Journal of
Cardiology & Cardiovascular Therapy
ISSN: 2474-7580

Juniper Publishers
key to the Researchers

Opinion
Volume 6 Issue 4 – July 2017
DOI: 10.19080/JOCCT.2017.06.555695

J Cardiol & Cardiovasc Ther

Mutation in one Molecule Induces Beating Rate Changes by Affecting the Coupled Clock Pacemaker Function

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Submission: July 07, 2017; **Published:** July 26, 2017

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Abstract

Pacemaker function is orchestrated through molecules on the membrane and on the sarcoplasmic reticulum that are coupled by Ca^{2+} and post-translation modification signaling. These molecules and signaling cascades form one coupled-clock system. Experimental and computational evidence highlight the coupling between components in this system. However, most studies examine how a given pacemaker mutation causes bradycardia or tachycardia and report changes only for the affected molecule without capturing the overall effect on the coupled-clock system. Here, we provide our opinion on how a mutation in one molecule impacts the beating rate by affecting the coupled clock pacemaker function (and thus not only a single molecule). A better understanding of changes in the coupled-clock system due to a given pacemaker mutation may provide new insights into the changes in physiological processes in health and disease and support the design of new drug therapeutics for treating cardiac conditions.

Keywords: Arrhythmia; Funny current; Protein kinase A

Introduction

The sinoatrial node consists of hundreds of pacemaker cells that initiate the heartbeat. Evidence has shown that pacemaker cell function is orchestrated not only by one molecule, but through molecules on the membrane and on the sarcoplasmic reticulum that are coupled by Ca^{2+} and post-translation modification signaling (reviewed in [1]). These molecules and their associated coupling nodes create the coupled-clock system that controls pacemaker function. Both experimental [2,3] and computational [4-6] evidence confirm the theory that any change in the function of any membrane or intracellular molecule should indirectly affect the function of the other molecules, and that the state of the ensemble of molecules should determine the pacemaker cells' beating rate. With the recent advances in gene research and the ability to identify mutations in membrane and intracellular molecules, mutations have been associated with several cardiac diseases [7,8]. Several groups have identified mutations in pacemaker cells involved in either bradycardia or tachycardia. Hategan et al. [9] reported that the HCN_4 mutation c.1737+1G>T leads to bradycardia, which they interpreted to exist only by reduction in I_f through altered cAMP binding to HCN_4. Similarly, Biel et al. [10] reported that the HCN_4 mutation V492F leads to Brugada syndrome. The HEK293 cell line that expressed this mutation showed that I_f was responsive to cAMP, but required a more negative voltage for activation. These authors also concluded that "modulation of HCN_4 activity could be the cause of the diagnosed cardiac abnormality". Finally, Duhme et al. have shown that the HCN_4 mutation K530N is associated with ventricular tachyarrhythmia. The HEK293 cell line that expressed this mutation showed a shift in the half-maximal activation voltage of I_f. The authors concluded that "f-channel dysfunction contributes to the development of a trial tachyarrhythmia". However, mutation in HCN_4 also alters other mechanisms of the coupled-clock system, which together change the heart rhythm [3,4,11]. At the single cell level, experimental and computational evidence have shown that blocking I_f by ivabradine increases the beating interval [3] and beating rate variability [11], not only through the direct effect of the I_f current, but through changes in Ca^{2+} signaling and I_{NCX}. Further computational evidence has shown that mutations that increase cAMP binding to HCN_4 or alter $V_{1/2}$ lead to tachycardia and bradycardia, respectively, by the afferent mechanisms and changes in post-translation modification signaling [4]. Thus, both the direct effect on the mutant HCN_4 and the indirect effect on other coupled-clock molecules lead to either bradycardia or tachycardia.

Not only have mutations in HCN_4 been associated with bradycardia or tachycardia. Glukhov et al. [12] have shown that mutations in Calsequestrin 2 lead to loss of pacemaker function. The authors concluded that mutations in Calsequestrin 2 lead to fibrosis and altered Ca^{2+} signaling. Additionally, the Gómez lab has shown that mutations in the ryanodine channel (either R4496C or R420Q) are involved in catecholaminergic polymorphic ventricular tachycardia [13,14]. Although, both groups explored the mutation in one molecule, in contrast to the former groups they documented other altered mechanisms that together led to arrhythmogenic episodes. Similar to the HCN_4 case, mutation in intracellular molecules also alter other mechanisms of the coupled-clock system, which together change the heart rhythm.

Conclusion

There is no "one important molecular determinant of heart rate regulation," but rather interaction among coupled-clock molecules, which define the heart rate and rhythm. Direct pharmacological treatments that affect cAMP binding to HCN_4 or restore I_f do not exist. Similarly, drugs to compensate for the loss of Calsequestrin 2 or efficiently restore ryanodine function do not exist. However, it may be possible to restore the pacemaker function by using drugs that will alter other pacemaker clock molecules or coupling nodes, thus re-establishing the normal coupling between the two pacemaker clocks.

Acknowledgment

The work was supported by the NSFC-ISF Joint Research Program, No. 398/14 (Y.Y), the Israel Ministry of Science (Y.Y), an Aly-Kaufman Postdoctoral Fellowship (JB), and The Center for Absorption in Science, Ministry of Immigrant Absorption, and State of Israel (JB).

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DOI: 10.19080/JOCCT.2017.06.555695