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COMMENTARY

A privileged role for neuronal Na^+ channels in regulating ventricular $[Ca^{2+}]$ and arrhythmias

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In cardiac myocytes, electrical signaling and Ca^{2+} signaling are closely coupled. Electrical signals, in the form of action potentials, produce periodic increases and decreases in intracellular $[Ca^{2+}]$—so-called "Ca^{2+} transients"—and these Ca^{2+} signals can, in turn, influence action potentials. More specifically, depolarization of the myocyte opens voltage-gated L-type Ca^{2+} channels (LTCCs) in the cell membrane, and Ca^{2+} entering the cell through these channels triggers release of additional Ca^{2+} from the SR. Intracellular $[Ca^{2+}]$, in turn, affects the cell's membrane potential via numerous Ca^{2+}-dependent ion transport pathways: LTCCs, which are inactivated by Ca^{2+} (Ben-Johny and Yue, 2014); Ca^{2+}-sensitive K^+ currents such as the slow delayed rectifier current (Bartos et al., 2017); and the electrogenic Na^+–Ca^{2+} exchanger (NCX), whose usual role is to extrude one Ca^{2+} ion while importing three Na^+ ions. Two general rules follow from these associations. One is that intracellular Ca^{2+} regulation and Na^+ regulation are closely coupled because of the fact that NCX exchanges one ion for the other. The second is that spatial relationships between the relevant proteins are extremely important in determining how the ion transport pathways influence each other. In this issue of the *Journal of General Physiology*, Koleske et al. investigate the role of neuronal isoforms of voltage-gated Na^+ (nNa_V) channels in ventricular myocytes. Their results emphasize the importance of spatial relationships between ion channels, pumps, and transporters and show how these relationships can produce pathological behavior under particular conditions.

Spatial relationships between proteins involved in cardiac Ca^{2+}-voltage coupling

Tight regulation of membrane potential and Ca^{2+} dynamics in cardiac myocytes is achieved by the spatial relationships between the proteins involved. Because, for example, a Ca^{2+}-dependent ion channel will respond more readily to Ca^{2+} passing through an adjacent channel than to one located a few micrometers away, ventricular myocytes arrange many of the critical proteins into microdomains, thereby enabling adequate coupling of these processes. Transverse tubules (T-tubules)—protrusions of the sarcolemmal membrane into the cell interior—contain numerous microdomains known as "couplons" (Ríos et al., 2015). In these couplons, LTCCs are brought into close proximity with RyRs, the Ca^{2+} release channels of the SR, and additional relevant ion transport proteins.

The complexity of coupling between Ca^{2+} and membrane potential has important implications for the maintenance of stable cardiac electrical activity. In particular, dangerous and potentially lethal ventricular arrhythmia syndromes can result when ion transport is disrupted by mutations, drugs, changes in gene expression, or pathological posttranslational modifications. Indeed, two of the most well-studied congenital arrhythmia syndromes, long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT), can result from mutations in a wide range of ion channels and Ca^{2+}-handling proteins. At present, 15 forms of LQTS (Bohnen et al., 2017) and 5 forms of CPVT (Landstrom et al., 2017) have been described. These two disorders show clear differences in clinical presentation and, at the cellular level, different mechanisms are thought to underlie "triggered activity"—i.e., the inappropriate membrane depolarizations that initiate arrhythmias. Specifically, triggered activity in LQTS is often considered to be purely voltage driven (Weiss et al., 2010); prolonged repolarization allows LTCCs to recover from inactivation, and reactivation of these channels during the repolarization phase can cause a secondary action potential upstroke known as an early afterdepolarization (EAD). In contrast, arrhythmias in CPVT are thought to arise from a different form of triggered activity, namely, delayed afterdepolarizations (DADs). These events result from spontaneous, aberrant release of Ca^{2+} from the SR after the cell membrane has fully repolarized (Sobie et al., 2017).

