Role of Protein Kinase A in Long-Term Agonist-Promoted Desensitization of the β-Adrenergic Receptor

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β-adrenergic receptor (βAR) signaling, desensitization, and downregulation are fundamental mechanisms that contribute to both normal and altered myocardial function. Phosphorylation of the βAR is the initial event that underlies rapid agonist-promoted desensitization. Associated with βAR activation is the auto-regulatory process of receptor desensitization. This process operates as a safety device to prevent overstimulation of receptors in the face of excessive βagonist exposure. However, the role of phosphorylation in mediating long-term βAR desensitization is not known. To investigate this possibility, we examined isoproterenol (ISO)-induced intracellular signal transduction pathways in heart and cerebral artery of cardiac hypertrophied rabbits. The result shows that PKA activity decreased ~2 fold over the basal state and mRNA level of βAR also decreased in both tissues. The lower level of PKA activity after long-term agonist exposure may therefore have contributed to the resensitization of βAR without an increase in quantity. In addition, we found the activation of Ras in hypertrophied heart but inactivation in hypertrophied cerebral artery. There may be differences between the heart and cerebral artery with regard to the molecular mechanisms that induce cardiac hypertrophy by stimulation of βAR.