

## **A Novel Mechanism for Inhibition of Pacemaker Channels by Receptor-like Tyrosine Phosphatase alpha**

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We have previously reported an important role of increased tyrosine phosphorylation activity by Src in the modulation of Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) channels. Using a combination of whole-cell patch clamp technique, western blot, and confocal fluorescence imaging, we assessed the hypothesis that decreased tyrosine dephosphorylation may enhance HCN channel activity as well. We discovered that the receptor-like protein tyrosine phosphatase alpha (RPTPalpha) significantly inhibited or even eliminated HCN2 currents expressed in HEK293 cells. Biochemical evidence showed that the surface expression of HCN2 is reduced by RPTPalpha, which was in parallel to the decreased tyrosine phosphorylation of the channel protein. Confocal imaging confirmed that the surface expression of HCN2 channel is inhibited by RPTPalpha. Moreover, we detected the presence of RPTPalpha proteins in rat cardiac ventricles and the levels of RPTPalpha expression changed during development. Inhibition of tyrosine phosphatase activity by phenylarsine oxide (a non-selective inhibitor for tyrosine phosphatases) shifted ventricular I(f) (generated by HCN channels) activation from non-physiological voltages to the physiological voltages associated with accelerated activation kinetics. In conclusion, we demonstrated a critical role RPTPalpha plays in gating of HCN channels via tyrosine dephosphorylation mediated by RPTPalpha. These findings are also important to neurons where HCN and RPTPalpha are richly expressed.