Spatial and temporal patterns of cAMP production in cardiovascular physiology and pathophysiology using FRET

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The diffusible second messenger cAMP plays a central role in autonomic regulation of the electrical, mechanical, and metabolic activity of cardiac myocytes. This includes sympathetic responses involving the β_1-adrenergic receptor and parasympathetic responses involving the M_2 muscarinic receptor. It is often assumed that activation of these receptors produces either a uniform increase or decrease in cAMP levels throughout the entire cell. However, this does not easily explain some experimental observations, especially those associated with certain potentially pathologic responses. Therefore, we employed a systems biology approach to test the hypothesis that cAMP signaling in cardiac myocytes is compartmentalized. Live cell imaging of fluorescence resonance energy transfer (FRET)-based biosensors expressed in different subcellular locations was used to measure spatial and temporal changes in cAMP activity in adult ventricular myocytes. It was then determined if those results are consistent with the predictions of a quantitative computational model of compartmentalized cAMP signaling in a myocyte made up of two sub-membrane microdomains (caveolar and extra-caveolar) and one bulk cytosolic domain. This model was created using published information on the subcellular distribution and kinetic properties of β_1-adrenergic and M_2 muscarinic receptors, stimulatory and inhibitory G proteins, as well as different adenylyl cyclase and phosphodiesterase isoforms. Our findings support the conclusion that even under basal conditions there are significant differences in the concentration of cAMP found in various microdomains within cardiac myocytes. Furthermore, compartmentation of cAMP signaling can explain both simple and complex temporal responses associated with β_1-adrenergic and M_2 muscarinic receptor activation.