BMC Pharmacology

Oral presentation

Open Access

Chronic inhibition of cyclic GMP phosphodiesterase 5A prevents and reverses endothelial dysfunction and oxidative stress associated with the metabolic syndrome

Behr-Roussel Delphine*[1], Alexandra Oudot[1], Stephanie Caisey[1], Olivier Le Coz[1], Diane Gorny[1], Jaques Bernabé[1], Chris Wayman[2], Laurent Alexandre[1] and Francois Giuliano[3]

Address: [1]Pelvipharm, Gif-sur-Yvette, France, [2]Department of Sexual Health, Pfizer Global Research and Development, Sandwich, Kent, UK and [3]Department of Neurological Rehabilitation, AP-HP Raymond Poincaré hospital, Garches, France

Email: Behr-Roussel Delphine* - d.behr.roussel@pelvipharm.com

* Corresponding author

from 3rd International Conference on cGMP Generators, Effectors and Therapeutic Implications
Dresden, Germany. 15–17 June 2007

Published: 25 July 2007

BMC Pharmacology 2007, **7**(Suppl 1):S28 doi:10.1186/1471-2210-7-S1-S28

This abstract is available from: http://www.biomedcentral.com/1471-2210/7/S1/S28

Background

Patients with metabolic syndrome exhibit generalized endothelial dysfunction with decreased NO production and increased vascular oxidative stress. We postulated that chronic treatment with sildenafil could upregulate the NOS/cGMP pathway and improve endothelial function in fructose-fed rats.

Materials and methods

Wistar rats (n = 10–14 per group) were fed a standard chow (CONT) or a 60% fructose/5% fat (% by weight)-enriched diet for 8 weeks (FFR). From week 5 through 8, sildenafil was administered twice a day (sc, 20 mg/kg, FFR+SIL), thus reaching clinically relevant plasma concentrations *circa* 20 nM unbound known to give efficacy in man (*Pfizer Inc., data on file*), then a 1-week wash-out period from sildenafil was observed. Isometric tension studies were performed on isolated aortic and superior mesenteric arterial (SMA) rings precontracted with noradrenaline to build concentration-response curves (CRC) to endothelium-dependent (ACh and A23187) and -independent (SNP) relaxants in presence of indomethacin. Urinary 8-isoprostanes (IPT) and plasma levels of IL-6 and TNF-α were also evaluated.

Results

Relaxations to ACh were reduced in aortas of FFR (10^{-5} M: -102.6 ± -2.4% vs -89.2 ± 4.7, $p < 0.001$) while only slightly affected in SMA rings. Relaxations to A23187 were significantly reduced both in aortic and SMA rings of FFR. In aortas, sildenafil treatment restored normal endothelium-dependent relaxations to ACh (10^{-5} M: -104.2 ± 3.0%, $p < 0.001$) even after one week of wash-out from treatment. In SMA rings, a leftward shift of the CRC to ACh could be detected (pD2: -8.12 ± 0.11 vs -8.60 ± 0.08, $p < 0.05$). Relaxations to A23187 were also restored by sildenafil in both aortic and SMA rings of FFR. Enhanced compensatory endothelium-independent relaxations to SNP in FFR were not modified by sildenafil treatment. Neither IL-6 nor TNF-α were modified by the fructose or sildenafil treatment. Urinary IPT levels was normalized by the sildenafil treatment (FFR: 2.07 ± 0.36 vs CONT:0.95 ± 0.14 vs FFR+SIL: 0.88 ± 0.13 ng/ml/24 h, $p < 0.05$).

Conclusion

Endothelial dysfunction and oxidative stress associated with the metabolic syndrome can be reversed in FFR by a chronic treatment with sildenafil, even 7 days after treatment has ceased. This sustained improvement in endothelial function suggests that chronic administration of

sildenafil may lead to structural and molecular changes within the vascular wall that may be of benefit in vascular cardio-metabolic indications.

Acknowledgements

This study was supported by an independent investigator research grant from Pfizer.