Protein Kinase A is a Master Regulator of Physiological and Pathological Hypertrophy

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Background: The sympathetic/adrenergic system and its major effector PKA (protein kinase A) are activated to maintain cardiac output of stressed hearts. If and how PKA plays a role in physiological (PhCH) and pathological (PaCH) cardiac hypertrophy are not clear, which are the aims of this study.

Methods: A transgenic mouse model expressing a PKA inhibition peptide (PKAi)-GFP fusion protein in a cardiac-specific and inducible manner (cPKAi) was used to determine the roles of PKA in PhCH during postnatal growth or caused by swimming, and in PaCH induced by transaortic constriction (TAC) or augmented Ca^{2+} influx. Echocardiography was used to determine cardiac morphology and function. Western blotting and immunostaining were used to detect protein abundance and phosphorylation. Protein synthesis were assessed by puromycin incorporation and by protein ubiquitination and proteasome activity measurements, respectively. Neonatal rat cardiomyocytes (NRCMs) infected with AdGFP or AdPKAi-GFP were used to determine the effects and mechanisms of cPKAi on myocyte hypertrophy.

Results: (1) cPKAi delayed postnatal cardiomyocyte growth and blunted exercise-induced PhCH; (2) PKA was activated in hearts within 2 weeks after TAC due to activated SAS, the loss of endogenous PKIα and the stimulation by non-canonical PKA activators; (3) cPKAi reduced PaCH induced by TAC and NRCM hypertrophy induced by isoproterenol and phenylephrine; (4) cPKAi alleviated PaCH induced by increased Ca^{2+} influxes; (5) cPKAi prevented TAC-induced increases in protein synthesis by inhibiting mTOR signaling through

reducing Akt activity, but enhancing GSK-3α and GSK-3β activities; (6) cPKAi also reduced protein degradation by the ubiquitin-proteasome system via decreasing RPN6 phosphorylation; (7) cPKAi itself increased the expression of antihypertrophic molecule ANP; (8) cPKAi could reverse and ameliorate established PaCH and improve animal survival.

Conclusions: Cardiomyocyte PKA is the master regulator of physiological and pathological cardiac hypertrophy through regulating protein synthesis and can be a novel target to treat PaCH.