Novel Pathways for Regulation of Sinoatrial Node Plasticity and Heart Rate

Peter J. Mohler, Thomas J. Hund

Heart rate is an amazingly adaptive process with redundant pathways for both acute and chronic regulation in response to a wide range of environmental stimuli. Dramatic changes to basal heart rate are common not only in cardiovascular disease but also under physiological conditions (eg, exercise) as a way to match cardiac output with demand. Driving these changes in heart rate is alterations in activity of the sinoatrial node (SAN), a heterogeneous collection of specialized myocytes located in the right atrium. Defects in SAN function are increasingly common in an aging population (effects ≈1 in 600 patients over the age of 65 years) and manifest as prominent issues with heart rate control.[1] Given the growing prevalence of SAN dysfunction and the limitations of available therapies, there is a great need to better understand the various ways the heart has evolved to control intrinsic rate.

Article, see p 1058

Normal SAN function depends on a delicate balance between the activity of a relatively small number of automatic cells capable of spontaneously generating an action potential (AP) and the demands of surrounding atrial cells that require external stimulus for activation. This balance (and therefore heart rate) is readily tuned by perturbations at the cell and tissue level. SAN cell automaticity itself depends on a distinct ion channel expression profile that differs substantially from the ion channel signature present in atrial or ventricular cells.[2] In contrast to ventricular and atrial cells, the SAN myocyte expresses virtually no inward rectifier K^+ current (I_{K1}), contributing to an AP without a stable rest potential. Instead, on reaching a maximum diastolic potential (≈−60 mV), the SAN AP undergoes spontaneous depolarization eventually reaching threshold for generation of another AP. The hyperpolarization-activated "funny" current (I_f) (due primarily to HCN4 in SAN cells) generates an important depolarizing current during this phase, together with the Na^+/Ca^{2+} exchanger in response to local Ca^{2+} release events from sarcoplasmic reticulum ryanodine receptor Ca^{2+} release channels.[3,4] Eventually, the membrane potential reaches threshold (around −50 mV) for activation of transient or T-type Ca^{2+} channels ($Ca_v3.1$, $Ca_v3.2$, $Ca_v3.3$) that generate a depolarizing current to accelerate spontaneous depolarization. L-type Ca^{2+} channels ($Ca_v1.3$, $Ca_v1.2$) activate around −40 mV, triggering the SAN AP upstroke, that is much slower when compared with atrial or ventricular APs because of the relatively low expression of voltage-gated Na^+ channel (Na_v). Although Na_v does not contribute significantly to the SAN AP upstroke (especially in the central SAN region), Na_v expression in atrial tissue surrounding the SAN (and SAN periphery itself) helps to ensure robust pacemaking. A host of voltage-gated K^+ channels govern SAN AP repolarization. The transient outward K^+ current (I_{to}, $K_v1.4$, $K_v4.2$, and $K_v4.3$) is responsible for the early repolarization, whereas ultrarapid (I_{Kur}, $K_v1.5$), rapid (I_{Kr}, ERG), and slow (I_{Ks}, K_vLQT1) delayed rectifier K^+ currents determine late repolarization phase along with the maximal diastolic potential (I_{Kr}, in particular, in the absence of I_{K1}). Currents such as ATP- and acetylcholine-sensitive K^+ currents ($I_{K,ATP}$, $I_{K,Ach}$, respectively) impart dynamic responsiveness of the SAN to parasympathetic and metabolic factors.

Underlying the adaptability of heart rate is plasticity of the SAN. A major pathway for acute regulation of SAN function (and therefore heart rate) is through altered gating of ion channels important for SAN cell automaticity, either through ligand binding (eg, I_f, $I_{K,ATP}$, $I_{K,ACh}$) or post-translational modification. In particular, the impact of adrenergic stimulation on phosphorylation of SR Ca^{2+} release channels, SAN cell excitability, and pacemaker function has been well characterized.[4] Of course, changes in expression of ion channels have been documented as an important cause of altered SAN function and heart rate in the setting of chronic stimuli (eg, disease, aging, long-term exercise training) although the upstream determinants of these remodeling changes remain unclear. Finally, alterations in structure of the SAN itself, for example, because of fibrosis, may alter the source–sink balance between the SAN and surrounding atrial tissue to produce changes in heart rate.[5]

