

ORAL PRESENTATION

Open Access

# cGMP kinase I, cardiac hypertrophy and PDE inhibition

Enrico Patrucco<sup>1\*</sup>, Robert Lukowski<sup>1</sup>, Sergei Rybalkin<sup>2</sup>, Joe Beavo<sup>2</sup>, Franz Hofmann<sup>1</sup>

From 5th International Conference on cGMP: Generators, Effectors and Therapeutic Implications  
Halle, Germany. 24-26 June 2011

## Background

The heart responds to maladaptive pro-hypertrophic stimuli by stimulating intrinsic signals that contrast and dampen the onset and development of hypertrophy. Cyclic guanosine monophosphate (cGMP) and its downstream effector cGMP kinase I (cGKI) have been suggested to be an important anti-hypertrophic signalling pathway (1). Intracellular levels of cGMP can be raised by the action of nitric oxide (NO) and natriuretic peptides (ANP, BNP), or by inhibiting cGMP-degrading phosphodiesterases (PDE).

## Results

A growing body of evidence suggests that the PDE5 specific inhibitor Sildenafil (Sil) prevents and reverses hypertrophy and chamber remodelling in the heart of mice subjected to thoracic aorta constriction (TAC) by elevating cGMP levels and cGKI activation (1). In contrast, using a mouse model that lacks cGKI expression in CM (2), we recently showed that the absence of this kinase does not alter the onset of hypertrophy induced by TAC or isoproterenol infusion (2).

Sil is believed to increase cardiac cGMP levels, although it is unclear, if its target (PDE5) is expressed in CM (2). Sil may act on other PDEs, such as PDE1C which is abundant in CMs. It is also unclear if Sil effects are mediated by other cardiac cell types, in particular by cardiomyoblast.

## Conclusion

To answer these questions, we are currently investigating whether Sil is able to prevent hormone induced cardiac hypertrophy in the absence of cGKI in CM. Preliminary results on  $\beta$ Res mice show that even in the case of chronic AngII infusion, lack of cGKI in CM does not alter the induction of hypertrophic response, at least in

the initial phase (7days of AngII infusion at 2mg/kg/day). Interestingly,  $\beta$ Res mice showed impaired cardiac function, as indicated by decreased Fractional Shortening. Sil was able to partially block the onset of cardiac hypertrophy in WT animals, but not in  $\beta$ Res mice, indicating a requirement of cGKI in this process. In particular, Sil was able to block the transcription of pro-fibrotic genes such as TGF $\beta$ , CTGF, Collagen I and Fibronectin.

## Author details

<sup>1</sup>FOR923, Institut für Pharmakologie und Toxikologie, TU, München, Germany.

<sup>2</sup>Department Pharmacology, University of Washington, Seattle, USA.

Published: 1 August 2011

## 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. Lukowski R, Rybalkin SD, Loga F, Leiss V, Beavo JA, Hofmann F: **Cardiac hypertrophy is not amplified by deletion of cGMP-dependent protein kinase I in cardiomyocytes.** *Proc Natl Acad Sci USA* 2010, **107**:5646-5651.

doi:10.1186/1471-2210-11-S1-O19

Cite this article as: Patrucco et al.: cGMP kinase I, cardiac hypertrophy and PDE inhibition. *BMC Pharmacology* 2011 **11**(Suppl 1):O19.

Submit your next manuscript to BioMed Central  
and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at  
www.biomedcentral.com/submit



\* Correspondence: patrucco@lrz.tum.de

<sup>1</sup>FOR923, Institut für Pharmakologie und Toxikologie, TU, München, Germany  
Full list of author information is available at the end of the article