Cardiac Sodium Channel $\text{Na}_1.5$ Mechanosensitivity Is Inhibited by Ranolazine

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The cardiac action potential is initiated by the depolarizing inward sodium current ($I_{\text{Na}}$). The pore-forming subunit of the cardiac sodium channel, $\text{Na}_1.5$, is the main ion channel that conducts $I_{\text{Na}}$ in cardiac cells. Despite the large number of studies investigating $\text{Na}_1.5$, year after year, we are still learning new aspects regarding its roles in normal cardiac function and in diseased states. The clinical relevance of this channel cannot be understated. The cardiac $I_{\text{Na}}$ is the target of the class 1 antiarrhythmic drugs, which are nowadays less frequently prescribed because of their well-documented proarrhythmic properties. In addition, since the first description in 1995 by Keating’s group of mutations in patients experiencing congenital long-QT syndrome type 3, several hundred genetic variants in SCN5A, the gene coding for $\text{Na}_1.5$, have been reported and investigated. Interestingly, many of these genetic variants have been found in patients with diverse cardiac manifestations, such as congenital long QT syndrome type 3, Brugada syndrome, conduction disorders, and more recently, atrial fibrillation and dilated cardiomyopathy. This impressive list underlines the importance of $\text{Na}_1.5$ in cardiac pathologies and raises the question about possible unknown roles and regulatory mechanisms of this channel in cardiac cells. Recent studies have provided experimental evidence that the function of $\text{Na}_1.5$, among many other described regulatory mechanisms, is also modulated by the mechanical stretch of the membrane in which it is embedded, thus suggesting that $\text{Na}_1.5$, like other ion channels, is mechanosensitive. What does this mean? Mechanosensitivity of an ion channel is characterized by modulation of its intrinsic biophysical properties such as conductance, gating, or voltage-dependence of transition between the different states of the channel by the mechanical stretch of the cell membrane and its membrane-associated proteins. Some channels are activated mainly by stretch (the so-called stretch-activated channels or mechanically-gated channels), whereas other channels, such as voltage-gated channels, may be only modulated by stretch.

On the basis of the observation that $\text{Na}_1.5$ is expressed in smooth muscle cells of the jejunum, a few years ago, Ou and colleagues showed that the voltage-gated $I_{\text{Na}}$ in intestinal smooth muscle cells was increased on stretch of the cell membrane caused by superfusion of the cells with a physiological solution. Recent evidence indicated that this $I_{\text{Na}}$ increase, attributable to mechanical stretch, relies on the interaction of $\text{Na}_1.5$ with cytoskeletal elements via proteins of the syntrophin family. Our group has shown that $\text{Na}_1.5$ is indeed complexed with the dystrophin macromolecular complex, which comprises adapter syntrophin proteins that are located at the lateral membranes of cardiomyocytes. Later, Morris and coworkers studied $\text{Na}_1.5$ expressed in Xenopus oocytes, and observed that, by stretching a patch of membrane by applying underpressure on the glass pipette, both the kinetics of activation and inactivation of $\text{Na}_1.5$ are accelerated. These findings were then confirmed and extended in the study by Beyder and colleagues, who studied the stretch-induced biophysical alterations of $\text{Na}_1.5$ expressed in HEK293 cells through the same technique of applying under- or overpressure to the pipette with a cell-attached patch of membrane. As summarized in the Figure, it has been found that stretch increases the peak $I_{\text{Na}}$ by accelerating the macroscopic activation kinetics, but it has also been found that the inactivation kinetics are hastened as well. Stretch of the membrane also shifts the voltage dependence of inactivation (availability curve) and activation toward more hyperpolarized potentials. This phenomenon was clearly demonstrated to be dose/stretch-dependent (see Figure 3 of Beyder et al). In this issue of Circulation, the same group, in a study carrying out sophisticated biophysical experiments, now shows that the endogenous $I_{\text{Na}}$, recorded in freshly isolated mouse cardiomyocytes, displays very similar mechanosensitive properties as those recorded in HEK293 cells. This, by itself, is remarkable because it is obvious that these are very different types of cells. Furthermore, the authors convincingly demonstrate that ranolazine, an FDA-approved drug, dose-dependently inhibits the mechanosensitivity of $\text{Na}_1.5$. Ranolazine is an interesting compound, which was approved by the FDA in 2006 for its use as an antianginal drug, but which can also inhibit many different cardiac ion channels. Thus, it has been proposed to be potentially useful to treat ventricular as well as supraventricular arrhythmias. The mechanisms of action of ranolazine are various, and the sodium channel $\text{Na}_1.5$ is 1 of its well-studied targets. As depicted in the Figure (A), ranolazine reduces the cardiac peak $I_{\text{Na}}$ and shifts the voltage-dependence of inactivation toward more hyperpolarized potentials by stabilizing the inactivated state, actions similar to all classical sodium channel blockers of the local anesthetic class. But most importantly, ranolazine has been shown to block the persis-
tent (also called late) sodium current, a defect in inactivation of the \( I_{Na} \) found in patients with congenital long QT syndrome type 3. This effect of ranolazine on the mechanosensitivity of Nav1.5 is original and unexpected. As stated in the title of this study, this represents a novel mechanism of drug action. Hence, this study may turn out to be a seminal work, opening new possibilities for the treatment of cardiac arrhythmias. One has to say, however, that, as always with important and unexpected experimental observations, this study raises many questions that will have to be addressed by the community of ion channel scientists.