Although this general paradigm fits the majority of clinical and cellular observations, recent work suggests that, under some conditions, the picture may be more nuanced. In particular, arrhythmia susceptibility in LQTS might not always result

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from purely voltage-dependent mechanisms, but can sometimes depend on Ca^{2+}-voltage coupling (Terentyev et al., 2014). Along these lines, Koleske et al. (2018) provide important new insight. The results presented in this study show how the action potential prolongation seen in certain models of LQTS can lead to SR $[Ca^{2+}]$ overload and arrhythmogenic spontaneous Ca^{2+} release. The data also offer novel suggestions regarding the spatial relationships between ion transport proteins. Specifically, the authors suggest that nNa_V channels may have a privileged role that makes them attractive drug targets for these disorders.

Neuronal Na^+ channels can influence ventricular arrhythmic behavior

The current study builds on previously published results from the same research group. In 2016, many of the same investigators used a mouse model of RyR dysfunction to show that catecholamine-stimulated Na^+ influx through nNa_Vs can trigger arrhythmias (Radwański et al., 2016). In the current study (Koleske et al., 2018), the authors expand on this finding in an effort to uncover the underlying mechanisms. One of the major strengths of this study is the comprehensive approach taken by the authors. Multiple combinations of pharmacological perturbations were performed, both membrane potential and intracellular $[Ca^{2+}]$ were simultaneously monitored, and cellular as well as organ-level physiology were assessed.

The following general experimental strategy was used: A cellular environment encouraging arrhythmic dynamics (through EADs and/or DADs) was created, then Na^+ channels were blocked systematically to pinpoint the key player(s) contributing to triggered activity. First, in WT mouse ventricular myocytes, the authors induced a proarrhythmic LQTS phenotype using 4-Aminopyridine (4AP), an inhibitor of transient outward current (I_{to}), accompanied by β-adrenergic stimulation with isoproterenol (ISO). Inhibition of I_{to}, the major repolarizing current in these cells, increases action potential duration (APD), leading to enhanced Ca^{2+} entry through LTCCs and elevated SR Ca^{2+} load (Devenyi and Sobie, 2016). ISO also augments Ca^{2+} entry through LTCCs and Ca^{2+} uptake into the SR, further elevating the SR load. The combination of these two perturbations by Koleske et al. (2018) caused the cells to exhibit frequent triggered activity and aberrant intracellular Ca^{2+} release. Three Na_V-blocking agents were then applied to assess the potential role of nNa_Vs. Although the global Na^+ channel blocker lidocaine did not reduce the frequency of either triggered activity or aberrant Ca^{2+} release, the nNa_V-specific blockers riluzole and 4,9-anhydro-tetrodotoxin (4,9-ah-TTX) significantly reduced both. None of the three Na_V blockers reversed the action potential prolongation induced by 4AP+ISO treatment, indicating that the antiarrhythmic effects of the drugs do not simply result from changes in action potential shape.

After these initial results suggesting that nNa_V blockade can inhibit arrhythmic behaviors, the authors investigated two additional experimental models to obtain further support, with a particular focus on unstable intracellular Ca^{2+} dynamics in the form of DAD-inducing Ca^{2+} waves. In the first model, APD prolongation was induced by nonselective augmentation of Na^+ influx with Anemone toxin II. They found that riluzole or 4,9-ah-TTX treatment largely reduced the frequency of EADs and DADs, and abolished the LQT phenotype. This assessment was repeated for a model in which the LQT phenotype was induced with the LTCC-augmenting drug Bay K 8644, and consistent results were observed.

The last two sets of experiments were performed in myocytes from mice with cardiac-specific deletion of calsequestrin (*CASQ2*), the primary SR Ca^{2+} buffer. Mutations in *CASQ2* account for a recessive form of CPVT (Faggioni et al., 2012), and the *CASQ2*-null mouse has been a reliable CPVT model for more than a decade (Knollmann et al., 2006). Although the substantial action potential prolongation induced by the pharmacological treatments is not typical of the CPVT phenotype, these experiments may nevertheless help to provide insight into heart failure. This condition is associated with both action potential prolongation and unstable SR Ca^{2+} release (Bers et al., 2006), although many additional alterations contribute to the phenotype.