In this issue of *Circulation Research*, D'Souza et al[6] explore the molecular and cellular mechanisms underlying regulation of exercise training–induced sinus bradycardia and uncover a novel pathway for control of ion channel expression and SAN plasticity. The role of I_f in animals for heart rate regulation has been the subject of controversy for many years. *Hcn4* deletion in 1 mouse model results in frequent sinus pause,[7] where in a second model, *Hcn4* deletion has a significant impact on heart rate (bradycardia).[8] Because of the critical role of cardiac pacemaking for vertebrate survival (eg, fight or flight

From the Dorothy M. Davis Heart and Lung Research Institute, College of Medicine (P.J.M., T.J.H.), Department of Physiology & Cell Biology (P.J.M.), Division of Cardiovascular Medicine, Department of Internal Medicine, (P.J.M., T.J.H.), The Ohio State University College of Medicine and Wexner Medical Center, Columbus; and Department of Biomedical Engineering, The Ohio State University College of Engineering & Cell Biology, Columbus (T.J.H.).

Correspondence to Peter J. Mohler, PhD, 473 W 12th Ave, DHLRI 110G, Columbus, OH 43210. E-mail peter.mohler@osumc.edu

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response), a host of likely redundant pathways have evolved to modulate sinus node depolarization. Nonetheless, although I_f elimination is insufficient to eliminate pacemaking, it serves a critical central role in sinus node activity.

Work from this group and others strongly supports the role of the HCN4 and I_f in exercise training–induced bradycardia. Specifically, in 2014, D'Souza et al[9] reported in multiple animal models that exercise training–induced bradycardia is independent of autonomic nervous system block but is associated with remodeling (downregulation) of I_f. Furthermore, I_f inhibition was sufficient to mitigate the change in heart rate of exercise-trained versus sedentary animals.[9] However, because of potential differences in animal models, methodologies (eg, questions of complete versus incomplete autonomic blockade), lack of direct human data, and the role of intrinsic sinus node mechanisms versus the autonomic nervous system for heart rate modulation in response to exercise training has remained controversial.[10,11] Here, D'Souza et al[6] take a step forward in investigating the mechanisms underlying heart rate regulation using an elegant series of experiments in humans and animal models. First, similar to findings in animal models, intrinsic heart rate was reduced in male athletes versus nonathletes. Second, in line with prior animal work from this group, the heart rate lowering impact of ivabradine (I_f blocker) was correlated with intrinsic heart rate, supporting the role of I_f suppression in response to exercise training. Third, in parallel experiments, in swim-trained mice, the group identified a distinctive signature of miR remodeling. Notably, miR-423-5p remodeling was highlighted and directly linked with HCN4. In fact, in a direct test of miR-423-5p in heart rate regulation, anti–miR-423-5p introduction was sufficient to reverse exercise-induced heart rate regulation through (at least partially) HCN4/I_f. Finally, the authors elucidate the downstream pathways associated with this remodeling. Specifically, the authors provide supporting evidence that miR-423-5p and NSRP1 are modulated by an increase in Nkx2.5.

This new work provides further support for the role of HCN4/I_f in exercise-training–induced bradycardia. Although there will likely continue to be disagreements on the relative role of cardiac intrinsic (eg, HCN4) versus extrinsic (eg, autonomic nervous system) mechanisms for this adaptation, this new work is an important step forward in our effort to understand the systems in place to tune SAN function and heart rate. Given the growing incidence of SAN dysfunction in the aging population,[1] the identification of potential new therapeutic targets for SAN disease (and on a larger scale atrial arrhythmias) is paramount. Although the discovery of I_f and Nkx2.5 pathways for SAN remodeling will require additional validation (eg, what underlies miR-423-5p changes? What is the spectrum of other miR-423-5p targets?), this work sets the stage for important new discovery in this field that may have implications for other areas of human excitable cell biology.

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Disclosures

None.

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