First, one would like to understand 2 important phenomena: what are the molecular mechanisms of Nav1.5 mechanosensitivity, and as well how does this property influence the electric activity of cardiac cells? Are specific domains of Nav1.5, such as the S4-voltage sensors, key determinants for its modulation by stretch as suggested by Bandareli et al? Or is it the interaction with cytoskeletal proteins that mediates the observed membrane stretch modulation?

Second, how does ranolazine (and also lidocaine, as described in this study), interfere with Nav1.5 mechanosensitivity? The authors provide evidence that the classical local anesthetic drug binding site does not seem to be involved, because channels with a mutated key residue were still found to be sensitive to ranolazine. Their experiments also suggest that only noncharged forms of drugs interfere with Nav1.5 mechanosensitivity, thus leading the authors to speculate that ranolazine obtains access to the channel by partitioning within the lipid bilayer of the cell membrane. Even more speculative is the possibility that it may gain access to the channel protein via the side fenestrations of voltage-gated sodium channels.

And third, a question arises that is more clinically relevant: can this modulation of the mechanosensitivity of Na\(_{1.5}\) be used as a novel antiarrhythmic principle for potential therapies? Here, much more work remains to be done, because one has to understand the detailed physiological and pathophysiological consequences of this membrane sensitivity to stretch. This may not be an easy task to demonstrate in vivo. On the other hand, it has also been a lesson from the studies of the past 15 years on Na\(_{1.5}\), that subtle alterations in the biophysical properties of Na\(_{1.5}\) may have very deleterious consequences that can lead to lethal forms of ventricular arrhythmias.

Efficacious and safe pharmacological treatment of arrhythmias has proven to be an extremely challenging task, notably because of the proarrhythmic properties of many antiarrhythmic drugs. Nevertheless, the principle of targeting membrane proteins such as ion channels with small organic molecules is, without a doubt, a very effective approach in the treatment of many pathologies. In theory, this should also be possible for complex cardiac arrhythmias. Studies such as the one by Beyder et al in this issue of Circulation are very important because they (1) demonstrate for us new ways to influence cardiac ion channels with the aim of treating arrhythmias and (2) provides us with a hope that there is still much more to understand about the roles of ion channels in cardiac physiology and pathophysiology.

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Disclosures

None.

References


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