Leaky channels could contribute to unusual heart arrhythmias

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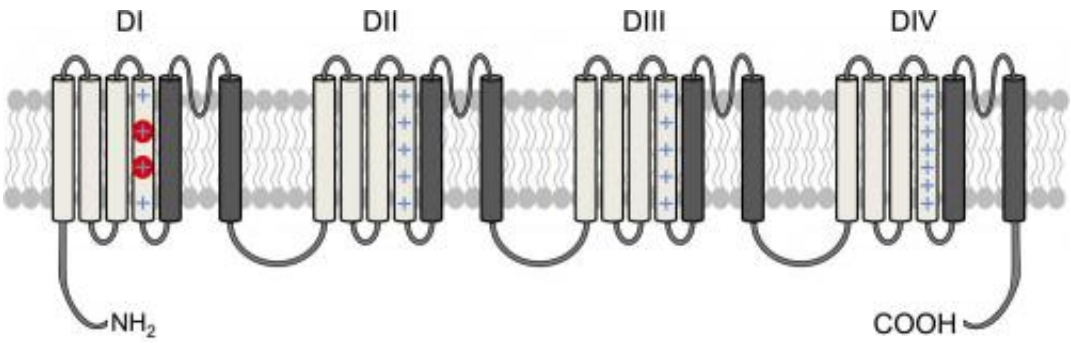


Illustration of the cardiac $Na_v1.5$ channel. The red circles indicate the locations of the R222Q and R225W mutations in the voltage-sensing region of domain 1 (DI). Credit: Moreau et al., 2015

Leaks are not just problems for plumbers and politicians; researchers in Canada reveal how leaky transmembrane channels could cause disruptions in normal heart function. The study, published in *The Journal of General Physiology*, suggests that ion leaks in mutant sodium channels might contribute to an unusual set of cardiac arrhythmias.

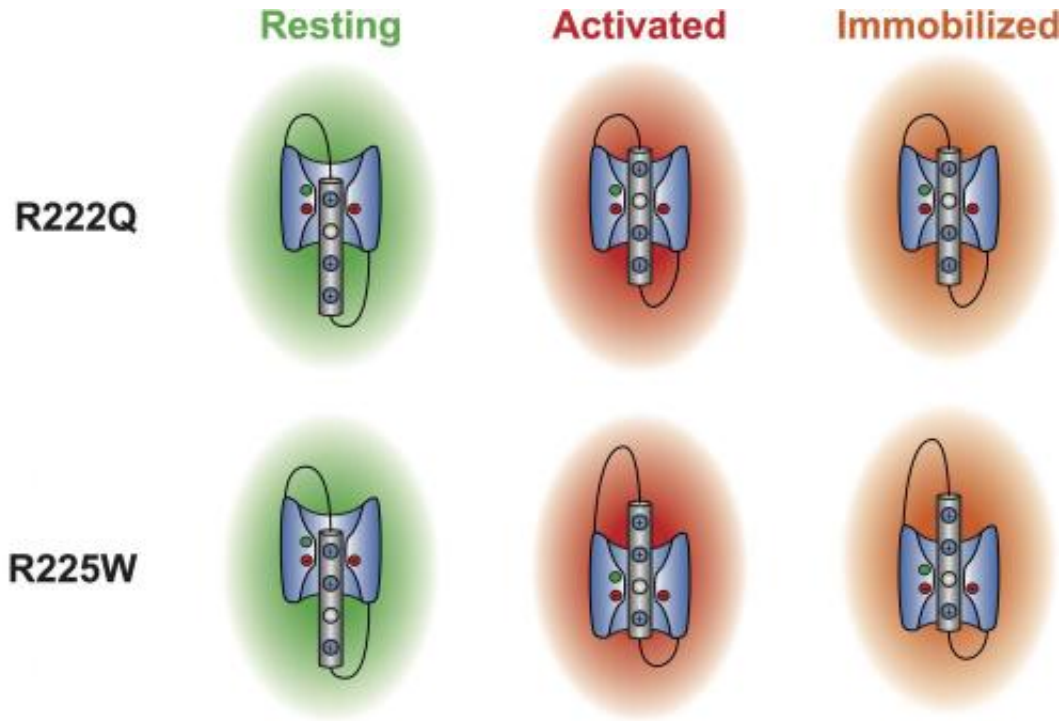
Voltage-gated sodium (Na_v) channels are responsible for mediating an "action potential" in muscle cells that leads to contraction. $Na_v1.5$ is the primary Na_v channel expressed in the muscle cells of the heart, and $Na_v1.5$ mutations that disrupt its function are associated with many well-defined cardiac arrhythmias. Recent studies have linked two $Na_v1.5$ mutations (R222Q and R225W) to an unusual group of arrhythmias that

are associated with dilated cardiomyopathy, a condition in which the heart becomes enlarged and cannot pump blood efficiently.

Oddly enough, the two mutant channels have opposite effects on channel function, with one expected to promote premature firing of the action potential and the other expected to interfere with action potential initiation. It's therefore unclear how they could be linked to similar cardiac pathologies.

In search of a unifying mechanism, Mohamed Chahine and colleagues in Quebec City investigated the properties of the mutant channels. Voltage-gated channels contain four segments called voltage sensor domains (VSDs), which are typically nonconductive and distinct from the regions that make up the channel pore; the R222Q and R225W mutations are both located on one of these VSDs. During initiation of the cardiac action potential, however, when the negative internal charge of the cell becomes positive so that the cell becomes "depolarized," the researchers found that both mutations caused the VSD assume a conformation that created an abnormal pathway allowing positively charged ions to pass through this normally nonconductive region. Moreover, the VSD seemed to become immobilized following depolarizations comparable in length to the cardiac action potential instead of returning to resting position, allowing charged sodium ions to continue leaking into the cell.

Chahine and colleagues think that the resulting overload of sodium ions within the cell could contribute to disruptions in normal cardiac function. And because the ion leak is the only property common to both mutations, their findings suggest that it could be a key mechanism linking them—and possibly other $Na_v1.5$ mutations in the VSD—to the atypical group of arrhythmias mixed with dilated cardiomyopathy.



This illustration depicts how a segment in the two mutant $Na_v1.5$ channels becomes immobilized during the cardiac action potential rather than returning to resting position, allowing charged ions to continue to leak into heart muscle cells. Credit: Moreau et al., 2015

More information: Moreau, A., et al. 2015. *J. Gen. Physiol*. DOI: 10.1085/jgp.201411304

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