Overall, the study demonstrated a protective, antiarrhythmic effect of nNa_V blockade in three separate experimental models of mouse ventricular arrhythmia. These results suggest a privileged role of neuronal Na_V channels in mediating cellular triggered activity and arrhythmia via a mechanism that involves Ca^{2+}-voltage coupling.

Subcellular microdomains enable nNa_Vs to influence Ca^{2+}-voltage coupling

How can we understand the results presented by Koleske et al. (2018), which suggest that Na^+ influx through nNa_Vs plays a particularly important role in determining arrhythmic behavior? A straightforward potential explanation is illustrated schematically in Fig. 1 A, which shows the subcellular location of nNa_Vs at an influential position near the couplon. Classical cardiac Na^+ channels, cNa_Vs (i.e., $Na_V1.5$), are for simplicity shown in the T-tubule membrane but distant from the couplon, although localization and functional data suggest that these channels cluster in the intercalated disk regions between adjacent myocytes (Lin et al., 2011; Westenbroek et al., 2013). The arrangements illustrated in Fig. 1 A imply that augmentation of either nNa_Vs or cNa_Vs would lead to action potential prolongation, which would then increase Ca^{2+} influx and diastolic SR $[Ca^{2+}]$ load. However, selective augmentation of nNa_Vs would be predicted to cause more pronounced effects than selective augmentation of cNa_Vs, as illustrated by the hypothetical action potential, intracellular $[Ca^{2+}]$, and SR $[Ca^{2+}]$ time courses shown in Fig. 1 B. Because nNa_Vs are located in much closer proximity to the couplon than cNa_Vs, a local increase in $[Na^+]$ near the couplon would reduce the efflux of Ca^{2+} through NCX. This would allow more local Ca^{2+} to be taken into the SR by the SR Ca^{2+} ATPase pump, leading to a greater increase in SR $[Ca^{2+}]$ load than would occur in the absence of elevated local $[Na^+]$. Elevated SR $[Ca^{2+}]$ load caused by nNa_V augmentation would increase the risk of spontaneous SR Ca^{2+} release and DADs. This model can also explain why, when SR $[Ca^{2+}]$ is increased through various interventions, selective blockade of nNa_Vs (as in the experiments of Koleske et al., 2018) reduce the frequency of both Ca^{2+} waves and triggered activity. In contrast, nonspecific Na^+ channel blockade using lidocaine did not correct triggered activity, suggesting that local increases

