
Myocardial overexpression of the C-terminus of beta-adrenergic receptor kinase (betaARKct) has been shown to result in a positive inotropic effect or an improvement of survival in heart failure. However, it is not clear whether this beneficial effect is mainly because of dominant-negative inhibition of betaARK1, and a consecutive resensitization of beta-adrenergic receptors (betaAR), or rather due to inhibition of other Gbetagamma-mediated effects. In this study, we tested whether overexpression of N-terminally truncated phosducin (nt-del-phosducin), another Gbetagamma-binding protein that does not resensitize betaARs owing to simultaneous inhibition of GDP release from Galpha subunits, shows the same effects as betaARKct. Adenoviral gene transfer was used to express nt-del-phosducin and betaARKct in isolated ventricular cardiomyocytes and in myocardium of rabbits, which suffered from heart failure because of rapid ventricular pacing. BetaAR-stimulated cAMP formation was increased by betaARKct, but not by nt-del-phosducin, whereas both proteins inhibited Gbetagamma-mediated effects. Both transgenes also increased contractility of normal and failing isolated cardiomyocytes and improved...
contractility in rabbits with heart failure after gene transfer in vivo. In conclusion, overexpression of nt-del-phosducin enhances the contractility of cardiomyocytes to the same extent as betaARKct, suggesting that the effects of betaARKct might be owing to inhibition of Gbetagamma rather than to betaAR resensitization.