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Commentary: Reciprocal Modulation of I_{K1}–I_{Na} Extends Excitability in Cardiac Ventricular Cells

*Birgit Goversen, Teun P. de Boer and Marcel A. G. van der Heyden **

Division of Heart and Lungs, Department of Medical Physiology, University Medical Center Utrecht, Utrecht, Netherlands

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A commentary on

Reciprocal Modulation of I_{K1}–I_{Na} Extends Excitability in Cardiac Ventricular Cells
by Varghese, A. (2016). Front. Physiol. 7:542. doi: 10.3389/fphys.2016.00542

We read with great interest the excellent paper by Varghese (2016) who describes an *in silico* approach to study the consequences of reciprocal regulation of expression of the sodium current (I_{Na}) and the inward rectifier potassium current (I_{K1}) in the ventricle for cardiac excitability and conduction. The *in silico* approach follows the experimental results obtained by Milstein et al. (2012) who demonstrated functional co-regulation of the sodium and inward rectifier currents, and their underlying channel proteins $Na_v1.5$ and $K_{IR}2.1$ respectively, and electrophysiological consequences upon overexpression in rodent cardiomyocytes with respect to action potential duration and re-entry based arrhythmia propensity. Varghese adapted the guinea pig ventricular cardiomyocyte model, developed by Noble et al. (1998), that is extrapolated to simulations for one dimensional cardiac fibers, in which the fiber is represented as a linear cable model. Varghese changed either the conductance for I_{Na} and I_{K1} individually or in tandem, to assess their influence on the excitability of mammalian ventricular cardiomyocytes. One of the most interesting findings in this paper is the dominance of I_{K1} over I_{Na} in regulation of cardiac excitability, which yields important questions about the significance of the inward rectifier in this process (Varghese, 2016). This commentary will put these results in a broader context in order to provide a framework for future research questions.

The experimental data of Milstein et al. (2012) point to the existence of a macromolecular complex in which the SAP97 protein may have a major role in reciprocal regulation of expression of $Na_v1.5$ and $K_{IR}2.1$ proteins, since both channels present binding motifs for SAP97. Milstein and colleagues stress that the cell biological principles underlying reciprocal expression at the sarcolemma are only partly resolved and propose a role for ion channel trafficking in the process. Indeed, $Na_v1.5$ promotes $K_{IR}2.1$ protein to be presented at the cell surface, and it decreases $K_{IR}2.1$ internalization. Whether and to which extent $K_{IR}2.1$ affects $Na_v1.5$ protein trafficking still needs to be resolved. Furthermore, a number of additional proteins are candidate in establishing $Na_v1.5$-$K_{IR}2.1$ macromolecular complexes at the plasma membrane as well as intracellularly (Willis et al., 2015). Finally, the subcellular localization of $K_{IR}2.1$ and $Na_v1.5$, e.g., intercalated disc vs. lateral membranes, may very well depend on the nature of the macromolecular complex. When location specific complexes exist, we may predict that these respond differently to disease causing factors and thereby change anisotropy. For now, the field has to elucidate the composition of (additional) molecular complexes from native cell types and more importantly, gain knowledge on $Na_v1.5$ and $K_{IR}2.1$ stoichiometry in such complexes and determine whether variations in stoichiometry between complex types exist, and if so, decipher its significance.

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Carol Ann Remme, University of Amsterdam, Netherlands

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****Correspondence:***
Marcel A. G. van der Heyden
m.a.g.vanderheyden@umcutrecht.nl

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In contrast to $Na_v1.5$, which is predominantly present in the heart, $K_{IR}2.1$ channels are expressed in many excitable tissue types, like skeletal and smooth muscle, neuronal cells, but also in non-excitable tissues (reviewed in De Boer et al., 2010). This sets the stage for efforts to explore potential reciprocal modulation of $K_{IR}2.1$ and various sodium channel subtypes in non-cardiac tissues, a hypothesis already put forward in the field of epilepsy (Ambrosini et al., 2014). Not only does $K_{IR}2.1$ protein distribution differ between tissue types, there is also variation within the heart. For example, atria and Purkinje fibers express less $K_{IR}2.1$ channels than ventricles. This spatial variation also holds true for development and disease. Transcriptional differences have been seen in development and upregulation of $K_{IR}2.1$ has been associated with progression of atrial fibrillation (De Boer et al., 2010). All these expressional differences likely play a role in action potential formation and propagation, and it may be clear that a complete set of *in silico* models, representing different cardiac tissue types and developmental stages may be required to fully appreciate the functional roles of reciprocal modulation. Currently, both the guinea pig ventricular cardiomyocyte model as the linear cable model do not inhabit these dynamic features and by definition cannot provide clues on anisotropy.

The findings by Varghese might be of importance to the field of induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs). iPSC-CMs are of interest for tissue engineering and *in vitro* drug screening purposes, but their electrical immaturity has to be considered carefully (Jonsson et al., 2012). Aside from an ill-developed sarcoplasmic reticulum, their main drawback is spontaneous beating activity due to a lack of I_{K1} (Jonsson et al., 2012). Restoration of $K_{IR}2.1$ and therefore I_{K1} might electrically mature these iPSC-CMs. Since the absence of I_{K1} is closely linked to very low transcription levels of the $K_{IR}2.1$ producing gene (*KCNJ2*) in this cell type, it appears obligatory to resolve *KCNJ2* promoter regulation first and subsequently use gene specific transcription factors or their upstream regulatory pathways to increase $K_{IR}2.1$ mRNA expression levels. Once $K_{IR}2.1$ protein expression level is elevated, the reciprocal modulation of sodium and inward rectifier channels might provide additional means to enhance $K_{IR}2.1$ and thus I_{K1} in iPSC-CMs. The study by Varghese shows that the interaction between sodium channel and the inward rectifier yields functional implications that cannot be ignored.

AUTHOR CONTRIBUTIONS

BG, TdB, and MvdH wrote the submitted commentary on an original contribution by Anthony Varghese.

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