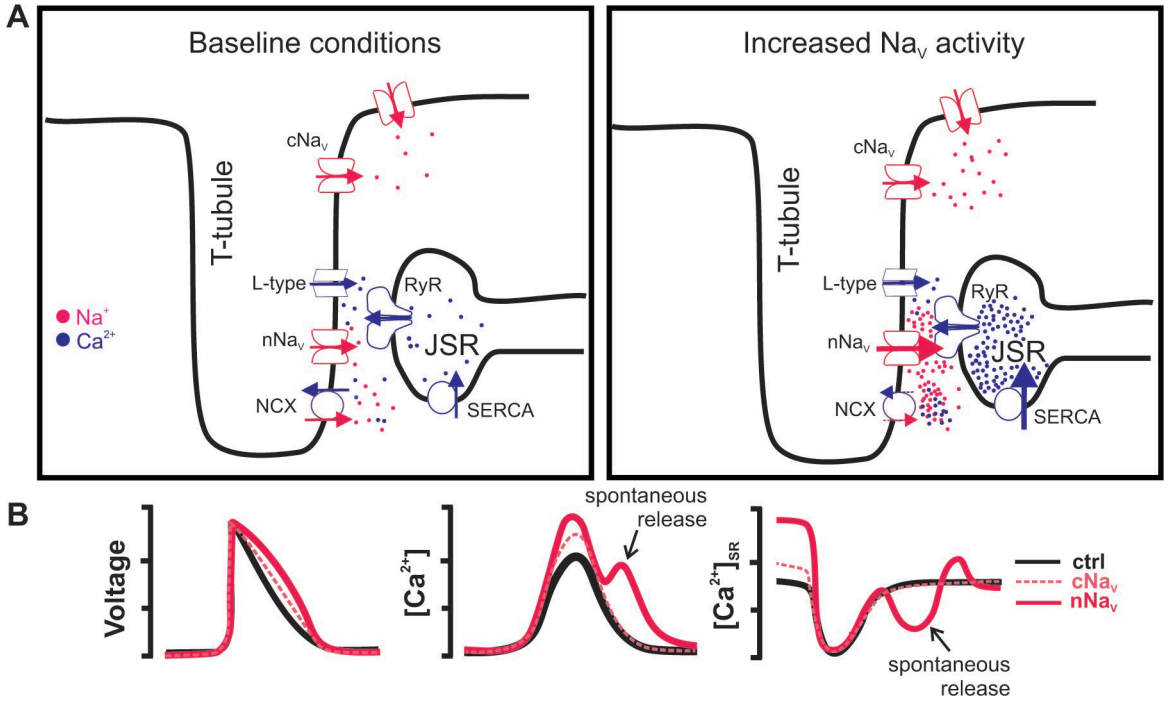

Figure 1. **The proximity of nNa$_V$s to the excitation–contraction coupling machinery can be proarrhythmic. (A)** Inferred locations of proteins important in excitation–contraction coupling are shown under control conditions (left) and after augmentation of flux through Na$_V$s (right). Compared with cNa$_V$s, nNa$_V$s appear to be located closer to the excitation–contraction coupling machinery, including LTCCs and NCX in the T-tubule membrane and RyRs and SERCA in the local SR membrane. An increase in Na$^+$ influx through nNa$_V$s will lead to increased local [Na$^+$] (red dots), reduced Ca^{2+} removal via NCX, and increased SR [Ca^{2+}] (blue dots). **(B)** Hypothetical action potentials (left), intracellular [Ca^{2+}] (middle), and SR [Ca^{2+}] (right) under control conditions (solid black lines), after augmentation of cNa$_V$s (dashed red lines), and after augmentation of nNa$_V$s (solid red lines). Increased flux through either cNa$_V$s or nNa$_V$s will prolong the AP and increase SR [Ca^{2+}] load. When this occurs through nNa$_V$s, however, the local signaling means that the increase in SR [Ca^{2+}] will be greater, increasing the risk of spontaneous, arrhythmogenic Ca^{2+} release.

in Na$^+$ near other Na$^+$ channels, i.e., cNa$_V$s, do not significantly affect Ca^{2+} efflux through NCX.

A potentially important protein that is not depicted in Fig. 1 A is Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). This kinase can phosphorylate both RyRs and nNa$_V$s, increasing their open probability (Wehrens et al., 2004) and augmenting the current through these channels (Radwański et al., 2016), respectively. Prior studies have suggested that a deleterious feedback loop involving elevated intracellular [Na$^+$], intracellular [Ca^{2+}], and CaMKII can be proarrhythmic in mouse myocytes (Morotti et al., 2014). Because agonists such as isoproterenol lead to activation of CaMKII in addition to the classical downstream effector protein kinase A (Curran et al., 2007; Gutierrez et al., 2013; Poláková et al., 2015), the proarrhythmic state seen during β-adrenergic stimulation is likely to involve CaMKII activation in addition to the steps outlined above. Indeed, Radwański et al. (2016) previously showed that CaMKII inhibition can be beneficial during conditions associated with increased Na$^+$ flux through nNa$_V$s.

