Regulation of Cardiomyocyte Viability: Precision Mechanisms

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Abstract

Cardiomyocyte (CM) death is associated with many cardiac diseases, such as myocardial infarction, ischemia-reperfusion injury, chemotherapy-induced cardiotoxicity, myocarditis, and heart failure. Cyclic nucleotide second messenger, cAMP, regulates numerous biological processes in CMs, including the inotropic/chronotropic function, metabolism, and viability. Intracellular cAMP can be generated by membrane-associated adenylyl cyclases (ACs) via stimulating various stimulated G-proteins (Gs) coupled receptors (GsPCRs) and degraded by phosphodiesterases (PDEs). Many different GsPCRs, ACs, and PDSs are expressed in CMs. Increasing evidence has indicated that elevating intracellular cAMP by stimulating different GsPCRs, activating different ACs, or inhibiting different PDEs exhibits distinct, even opposite effects, on CM viability. We aim to investigate how different cAMP signaling differentially regulates CM viability with in *vitro*, *ex vivo,* and *in vivo* models. For pro-death GsPCRs, we chose beta1-adrenergic-receptor (b1AR) and histamine-H2-receptor (H2R). We found that the pro-death effects were dependent on AC5 activation, ATP release to the extracellular space via pannexin-1 (PANX1) channel, and extracellular ATP (e[ATP])-mediated signaling involving in P2X purinoceptor 7 (P2X7R) and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). b1AR or H2R was localized proximately to PANX1, which permits ATP release. PANX1 phosphorylation at Serine-206 by cAMP-dependent-protein-kinase-A (PKA) promoted PANX1 activation, which was critical in b1AR- or H2R-induced CM death *in vitro* and *in vivo*. For pro-survival GsPCRs, we chose adenosine-A2-receptor (A2R),

calcitonin-gene-related-peptide-receptor (CGRPR), and relaxin-family-peptide-receptor 1 (RXFP1). Their pro-survival effects were dependent on AC6 activation, cAMP efflux via multidrug-resistance-protein-4 (MRP4), extracellular cAMP metabolism to adenosine (e[cAMP]-to-e[ADO]), and e[ADO]-mediated signaling. A2R, CGRPR, or RXFP1 was localized proximately to MRP4, which enables cAMP efflux. Interestingly, exogenously increasing e[cAMP] levels by membrane-impermeable cAMP protected against CM death *in vitro* and in *ex vivo* and *in vivo* mouse hearts with ischemia-reperfusion (IR) injuries. Taken together, our findings significantly advance the biological insights into how different GsPCR/cAMP signaling differentially regulate CM viability through forming unique cAMP signalosomes that determine the fate of cAMP: either stimulate a pro-death mechanism involving PKA-induced ATP release or the pro-survival mechanism involving MRP4-mediated efflux to be e[cAMP]. These findings may reveal novel molecular targets and pharmacological strategies to increase CM viability.