Topic 16 – Electrophysiology: conduction – A

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0290

Unprovoked atrial tachyarrhythmias in aging spontaneously hypertensive rats: the role of the autonomic nervous system

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Aims: Experimental models of unprovoked atrial tachyarrhythmias (AT) in conscious, ambulatory animals are lacking. We hypothesized that the aging, spontaneously hypertensive rat (SHR) may provide such a model.

Method: Baseline ECG recordings were acquired with radiotelemetry in eight young (14-wk-old) and eight aging (55-wk-old) SHRs and in two groups of four age-matched Wistar-Kyoto (WKY) rats. Quantification of AT and heart rate variability (HRV) analysis were performed based on 24-h ECG recordings in unrestrained rats. All animals were submitted to an emotional stress protocol (air-jet). In SHRs, carbamylcholine injections were also performed.

Results: Spontaneous AT episodes were observed in all eight aging SHRs (median, 91.5; range, 4-444 episodes/24 h), but not in young SHRs or WKY rats. HRV analysis demonstrated significantly decreased low frequency components in aging SHRs compared with age-matched WKY rats ($P<0.01$) and decreased low/high frequency ratios in both young ($P<0.01$) and aging ($P=0.01$) SHRs compared with normotensive controls. In aging SHRs, emotional stress significantly reduced the number of arrhythmic events, whereas carbamylcholine triggered AT and significantly increased atrial electrical instability.

Conclusion: This study reports the occurrence of unprovoked episodes of atrial arrhythmia in hypertensive rats, and their increased incidence with aging. Our results suggest that autonomic imbalance with relative vagal hyperactivity may be responsible for the increased atrial arrhythmogenicity observed in this model. We also provide evidence that, in this model, the sympatho-vagal imbalance preceded the occurrence of arrhythmia. These results indicate that aging SHRs may provide valuable insight into the understanding of atrial arrhythmias.

0252

Bradycardia and arrhythmia caused by cardiac-specific suppression of the "funny" (If) current are rescued by Girk

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The spontaneous activity of pacemaker myocytes controls the heartbeat. Automaticity is due to the presence of the slow diastolic depolarization phase, which leads the membrane potential from the end of the repolarization phase to the threshold of the following action potential. f- (HCN) channels underlying the hyperpolarization-activated "funny" current (I_f) are thought to play a key role in the generation and autonomic regulation of the diastolic depolarization and heart rate, but their role is still subject of controversy. Here we show that conditional and time-controlled expression of a dominant-negative non-conductive human HCN4 channel subunit (hHCN4-AYA) in the mouse heart leads to virtually complete silencing of I_f current (>95%) in the diastolic depolarization range in the sino-atrial node and in the conduction system. Heart-specific I_f silencing induced sino-atrial bradycardia, sinus pauses, severe dysfunction of atrioventricular conduction and ventricular arrhythmias. In comparison to control myocytes, the basal automaticity of hHCN4-AYA SAN myocytes was reduced by 76% and by 67% in myocytes of the conduction system. However, the relative maximal positive chronotropic effect of b-adrenergic activation on *in vivo* heart rate, isolated atria or pacemaking of individual SAN and conduction myocytes was preserved showing that I_f does not play an exclusive role in heart rate regulation. Unexpectedly, crossing hHCN4-AYA mutant mice with mice lacking the cardiac muscarinic G-protein-activated channel Girk4 ($Girk4^{-/-}$) eliminated atrioventricular blocks and ventricular arrhythmias without preventing the autonomic regulation of heart rate. Our study shows, for the first time, the functional consequences of I_f silencing on heart rate and rhythm and indicates the possibility of managing cardiac disease related to HCN loss-of-function in humans by pharmacologic or genetic inhibition Girk4 channels.

0257

Genetic inactivation of Kir3.4 (GIRK4) channels improves heart rate and abolishes atrial tachyarrhythmias in a mouse model of sick-sinus syndrome

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Objectives: We aimed to test if genetic inactivation of the cardiac IKACh current could improve the phenotype of mice lacking L-type Cav1.3 Ca2+ channels (Cav1.3-/-), a mouse model recapitulating the sino-atrial node dysfunction and supraventricular arrhythmias typical of the "sick sinus" syndrome (SSS) in humans.

Background: SSS is an invalidating disease. The only currently available therapy consists in the implantation of an electronic pacemaker. Cav1.3-/- mice present several characteristics of the SSS, including bradycardia associated with atrial fibrillation or flutter, as well as type I and II atrioventricular conduction blocks. IKACh is involved in autonomic regulation of heart rate and in the triggering of atrial fibrillation by the parasympathetic nervous system, but its role in establishing the symptoms of SSS is unknown.

Methods: We crossed IKACh-deficient mice (Kir3.4-/-), with Cav1.3-/- mice to obtain double knockout (Cav1.3-/-/Kir3.4-/-) animals. Telemetric recordings of heart rate and ECG waveforms of wild-type, Cav1.3-/-, Kir3.4-/- and Cav1.3-/-/Kir3.4-/- mice were performed. The frequency of occurrence of episodes of atrial arrhythmias was evaluated by intracardiac recordings.

Results: Genetic inactivation of IKACh in Cav1.3-/-/Kir3.4-/- mice significantly improved the mean heart rate of Cav1.3-/- mice and completely abolished atrioventricular conduction blocks. Atrial fibrillation and flutter that were typical of Cav1.3-/- mice could not be observed or triggered in Cav1.3-/-/Kir3.4-/- mice.

Conclusion: Inactivation of IKACh effectively improved SSS in Cav1.3-/- mice. Our study indicates that SSS patients can benefit of IKACh suppression by gene therapy or selective pharmacologic inhibitors.

0222

The TRPM4 channel modulates mammalian sinus rhythm

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Background: The transient receptor potential melastatin 4 (TRPM4) channel produces a Ca2+-activated non-selective monovalent cationic current that was detected in several cardiac preparations, including mouse sino atrial node isolated cells. TRPM4 is known to participate in spontaneous electrical activities such as in neurons or in cardiac ventricular preparations submitted