Neuronal Na$^+$ channels in close proximity to excitation–contraction coupling machinery: an emerging theme

In addition to supporting the findings of the present study, the conceptual model shown in Fig. 1 A is consistent with recent work by other groups. For instance, when the cell membrane is depolarized and intracellular [Ca^{2+}] is low, NCX operates in reverse mode to import Ca^{2+} and export Na$^+$. Although early studies showed that this Ca^{2+} entry pathway is inefficient at triggering SR Ca^{2+} release when operating in isolation (Sipido et al., 1997), more recent investigations have demonstrated that LTCCs, NCXs, and nNa$_V$s can interact to boost the trigger for SR Ca^{2+} release (Sobie et al., 2008; Larbig et al., 2010; Chu et al., 2016). Indeed, selective blockade of nNa$_V$s with nanomolar concentrations of TTX can inhibit SR Ca^{2+} release, suggesting involvement of these isoforms (Torres et al., 2010). This can only occur if these ion transport pathways are in reasonably close proximity, as also suggested by Koleske et al. (2018).

The results of this study (Koleske et al., 2018) also improve our understanding of cellular arrhythmia initiation mechanisms under pathological conditions. As mentioned above, studies into LQTS have generally focused on arrhythmias initiated by EADs (Weiss et al., 2010), a process that can be understood without considering SR Ca^{2+} release. However, a series of recent investigations have suggested that, at least under some conditions, Ca^{2+} overload and spontaneous SR Ca^{2+} release can contribute to the arrhythmic phenotype in various forms of LQTS. This can take the form of triggered activity initiated by spontaneous Ca^{2+} waves and DADs, as reported here. However, this unstable Ca^{2+} release can be proarrhythmic in other ways. Secondary spontaneous Ca^{2+} releases during the action potential can prolong the repolarization phase, thereby making EADs caused by LTCC reactivation more likely (Edwards et al., 2014; Terentyev et al., 2014). Additionally, unstable spontaneous Ca^{2+} release can encourage

the formation of spatially discordant alternans, patterns of voltage and [Ca^{2+}] at the tissue level that can predispose hearts to arrhythmias (Liu et al., 2018). Overall, these recent studies paint a picture that spontaneous SR Ca^{2+} release is a critical proarrhythmic signal not only in CPVT, as is well established, but also in LQTS, where its role has been less appreciated. The current study (Koleske et al., 2018) makes a significant addition to this emerging paradigm, emphasizing the importance of SR Ca^{2+}-release in LQTS and drawing additional mechanistic links between the two arrhythmia disorders.

Future research on nNa$_V$s and cardiac arrhythmias

As with all important investigations, the study by Koleske et al. (2018) suggests avenues for future research. One will be to determine the precise roles played by different nNa$_V$ isoforms in promoting proarrhythmia. The schematic in Fig. 1 groups all nNa$_V$s into a single category because most of the results presented by Koleske et al. (2018) were not aimed at distinguishing between nNa$_V$ isoforms. However, the antiarrhythmic effectiveness of 4,9-ah-TTX, which preferentially blocks Na$_V$1.6, suggests a critical role for this isoform. This is consistent with prior studies (Noujaim et al., 2012; Westenbroek et al., 2013), including one by the same group (Radwański et al., 2016), indicating that Na$_V$1.6 may be more important in ventricular pathophysiology than other neuronal isoforms such as Na$_V$1.1 and Na$_V$1.3. Additional studies will be required, perhaps with cardiac-specific knockout mice (Noujaim et al., 2012), to fully elucidate the roles of the various isoforms.

A second issue to address in future work concerns the applicability of the results, obtained using mice, to arrhythmias in humans and larger animals. The mouse action potential is not only much shorter, but has a fundamentally different shape compared with action potentials seen in larger mammals. Repolarization in mouse myocytes depends primarily on transient outward current (I_{to}), whereas the rapid and slow delayed rectifier currents, I_{Kr} and I_{Ks}, are critical in humans, dogs, and rabbits. In contrast, the primary depolarizing currents, I_{Na} (carried by Na$_V$1.5) and I_{CaL} (carried by LTCCs), are similar in mice and humans. This means that mouse myocytes can serve as reasonable experimental models for LQT3 (caused by mutations in Na$_V$1.5) or LQT8 (caused by mutations in LTCCs), whether these models are genetic (Fredj et al., 2006; Drum et al., 2014) or pharmacological, as used here. Mice are much less useful for investigations of LQT1 or LQT2, caused by mutations in the genes responsible for I_{Ks} and I_{Kr}, respectively. Future studies using larger animals should address whether the proarrhythmic Na^+–Ca^{2+} signaling described in this paper plays an important role in LQT1 and/or LQT2. For such studies that compare results obtained in different experimental models, novel computational approaches to translate perturbation responses across cell types are likely to be extremely useful (Gong and Sobie, 2018).

