UKE Paper of the Month August 2018

Distinct submembrane localisation compartmentalises cardiac NPR1 and NPR2 signalling to cGMP

Subramanian H, Froese A, Jönsson P, Schmidt H, Gorelik J, Nikolaev VO

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ABSTRACT: Natriuretic peptides (NPs) are important hormones that regulate multiple cellular functions including cardiovascular physiology. In the heart, two natriuretic peptide receptors NPR1 and NPR2 act as membrane guanylyl cyclases to produce 3',5'-cyclic guanosine monophosphate (cGMP). Although both receptors protect from cardiac hypertrophy, their effects on contractility are markedly different, from little effect (NPR1) to pronounced negative inotropic and positive lusitropic responses (NPR2) with unclear underlying mechanisms. Here we use a scanning ion conductance microscopy (SICM) approach combined with Förster resonance energy transfer (FRET)-based cGMP biosensors to show that whereas NPR2 is uniformly localised on the cardiomyocyte membrane, functional NPR1 receptors are found exclusively in membrane invaginations called transverse (T)-tubules. This leads to far-reaching CNP/NPR2/cGMP signals, whereas ANP/NPR1/cGMP signals are highly confined to T-tubular microdomains by local pools of phosphodiesterase 2. This provides a previously unrecognised molecular basis for clearly distinct functional effects engaged by different cGMP producing membrane receptors.

STATEMENT: *This work addressed an important question of how two similar guanylyl cyclase receptors on the plasma membrane of cardiomyocytes produce functionally different cGMP signals visualized using cutting-edge imaging approaches. Recent development new drugs containing neprilysin inhibitors (e.g. Entresto) which increase natriuretic peptide levels in the circulation has made a significant impact on current heart failure therapy. However, the molecular basis for their effect on cardiac contractility has been unclear, as were their differential effects in heart failure with reduced and preserved ejection fraction, the latter accompanied by diastolic contractile dysfunction. Our study contributes exact understanding of a new cellular mechanism which, based on differential compartmentalization of cGMP signals generated by two membrane receptors NPR1 and NPR2 allows specific effects of natriuretic peptides ANP and CNP on cardiac contractility and diastolic function. This knowledge will be important for designing new therapeutic approaches and for the use of available drugs in different clinical forms of heart failure.*

BACKGROUND: This work was performed by the post-docs (Dr. H. Subramanian and Dr. A. Froese) working in the research group of Prof. V.O. Nikolaev, Director of the Institute of Experimental Cardiovascular Research. The research group focuses on cAMP and cGMP compartmentation and second messenger microdomain regulation in cardiomyocytes, and over the years has contributed multiple novel FRET-based sensors and cutting-edge biophysical techniques to investigate cAMP/cGMP dynamics by live cell imaging, in particular in healthy and diseased heart muscle cells. This work has been done in collaboration with Dr. Hannes Schmidt (University of Tübingen) and Prof. Julia Gorelik (Imperial College London). The work was funded DFG Forschergruppe 2060 (Tübingen-Hamburg-Würzburg) and Heinz Rose-Stiftung.