu *et al.* 2015; Shattock *et al.* 2015) and several original studies focused on these themes. Heart disease is the most prevalent cause of death in the developed world. In order to improve therapeutic approaches to treat heart disease, a deeper understanding of the fundamental mechanisms underlying altered heart function in specific diseases like arrhythmias, ischaemia and heart failure (HF) is essential. Cardiac function is controlled by three dynamically interacting systems – electrical, Ca^{2+} signalling, and contractile. To integrate these systems and reveal the detailed physiological and pathological mechanisms of cardiac function requires state-of-the-art experimental and computational approaches that span multiple system scales, that is, spatial scales ranging from molecules to the organism and time scales ranging from picoseconds to days or even years.

It is well recognized that Ca^{2+} handling not only governs contractile events (including systolic and diastolic function), but can undergo derangements that promote arrhythmogenesis through Ca^{2+}-dependent and coupled electrophysiological effects. Na^+ is increasingly appreciated as a major yet under-studied aspect of cardiac dysfunction (Despa & Bers, 2013; Clancy *et al.* 2015). This is because, in additional to the well-studied Na^+-dependent currents and intracellular $[Na^+]$ ($[Na^+]_i$) that are fundamental to cardiac excitability and contractility, $[Na^+]_i$ is tightly coupled to $[Ca^{2+}]_i$ regulation via electrogenic Na^+/Ca^{2+} exchange (NCX). This coupling between Na^+ and Ca^{2+} ion homeostatic subsystems means that disruption in either can have effects on contractility and arrhythmogenesis. Mitochondria also have a Na^+/Ca^{2+} exchanger (molecularly distinct from that on the sarcolemma), but this also means that $[Na^+]_i$ perturbations can also perturb Ca^{2+}-dependent energy metabolism and reactive oxygen production in mitochondria (Bay *et al.* 2013; Clancy *et al.* 2015). Thus Na^+ regulation in cardiac myocytes can have broad-reaching functional effects.

Recognizing the emerging role of Na^+ dysregulation in cardiac pathophysiology, and the need to extend our understanding from the molecular level to the integrated level of the organ, we hosted a 2 day symposium at the University of California, Davis in February 2014. The symposium *Na^+ channel and Na^+ transport* was the 3rd biennial UC Davis symposium in a series entitled *Systems approach to understanding cardiac excitation–contraction coupling and arrhythmias* (https://basicscience.ucdmc.ucdavis.edu/ucd-cvs-2014/). The symposia are conducted with a series of lectures, and an emphasis on open discussion time, aimed at bridging scales from molecules to whole heart. The symposia specifically bring together experimentalists and mathematical modellers from around the world to foster interdisciplinary discussion, interaction and collaboration. In this most recent symposium the emphasis was on the current state of research on Na^+ in the heart, with goals to identify points of consensus and also controversy (where more study is needed). A summary of the symposium is contained in the series of three white papers published in this special issue (Clancy *et al.* 2015; Chen-Izu *et al.* 2015; Shattock *et al.* 2015) in which the lectures, discussion and outstanding questions or controversies are highlighted.

The 2 day workshop had eight sessions: (1) 'Na^+-induced arrhythmias: from cellular level to the whole heart', (2) 'Disruption of Na^+ homeostasis', (3) 'Na^+ channel structure and function', (4) 'Na^+ channel regulation', (5) 'Trafficking, sequestration and complexing', (6) 'Na/Ca exchanger – structure, function and regulation', (7) 'Na/K pump – structure, function and regulation', and (8) 'Therapeutics'. In each session, speakers presented experimental results and modelling advancements, and discussion leaders, panelists and speakers held lengthy and lively debates over important questions that also highlighted critical knowledge gaps for future investigations. The white papers were jointly authored by speakers, discussion leaders and panelists and were intended to highlight the current status of these fields and emphasize questions and controversies. Clancy *et al.* (2015) entitled 'Deranged sodium to sudden death' addresses topics from Sessions 1, 2 and 8 above. Chen-Izu *et al.* (2015) entitled 'Na^+ channel function, regulation, structure, trafficking and sequestration' covers topics from Sessions 3, 4 and 5. Shattock *et al.* (2015) entitled 'Na^+/Ca^{2+} exchange and Na^+/K^+-ATPase in the heart' covers topics from Sessions 6 and 7.

This special issue also contains original research articles garnered in response to a call for papers on the topic of Na^+ and Ca^{2+} in the heart. The original research articles address some focal questions related to the Na^+ transport theme of the UC Davis symposium, and several contributions came from symposium participants.

Lin *et al.* (2015) studied mice with a Na^+ channel β subunit (*Scn1b*) knockout that has been linked with inherited arrhythmias in patients. The *Scn1b* knockout caused altered spatial distribution of Na^+ channels and current (I_{Na}) in mouse myocytes and increased the expression of the neuronal *Scn3a* gene (*vs.* the cardiac *Scn5a* gene that encodes $Na_V1.5$). They also found prolonged action potential (AP) duration (APD), delayed afterdepolarizations (DADs) and triggered beats. This study reveals a new mechanism by which altered Na^+ channel gene expression can disrupt myocyte Ca^{2+} homeostasis and trigger NCX-dependent arrhythmias.

