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Molecular Mechanisms of pH Modulation of Cardiac Sodium Channels ($Na_v1.5$)

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During ischemic heart disease, pH drops from 7.4 to 6.0 within 10 minutes of onset, severely affecting ion channel gating. The cardiac sodium channel ($Na_v1.5$) is particularly susceptible to this abrupt pH change, and its altered gating is thought to predispose patients suffering ischemia to arrhythmia and sudden cardiac death. We observed the voltage-sensing domains (VSDs) of $Na_v1.5$ to discover molecular mechanisms of its regulation by pH.

A cysteine mutation was made in each of the four VSDs (DI-DIV) of $Na_v1.5$. Synthesized RNA from these constructs was injected into *Xenopus oocytes*. Once channels were expressing, a fluorophore was tethered to the cysteine via a disulfide bond. By measuring the kinetics and change in magnitude of the fluorescence, we were able to track VSD conformational changes along with the current-voltage relationship.

We found that reducing the pH of the extracellular solution from 7.4 to 6.0 causes I_{Na} to decrease in magnitude by 50%, and shifts in both activation and fast inactivation rightward, consistent with previous results. At a pH of 6.0, time to peak was reduced by 300% while inactivation was only 10% slower. Observation of the VSDs showed that the DII-VSD is not affected by pH, and the DIII-VSD showed a small depolarizing activation shift ~6.65 mV. The DIV-VSD displayed a complex phenotype, not shifting after short pulses, but shifting prominently (23.27 mV) after prolonged pulses. Its kinetics were also slowed by a factor of 2 at a pH of 6.0.

These results suggest an important role for the DIV-VSD in determining regulation of $Na_v1.5$ by pH.