Overall, the study by Koleske et al. (2018) provides important novel insight into the role played by nNa$_V$s in creating proarrhythmic conditions in ventricular myocytes. The results emphasize the importance of spatial microdomains, in which ion channels, pumps, and transporters can closely interact, and they improve our understanding of the potential proarrhythmic consequences of Ca^{2+}-voltage coupling. The study is sure to inspire future investigations and may provide a roadmap for the development of novel antiarrhythmic therapeutics.

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References

Bartos, D.C., S. Morotti, K.S. Ginsburg, E. Grandi, and D.M. Bers. 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. https://doi.org/10.1113/JP273676

Ben-Johny, M., and D.T. Yue. 2014. Calmodulin regulation (calmodulation) of voltage-gated calcium channels. *J. Gen. Physiol.* 143:679–692. https://doi.org/10.1085/jgp.201311153

Bers, D.M., S. Despa, and J. Bossuyt. 2006. Regulation of Ca^{2+} and Na^+ in normal and failing cardiac myocytes. *Ann. N. Y. Acad. Sci.* 1080:165–177. https://doi.org/10.1196/annals.1380.015

Bohnen, M.S., G. Peng, S.H. Robey, C. Terrenoire, V. Iyer, K.J. Sampson, and R.S. Kass. 2017. Molecular Pathophysiology of Congenital Long QT Syndrome. *Physiol. Rev.* 97:89–134. https://doi.org/10.1152/physrev.00008.2016

Chu, L., J.L. Greenstein, and R.L. Winslow. 2016. Modeling Na^+-Ca^{2+} exchange in the heart: Allosteric activation, spatial localization, sparks and excitation-contraction coupling. *J. Mol. Cell. Cardiol.* 99:174–187. https://doi.org/10.1016/j.yjmcc.2016.06.068

Curran, J., M.J. Hinton, E. Ríos, D.M. Bers, and T.R. Shannon. 2007. Beta-adrenergic enhancement of sarcoplasmic reticulum calcium leak in cardiac myocytes is mediated by calcium/calmodulin-dependent protein kinase. *Circ. Res.* 100:391–398. https://doi.org/10.1161/01.RES.0000258172.74570.e6

Devenyi, R.A., and E.A. Sobie. 2016. There and back again: Iterating between population-based modeling and experiments reveals surprising regulation of calcium transients in rat cardiac myocytes. *J. Mol. Cell. Cardiol.* 96:38–48. https://doi.org/10.1016/j.yjmcc.2015.07.016

Drum, B.M., R.E. Dixon, C. Yuan, E.P. Cheng, and L.F. Santana. 2014. Cellular mechanisms of ventricular arrhythmias in a mouse model of Timothy syndrome (long QT syndrome 8). *J. Mol. Cell. Cardiol.* 66:63–71. https://doi.org/10.1016/j.yjmcc.2013.10.021

Edwards, A.G., E. Grandi, J.E. Hake, S. Patel, P. Li, S. Miyamoto, J.H. Omens, J. Heller Brown, D.M. Bers, and A.D. McCulloch. 2014. Nonequilibrium reactivation of Na^+ current drives early afterdepolarizations in mouse ventricle. *Circ Arrhythm Electrophysiol.* 7:1205–1213. https://doi.org/10.1161/CIRCEP.113.001666

Faggioni, M., D.O. Kryshtal, and B.C. Knollmann. 2012. Calsequestrin mutations and catecholaminergic polymorphic ventricular tachycardia. *Pediatr. Cardiol.* 33:959–967. https://doi.org/10.1007/s00246-012-0256-1

