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cAMP Imaging at Ryanodine Receptors Reveals β_2-Adrenoceptor Driven Arrhythmias

Berisha F, Götz KR, Wegener JW, Brandenburg S, Subramanian H, Molina CE, Rueffer A, Petersen J, Bernhardt A, Girdauskas E, Jungen C, Pape U, Kraft AE, Warnke S, Lindner D, Westermann D, Blankenberg S, Meyer C, Hasenfuß G, Lehnart SE, Nikolaev VO

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ABSTRACT: *Rationale*: 3',5'-cyclic adenosine monophosphate (cAMP) is a ubiquitous second messenger which, upon β-adrenergic receptor (β-AR) stimulation, acts in microdomains to regulate cardiac excitation-contraction coupling by activating phosphorylation of calcium handling proteins. One crucial microdomain is in vicinity of the cardiac ryanodine receptor type 2 (RyR2) which is associated with arrhythmogenic diastolic calcium leak from the sarcoplasmic reticulum (SR) often occurring in heart failure.
Objective: We sought to establish a real time live cell imaging approach capable of directly visualizing cAMP in the vicinity of mouse and human RyR2 and to analyze its pathological changes in failing cardiomyocytes under β-AR stimulation.
Methods and Results: We generated a novel targeted fluorescent biosensor Epac1-JNC for RyR2-associated cAMP and expressed it in transgenic mouse hearts as well in human ventricular myocytes using adenoviral gene transfer. In healthy cardiomyocytes, β_1-AR but not β_2-AR stimulation strongly increased local RyR2-associated cAMP levels. However, already in cardiac hypertrophy induced by aortic banding, there was a marked subcellular redistribution of phosphodiesterases (PDEs) 2, 3 and 4, which included a dramatic loss of the local pool of PDE4. This was also accompanied by measurable β_2-AR/AMP signals in the vicinity of RyR2 in failing mouse and human myocytes, increased β_2-AR-dependent RyR2 phosphorylation, SR calcium leak and arrhythmia susceptibility.
Conclusions: Our new imaging approach could visualize cAMP levels in the direct vicinity of cardiac RyR2. Unexpectedly, in mouse and human failing myocytes, it could uncover functionally relevant local arrhythmogenic β_2-AR/cAMP signals which might be an interesting antiarrhythmic target for heart failure.

STATEMENT: *Chronic heart failure is a common severe disease condition in the adult population (about 4 million patients in Germany) and one of the leading causes of hospitalization and death. It is defined by a loss of cardiac function which occurs, among other causes, due to molecular remodeling of the β-adrenergic receptor (β-AR) signaling cascade and microdomain-specific alterations of its major second messenger cAMP. In addition to the loss of pump function, many patients die due to life-threatening arrhythmias caused by diastolic calcium leak though ryanodine receptors (RyR). In this interdisciplinary work, we have for the first time developed a biosensor for live cell imaging of cAMP signals in the direct vicinity of the RyRs and monitored local cAMP responses in healthy and failing mouse and human cardiac myocytes. Unexpectedly, this approach has uncovered local arrhythmogenic β_2-AR/cAMP signals which could be an interesting new target to treat heart failure associated life threatening arrhythmias.*

BACKGROUND: This work was performed by Dr. F. Berisha from the UHZ together with Dr. H. Subramanian, Dr. C. Molina und Dr. A. Kraft working in the research group of Prof. V.O. Nikolaev, Director of the Institute of Experimental Cardiovascular Research. This project was performed in close

collaboration between this institute and the Clinics of Cardiology and Cardiac Surgery of the UHZ, as well as with colleagues from the German Heart Research Center (DZHK) at the University Medical Center Göttingen. The work was funded by the DZHK and the Gertraud und Heinz-Rose Stiftung.