Posphodiesterase 5 regulates the beating rate in murine neonatal cardiomyocytes

<u>Marisa Cornacchione</u>^{1,2}, Federica Barbagallo¹, Manuela Pellegrini^{1,2}, Alessandra Zevini¹, Maria Torre¹, Andrea M. Isidori³ and Fabio Naro¹

- ¹DAHFMO, "La Sapienza" University of Rome, 00161 Rome, Italy
- ² Dep. of Department of Health Science, University of Molise, 86100 Campobasso, Italy
- ³ Dep. of Experimental Medicine, "La Sapienza" University of Rome, 00161 Rome, Italy

Heart rate is finely regulated by the sympathetic nervous system through beta adrenoreceptors (β ARs) signaling. β -ARs stimulation induces cAMP/cGMP synthesis whereas phosphodiesterases (PDE) catalyze the hydrolysis of the cyclic nucleotides, however their precise interaction is not well defined (1, 2). The experimental model used to investigate the role of PDE5 inhibition on the heart function are the spontaneously beating cardiac myocytes from neonatal mice. Preliminary experiments were performed to determine whether neonatal cardiomyocyte cultures show the same PDEs expression pattern of adult mice hearts. We analyzed through RT-PCR and WB experiments the mRNA and protein levels of PDE1C, PDE2, PDE3A, PDE4 and PDE5 and we observed that are expressed both in hearts and in cultured neonatal cardiomyocytes. These data suggest that the cardiomyocyte is a suitable model to investigate the PDEs role in cardiac function.

Experiments performed to evaluate the contraction rate stimulated by β -AR signaling activation show: that PDE5 is a positive modulator through hydrolysis of cGMP, and the inhibition of PDE5 causes a positive chronotropic effects reduction by the PDE2 activation through the increase of cGMP level. Notably, the use of PDE2 knockout mice reverts the negative chronotropic effects obtained by PDE5 inhibition.

Finally, we observed that PDE5 selectively impacts heart rate interfering with β_2AR signaling in neonatal cardiac myocytes, with little or no effect on β_1AR signaling. These data show a novel role of PDE5 on the sympathetic regulation of cardiac beating and highlight the mechanicistic pathways of the long term effect of PDE5 inhibition in cardiac hypertrophy.

References

- [1] Mongillo M. and Zaccolo M. (2006) A complex phosphodiesterase system controls beta-adrenoceptor signalling in cardiomyocytes. Biochem Soc Trans 4: 510-511.
- [2] Francis S.H., Blount M.A., Corbin J.D. (2011) Mammalian cyclic nucleotide phosphodiesterases: Molecular mechanisms and physiological functions. Physiol Rev 91: 651–690.

Key	/WO	rds

PDE5, PDE2, sildenafil, cardiac beating assay, chronotropy, βAR.