Fredj, S., N. Lindegger, K.J. Sampson, P. Carmeliet, and R.S. Kass. 2006. Altered Na+ channels promote pause-induced spontaneous diastolic activity in long QT syndrome type 3 myocytes. *Circ. Res.* 99:1225–1232. https://doi.org/10.1161/01.RES.0000251305.25604.b0

Gong, J.Q.X., and E.A. Sobie. 2018. Population-based mechanistic modeling allows for quantitative predictions of drug responses across cell types. *NPJ Syst. Biol. Appl.* 4:11. https://doi.org/10.1038/s41540-018-0047-2

Gutierrez, D.A., M. Fernandez-Tenorio, J. Ogrodnik, and E. Niggli. 2013. NO-dependent CaMKII activation during β-adrenergic stimulation of

cardiac muscle. *Cardiovasc. Res.* 100:392–401. https://doi.org/10.1093/cvr/cvt201

Knollmann, B.C., N. Chopra, T. Hlaing, B. Akin, T. Yang, K. Ettensohn, B.E.C. Knollmann, K.D. Horton, N.J. Weissman, I. Holinstat, et al. 2006. Casq2 deletion causes sarcoplasmic reticulum volume increase, premature Ca^{2+} release, and catecholaminergic polymorphic ventricular tachycardia. *J. Clin. Invest.* 116:2510–2520.

Koleske, M., I. Bonilla, J. Thomas, N. Zaman, S. Baine, B.C. Knollmann, R. Veeraraghavan, S. Gyorke, and P.B. Radwański. 2018. Tetrodotoxin-sensitive Na_vs contribute to early and delayed afterdepolarizations in long QT arrhythmia models. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.201711909

Landstrom, A.P., D. Dobrev, and X.H.T. Wehrens. 2017. Calcium Signaling and Cardiac Arrhythmias. *Circ. Res.* 120:1969–1993. https://doi.org/10.1161/CIRCRESAHA.117.310083

Larbig, R., N. Torres, J.H. Bridge, J.I. Goldhaber, and K.D. Philipson. 2010. Activation of reverse Na^+-Ca^{2+} exchange by the Na^+ current augments the cardiac Ca^{2+} transient: evidence from NCX knockout mice. *J. Physiol.* 588:3267–3276. https://doi.org/10.1113/jphysiol.2010.187708

Lin, X., N. Liu, J. Lu, J. Zhang, J.M. Anumonwo, L.L. Isom, G.I. Fishman, and M. Delmar. 2011. Subcellular heterogeneity of sodium current properties in adult cardiac ventricular myocytes. *Heart Rhythm.* 8:1923–1930. https://doi.org/10.1016/j.hrthm.2011.07.016

Liu, W., T.Y. Kim, X. Huang, M.B. Liu, G. Koren, B.R. Choi, and Z. Qu. 2018. Mechanisms linking T-wave alternans to spontaneous initiation of ventricular arrhythmias in rabbit models of long QT syndrome. *J. Physiol.* 596:1341–1355. https://doi.org/10.1113/JP275492

Morotti, S., A.G. Edwards, A.D. McCulloch, D.M. Bers, and E. Grandi. 2014. A novel computational model of mouse myocyte electrophysiology to assess the synergy between Na^+ loading and CaMKII. *J. Physiol.* 592:1181–1197. https://doi.org/10.1113/jphysiol.2013.266676

Noujaim, S.F., K. Kaur, M. Milstein, J.M. Jones, P. Furspan, D. Jiang, D.S. Auerbach, T. Herron, M.H. Meisler, and J. Jalife. 2012. A null mutation of the neuronal sodium channel $Na_V1.6$ disrupts action potential propagation and excitation-contraction coupling in the mouse heart. *FASEB J.* 26:63–72. https://doi.org/10.1096/fj.10-179770

