

P008 Dynamic regulation of β -adrenergic signalling by compartmentalised PDE2.

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β -adrenergic signalling mediates the positive inotropic effect of catecholamines on cardiomyocytes, mainly through cAMP generation and subsequent activation of PKA.

Among all the potential targets of PKA in cardiomyocytes, only a subset regulates contractility, and a tight control of PKA activation is therefore needed to maintain signal specificity. PDE constitute the only cAMP degrading mechanism and are expressed in the cardiomyocyte in at least 5 family variants. Each PDE family is characterized by unique functional properties and contributes to a cAMP-degrading system enabling the control of PKA activation in a stimulus-specific manner. By performing real time imaging of cAMP in cultured rat cardiomyocytes, we have characterized the functional role of PDE2 in the regulation of the β -AR-dependent cAMP signal. Our experiments reveal that PDE2 is tightly coupled to the pool of adenylyl cyclases activated by $\beta_{1,2}$ -AR stimulation. This functional coupling is paralleled by the preferential localization of PDE2 in a specific subcellular compartment. By sensing cGMP levels, PDE2 also responds to the activation of β_3 -AR and NO generation. PDE2 is thus able to integrate cGMP and cAMP signals and plays a central role in a novel feedback loop of the beta-adrenergic pathway. Through this mechanism, activation of β_3 -AR enhances the degradation of cAMP generated upon stimulation of $\beta_{1,2}$ -AR. These results add to the knowledge of the complex PDE network and further our understanding on compartmented cAMP signalling.