The Role of Notch Signaling on Heart Rate and Atrial Conduction

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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 a predisposition to atrial fibrillation. Studies have shown that cardiac injury to the adult mouse heart electrically remodels the right atrium to induce symptoms resembling SSS.

Objective and Methods

Aim 1: Determine the effect of Notch signaling on heart rate.
- Determine whether Notch signaling affects heart rate through non-autonomous effects on the right atrium by performing ECGs.
- Determine whether Notch signaling affects heart rate through autonomous effects on the SAN by performing ectopic spontaneous 4th heart sounds.

Aim 2: Evaluate the effect of Notch on the morphological determinants of conduction velocity.
- Determine the changes in ion channel and gap junction expression in the SAN and atrial cardiomyocytes through immunostaining.
- Determine the amount of fibrosis through trichrome staining and hydroxyproline quantification.
- Determine if Notch reduces pathological hypertrophy by quantifying cell area.

The Role of Notch Signaling on Heart Rate and Atrial Conduction

Aim 1: Determine the effect of Notch signaling on heart rate.

Aim 2: Evaluate the effect of Notch on the morphological determinants of conduction velocity. Performing ECGs.

Determine the effect of Notch signaling on heart rate. Performing ECGs.

Determine the effect of Notch on the morphological determinants of conduction velocity. Performing ECGs.

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Notch Signaling Pathway

A. Notch
B. α-Actinin
C. DAP

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Preliminary Data: Heart Rate and Conduction Velocity Slope Lower Non-autonomous Notch Activation

Figure 2: Model of Non-autonomous Cardiomyocyte Notch Activation

Figure 3: Model of Autonomous SAN Notch Activation

Figure 4: Model of Notch Activation within all Cardiomyocytes

Figure 5: Model of Notch Activation within the Sinoatrial Node

Ongoing Plans & Future Directions

1. Investigate how different durations of Notch signaling may differentially affect electrical remodeling of the right atrium.
2. Investigate how autonomous Notch activation in CCS may decrease HR.
3. Investigate how different types of cardiac injury may differentially influence Notch activation in cardiomyocytes (MI, Transverse Aortic Constriction, Ischemia Reparation).
4. Investigate whether Notch signaling is working through other signaling pathways (such as Wnt signaling) to promote arrhythmogenesis.

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Elucidating the Role of Notch Signaling Activation in Atrial Arrhythmogenesis

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Abstract

Background: Heart disease is the leading and most costly cause of death in the United States as well as the world and the statistic has not changed in over a decade.1 About 50% of all cardiac-related deaths are due to sudden cardiac death (SCD).2 Fatal arrhythmias, which result from electrical dysfunction, are often the cause. Despite the major contribution of arrhythmias to mortality rates, there is very little known about the mechanism(s) of arrhythmogenesis. One of the major risk factors for SCD is myocardial infarction (MI).3 Notch signaling, a developmental signaling pathway important in cell processes including proliferation and differentiation, is upregulated following cardiac injury such as myocardial infarction (MI) in the cardiomyocytes (CMs) of the adult mouse and adult zebrafish heart.4-6 Notch signaling has the capability of converting a ventricular myocyte to a Purkinje-like phenotype by altering the electrical program of the cell when overexpressed during development.7,8 Therefore, it is also possible that Notch activation after cardiac injury in the adult is an important contributor to the development of cardiac arrhythmias through electrical remodeling of CMs. This may explain why individuals who undergo cardiac surgery are most likely to experience cardiac arrhythmias. Little is known about the role of Notch in the regulation of ion channels in atrial myocytes. Atrial myocytes are an often overlooked, yet important cell type to investigate because one of the most common types of arrhythmias is atrial fibrillation.9

Hypothesis: Notch activation regulates electrical remodeling of adult right atrial cardiomyocytes and this remodeling may be involved in the progression of arrhythmias after cardiac injury.

Preliminary Data

Figure 1: Notch activation causes sinus bradycardia. 8-week-old mice had Notch activated and Electrocardiogram (ECG) recordings were collected two different ways 3 weeks later. The heart rate significantly decreased in mutant mice compared to controls in both conscious and anesthetized ECGs.

Figure 2: Notch activation does not change action potential duration but does slow conduction velocity. A) Action potential duration, an intrinsic myocyte property, is not significantly increased as a result of CM-specific Notch activation at 8 weeks. B) Atrial conduction velocity is significantly decreased as a result of CM-specific Notch activation at 8 weeks.

Figure 3: Notch activation causes sinus bradycardia. Action potential waveforms vary based on location of cell in the heart. A) Action potential of a typical ventricular cardiomyocyte. Numbers on the action potential waveform represent the phase of the action potential. Action potential phases are characterized by a unique combination open and closed ion channels, and therefore a difference in currents.

Aims & Methods

Specific Aim 1: To investigate the mechanism for Notch-induced sinus bradycardia and electrical remodeling of atrial cardiomyocytes

Subaim 1.1: Determine whether Notch activation is causing morphological changes to the sinoatrial node

- Histological Staining
  - SAN: Cox2, Cox4

Subaim 1.2: Determine whether Notch activation is acting cell autonomously on sinoatrial nodal cells, or indirectly through effects on right atrial cardiomyocytes, to cause sinus bradycardia

- Single cell electrophysiology-current clamp
- Resting membrane potentials
- Action potential waveforms

Subaim 1.3: Determine which ionic currents are regulated by Notch in atrial cardiomyocytes

- Single cell electrophysiology-voltage clamp
- Ion channels (i.e. Voltage-gated Na+, Voltage-gated K+)

Subaim 1.4: Investigate the transcription effects of Notch activation in atrial myocardium using qPCR

- Ion channels (i.e. Scn5a)
- Gap junctions (i.e. Cx40)

References

7. Yen, A. et al. Notch activation after cardiac injury alters expression of ion channels and gap junctions in cardiomyocytes, promoting the onset of arrhythmias. The specific tissue sites of notch activation after different cardiac injuries are yet to be determined.

Ongoing Plans & Future Directions

1. Investigate the duration of Notch activation necessary to induce arrhythmogenesis and electrical remodeling of the right atrium (ongoing)
2. Investigate whether ‘rescuing’ the effect of Notch activation at 8 weeks of age by using Notch inhibitors prevents arrhythmogenesis and electrical remodeling of the right atrium
3. Investigate how different types of cardiac injury induce Notch activation in cardiomyocytes (MI, Transverse Aortic Constriction, Ischemia-Reperfusion)

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