Poláková, E., A. Illaste, E. Niggli, and E.A. Sobie. 2015. Maximal acceleration of Ca2+ release refractoriness by β-adrenergic stimulation requires dual activation of kinases PKA and CaMKII in mouse ventricular myocytes. *J. Physiol.* 593:1495–1507. https://doi.org/10.1113/jphysiol.2014.278051

Radwański, P.B., H.T. Ho, R. Veeraraghavan, L. Brunello, B. Liu, A.E. Belevych, S.D. Unudurthi, M.A. Makara, S.G. Priori, P. Volpe, et al. 2016. Neuronal Na^+ Channels Are Integral Components of Pro-arrhythmic Na^+/Ca^{2+} Signaling Nanodomain That Promotes Cardiac Arrhythmias During β-adrenergic Stimulation. *JACC Basic Transl. Sci.* 1:251–266. https://doi.org/10.1016/j.jacbts.2016.04.004

Ríos, E., L. Figueroa, C. Manno, N. Kraeva, and S. Riazi. 2015. The couplonopathies: A comparative approach to a class of diseases of skeletal and cardiac muscle. *J. Gen. Physiol.* 145:459–474. https://doi.org/10.1085/jgp.201411321

Sipido, K.R., M. Maes, and F. Van de Werf. 1997. Low efficiency of Ca^{2+} entry through the Na^+-Ca^{2+} exchanger as trigger for Ca^{2+} release from the sarcoplasmic reticulum. A comparison between L-type Ca^{2+} current and reverse-mode Na^+-Ca^{2+} exchange. *Circ. Res.* 81:1034–1044. https://doi.org/10.1161/01.RES.81.6.1034

Sobie, E.A., M.B. Cannell, and J.H.B. Bridge. 2008. Allosteric activation of Na^+-Ca^{2+} exchange by L-type Ca^{2+} current augments the trigger flux for SR Ca^{2+} release in ventricular myocytes. *Biophys. J.* 94:L54–L56. https://doi.org/10.1529/biophysj.107.127878

Sobie, E.A., G.S.B. Williams, and W.J. Lederer. 2017. Ambiguous interactions between diastolic and SR Ca^{2+} in the regulation of cardiac Ca^{2+} release. *J. Gen. Physiol.* 149:847–855. https://doi.org/10.1085/jgp.201711814

Terentyev, D., C.M. Rees, W. Li, L.L. Cooper, H.K. Jindal, X. Peng, Y. Lu, R. Terentyeva, K.E. Odening, J. Daley, et al. 2014. Hyperphosphorylation of RyRs underlies triggered activity in transgenic rabbit model of LQT2 syndrome. *Circ. Res.* 115:919–928. https://doi.org/10.1161/CIRCRESAHA.115.305146

Torres, N.S., R. Larbig, A. Rock, J.I. Goldhaber, and J.H. Bridge. 2010. Na^+ currents are required for efficient excitation-contraction coupling in rabbit ventricular myocytes: a possible contribution of neuronal Na^+ channels. *J. Physiol.* 588:4249–4260. https://doi.org/10.1113/jphysiol.2010.194688

Wehrens, X.H., S.E. Lehnart, S.R. Reiken, and A.R. Marks. 2004. Ca^{2+}/calmodulin-dependent protein kinase II phosphorylation regulates the cardiac ryanodine receptor. *Circ. Res.* 94:e61–e70. https://doi.org/10.1161/01.RES.0000125626.33738.E2

Weiss, J.N., A. Garfinkel, H.S. Karagueuzian, P.S. Chen, and Z. Qu. 2010. Early afterdepolarizations and cardiac arrhythmias. *Heart Rhythm.* 7:1891–1899. https://doi.org/10.1016/j.hrthm.2010.09.017

Westenbroek, R.E., S. Bischoff, Y. Fu, S.K. Maier, W.A. Catterall, and T. Scheuer. 2013. Localization of sodium channel subtypes in mouse ventricular myocytes using quantitative immunocytochemistry. *J. Mol. Cell. Cardiol.* 64:69–78. https://doi.org/10.1016/j.yjmcc.2013.08.004