Mishra *et al.* (2015), using a gene-silencing approach, reported that another neuronal Na^+ channel ($Na_V1.1$) may be relatively important in the late Na^+ current (I_{NaL}) that is known to both directly prolong APD (as seen in long QT3 mutations derived from mutations in $Na_V1.5$) and contribute to myocyte Ca^{2+} overloading. That can lead to triggered arrhythmias initiated by either DADs or early afterdepolarization (EAD). Thus, as discussed in Chen-Izu *et al.* (2015), the specific molecular basis and functional impact of I_{NaL} is still under active investigation.

Yang *et al.* (2015) used guinea-pig experiments and an updated AP model to show how a novel I_{NaL}-selective blocker

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could be beneficial in reducing the vulnerability of cells to small current perturbations during the vulnerable AP plateau phase. This raises a novel therapeutic strategy, along the lines addressed in both Clancy *et al.* (2015) and Chen-Izu *et al.* (2015) white papers.

While increased Na^+ influx via I_{Na} and I_{NaL} can cause sarcoplasmic reticulum (SR) Ca^{2+} release and NCX-dependent DADs (and some EADs), mutations in the cardiac ryanodine receptor (RyR2) linked to catecholaminergic polymorphic ventricular tachycardia (CPVT) can cause diastolic SR Ca^{2+} release that activates inward NCX and DADs that are independent of Na^+ loading. Lou *et al.* (2015) studied a CPVT mouse model of focal atrial arrhythmias, related to atrial fibrillation. Using simultaneous Ca^{2+}/voltage optical mapping, they found that arrhythmic events in CPVT mice with sensitized RyR2 required both diastolic SR Ca^{2+} release-driven DADs (via NCX current) and spatio-temporal synchronization via tetrodotoxin-sensitive current-driven APs. This exemplifies the tight Na^+–Ca^{2+} electrophysiological feedback discussed extensively at the UC Davis symposium. Hohendanner *et al.* (2015) addressed how SR Ca^{2+} release via inositol-1,4,5 trisphosphate ($InsP_3$) receptor channels can promote the recruitment of RyR2, both at rest and during paced beats. This resulted in both an increase in Ca^{2+} sparks and arrhythmogenic Ca^{2+} waves (as above), especially in atrial myocytes and in HF where these $InsP_3$ receptors are more highly expressed compared to normal ventricular myocytes. In HF rabbits this contributed to an increase of Ca^{2+} transients in atrial myocytes, *vs.* the depressed ventricular myocyte Ca^{2+} transients seen in this same HF model.

Myles *et al.* (2015) used whole heart optical mapping of arrhythmia induction in response to focal β-adrenergic challenge and SR Ca^{2+} release and NCX-driven DADs. They found that there was arrhythmogenic synergy between sensitized RyR2-mediated diastolic SR Ca^{2+} release and reduced function of the inward rectifier K^+ current I_{K1} (both of which occur in HF). Moreover, Poláková *et al.* (2015) reported that β-adrenergic activation of both protein kinase A (PKA) and Ca^{2+}-calmodulin-dependent protein kinase (CaMKII) may be required to maximally increase the propensity for spontaneous SR Ca^{2+} release. Hence, understanding the dynamic interactions between molecules involved in Na^+, Ca^{2+} and membrane voltage regulation is essential for deciphering the cardiac arrhythmia mechanisms.

Aronsen *et al.* (2015) studied Na^+/K^+-ATPase effects during hypokalaemia ($[K^+]_o$ = 2.7 mM), which is a known risk factor for cardiac arrhythmias. They found that hypokalaemia reduced Na^+/K^+-ATPase current and enhanced Ca^{2+} transient amplitude, but that selective inhibition of the Na^+/K^+-ATPase α2 isoform (the minor form in heart) prevented these effects of hypokalaemia. This agrees with a preferential role for the α2 subunit of Na^+/K^+-ATPase in modulating cardiac Ca^{2+} transients (Despa *et al.* 2012; Shattock *et al.* 2015). In related work Lewalle *et al.* (2014) recently developed a framework for mathematical modelling studies to help deal with the issue that models of Na^+/K^+-ATPase (and other transporters and channels) are often derived from experimental data in different animal species and under different conditions. They show how to retune model parameters using species-consistent data sets. This may be beneficial in a range of experiment–model continuity issues that was much discussed at the UC Davis symposium, as an inherent challenge in multispecies/multiscale modelling.

In conclusion, we hope that readers will find this special issue of interest for the collective group insights in the white papers on timely topics of Na^+-related effects in cardiac myocytes related to HF and arrhythmias, as well as for the related original contributions which further advance our detailed and integrative understanding of the dynamic and multiscale interactions between cardiac Na^+, Ca^{2+}, electrophysiology and contractility in both health and disease.

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