Volume 12

Washington University
Undergraduate Research Digest

Spring 2017

The Role of Notch Signalling on Heart Rate and Atrial Conduction Velocity

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Heart disease is the leading cause of death worldwide and can result in arrhythmias, or dysregulation in the electrical activation of the heart. Sick Sinus Syndrome (SSS) is characterized by sinus bradycardia (slowed heart rate, HR), slowed conduction through atrial myocardium, and can predispose to the development of atrial fibrillation. A developmental signaling pathway, Notch, regulates cellular identity through differentiation of cardiomyocytes (CMs) into cardiac conduction system-like cells. Previous data show that Notch electrically remodels the right atrium, causing slowed conduction velocity (CV) and hallmarks of SSS including sinus pauses, sinus bradycardia and a predisposition to atrial fibrillation. However, the molecular mechanisms behind these phenotypes are not known. We hypothesized that Notch activation produces slowed CV through downregulation of major cardiac voltage-gated sodium channel ($Na_V1.5$) and atrial gap junction (Connexin40, Cx40). A "Tet-On" doxycycline-activated system using transgenic adult mice was used to activate Notch specifically in CMs. We assayed various determinants of CV, including fibrosis, cellular hypertrophy, and Na^+ channel and gap junction expression. Trichrome stain and hydroxyproline assay indicated normal levels of non-conductive fibroblasts. To determine whether Notch activation is associated with pathophysiological hypertrophy, I quantified cell area using immunohistochemistry and found no difference in Notch activated hearts when compared with controls. Furthermore, immunohistochemistry indicated no gross changes in $Na_V1.5$ or Cx40 expression within the atrial myocardium. However, localization of $Na_V1.5$ and Cx40 within the plasma membranes of CMs, as well as post-translational modifications that may result in slowed conduction velocity are yet to be analyzed. Future studies will determine whether Notch-induced slowed HR is due to autonomous changes within the pace-making sinus node (SAN) region or non-autonomous changes within the atrial myocardium. Notch will be activated specifically in the SAN of the adult mouse heart using an HCN4-creER tamoxifen-inducible system and HR will be evaluated using electrocardiograms.