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Molecular modulators of cardiac stress targeted by PDE5 inhibition

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Background

Recent studies have revealed that PDE5a inhibition can suppress both acute and chronic cardiac stress responses. Acute modulation includes the blunting of beta-adrenergic stimulation, which has been observed using various PDE5a inhibitors and across several mammalian species including human. Chronic suppression of hypertrophy and contractile depression from PDE5a inhibitors has been observed in hearts subjected to sustained pressure-overload. To elucidate mechanisms for this stress modulation, we performed studies in isolated mouse myocytes and intact hearts employing genetically engineered animals and pharmacologic modulators.

Results

In isolated myocytes, 0.1–1 μM sildenafil suppresses the positive inotropic effect of isoproterenol (ISO, 1–10 nM). A potential mechanism to explain this response is the stimulation of the dual-substrate PDE – PDE2, which when activated by cGMP increases cAMP hydrolysis. However, selective inhibition of PDE2 with BAY 60–7550 did not alter sildenafil's suppressive effects. In contrast, inhibition of cGMP-dependent kinase (cGK-1) by DT-2 or rp-8Br-PET-cGMPs blocked the sildenafil anti-adrenergic effects. In mice expressing skeletal as opposed to cardiac Troponin I, the former lacking serines 23, 24 that are cGK-1 targets, sildenafil did not exhibit anti-adrenergic effects. TnI phosphorylation analysis suggests sildenafil enhances this above that achieved with isoproterenol, at a likely novel site. Since co-stimulation of cGMP by ISO is thought mediated in part by β3AR stimulation, we studied mice genetically lacking these receptors. Sildenafil had negligible basal effects in these mice (as previously reported in $eNOS^{-/-}$ mice, and did not suppress ISO. These data support β3-NOS-cGMP-PKG-TnI coupled modulation of adrenergic stimulation by PDE5a.

cGK-1 activation is also thought to suppress hypertrophic stimuli. Myocyte studies have shown that cGK-1 suppresses calcineurin-coupled NFAT activation and cell hypertrophy. *In vivo*, mice lacking GC-A show upregulation of this pathway, while sildenafil enhanced cGK-1 activity resulted in suppressed pressure-overload hypertrophy and reduced calcineurin and NFAT stimulation. We tested the critical role of this pathway in mice lacking calcineurin Aβ subunit (~80% knockdown of calcineurin). While such mice display ~50% of the hypertrophic response to aortic banding compared to littermate controls, this hypertrophy was still fully blocked by sildenafil. In contrast, mice lacking the regulator of G-coupled signalling 2 (RGS2), a negative modulator of Gαq signalling, had marked acceleration of hypertrophy and dilation to pressure-overload, and this was no ameliorated by sildenafil co-administration.

Conclusion

These new data confirm a direct role of PDE5s inhibition on cardiac myocyte and heart regulation, and identify key protein targets underlying its suppression of acute adrenergic and chronic pressure-overload stress.