BMC Pharmacology

BioMed Central

Oral presentation

Open Access

Role of PDE5a in cardiac stress response

Eiki Takimoto, Hunter Champion, Diego Belardi, Manxiang Li and David A Kass*

Address: John Hopkins Medical Institutions, Baltimore, MD, USA

Email: David A Kass* - dkass@jhmi.edu

* Corresponding author

from 2nd International Conference of cGMP Generators, Effectors and Therapeutic Implications
Potsdam, Germany, 10–12 June, 2005

Published: 16 June 2005

BMC Pharmacology 2005, **5**(Suppl 1):S26 doi:10.1186/1471-2210-5-S1-S26

PDE5a is a cGMP-selective phosphodiesterase that has been known to play a particularly important role in cGMP regulation within vascular smooth muscle of the corpus cavernosum and pulmonary vessels. Its involvement in cardiac muscle regulation has been previously considered minimal, in part due to low expression levels and the lack of change in basal heart function in response to selective PDE5a inhibition. However, PDE5a expression in cardiac myocytes appears localized (at z-bands) and confers targeted regulation of stress responses despite having little influence on basal function. In both intact hearts and isolated myocytes, PDE5a inhibition enhances cGK-1 activation and counters beta-adrenergic stimulated contractility. This effect depends upon the presence of NOS-3 activity, as both mice genetically lacking NOS3 and those with NOS inhibited pharmacologically do not display functional changes with PDE5a inhibition. The role of NOS3 appears specific, as alternative sources of cGMP (i.e. mediated by natriuretic peptides) do not appear to provide cGMP in the right compartment to influence PDE5a regulatory effects. Chronic isoproterenol stimulation (two weeks delivered by osmotic pump) of C57Bl6 mice results in cardiac hypertrophy and fibrosis. This is markedly inhibited by co-administration of a PDE5a inhibitor. Mice genetically lacking NOS3 also develop hypertrophy, but this is not affected by PDE5a inhibition. Similar results have been obtained using another hormonal stimulant of hypertrophy – angiotensin II.

A more comprehensive stress that stimulates both cardiac hypertrophy and pathological remodelling is pressure overload. Mice exposed to chronic trans-aortic constriction develop marked LVH and chamber dilation. Co-treatment with sildenafil (at doses yielding clinically relevant plasma concentrations) suppresses both hypertrophy and fibrosis while improving cardiac systolic and diastolic function, despite sustained pressure load. Sildenafil can also be administered after hypertrophy has been established and reverse it. While chronic PDE5a inhibition has negligible impact on cGK-1 activation in the unstressed heart, this is changed in the hypertrophied ventricle, where the contribution of PDE5A to total cGMP esterase activity nearly doubles, and PDE5A inhibition results in marked increases in cGK-1 activity. Suppression of hypertrophy is coupled to inhibition of multiple signaling-pathways (calcineurin-NFAT, PI3K-Akt, and ERK1/2), and appears to involve multiple targeted interactions. Additional pathways that appear involved are the STAT-3 pathway, and RhoA-RhoK pathway. Whether the anti-hypertrophic effect is due related to a single primary or multiple targets, whether factors other than cGK-1 mediate the effects from PDE5a inhibition, and how PDE5a is localized remain the focus of ongoing investigations.

References

1. Takimoto E, Champion HC, Li M, Belardi D, Ren S, Rodriguez ER, Bedja D, Gabrielson KL, Wang Y, Kass DA: **Chronic inhibition of cyclic GMP phosphodiesterase 5A prevents and reverses cardiac hypertrophy.** *Nat Med* 2005, **11:**214-222.
2. Takimoto E, Champion HC, Belardi D, Moslehi J, Mongillo M, Mergia E, Montrose DC, Isoda T, Aufiero K, Zaccolo M, Dostmann WR, Smith CJ, Kass DA: **cGMP catabolism by phosphodiesterase 5A regulates cardiac adrenergic stimulation by NOS3-dependent mechanism.** *Circ Res* 2005, **96:**100-109.
3. Senzaki H, Smith CJ, Juang GJ, Isoda T, Mayer SP, Ohler A, Paolocci N, Tomaselli GF, Hare JM, Kass DA: **Cardiac phosphodiesterase 5 (cGMP-specific) modulates β-adrenergic signaling in vivo and is down-regulated in heart failure.** *FASEB J* 2001, **15:**1718-26.