de Nucci et al. BMC Pharmacology and Toxicology 2013, 14(Suppl 1):P18
http://www.biomedcentral.com/2050-6511/14/S1/P18

BMC Pharmacology & Toxicology

POSTER PRESENTATION Open Access

The soluble guanylyl cyclase activator BAY 60-2770 ameliorates detrusor dysfunction in obese mice

Gilberto de Nucci[1,2*], Luiz Osorio Leiria[1], Fábio Henrique da Silva[1], Eduardo C Alexandre[1], Marina Calixto[1], Fabíola Zakia Mónica[1], Edson Antunes[1]

From 6th International Conference on cGMP: Generators, Effectors and Therapeutic Implications
Erfurt, Germany. 28-30 June 2013

Background

The obesity-associated insulin resistance has been shown to play an important role in the pathophysiology of overactive bladder in mice [1,2]. Therefore, we evaluated the beneficial effects of long-term administration of the sGC activator BAY 60-2270 in bladders from lean and obese mice.

Methods

Mice were fed for 12 weeks with either a standard chow diet (carbohydrate: 70%; protein: 20%; fat: 10%) or a high fat diet that induces obesity (carbohydrate: 29%; protein: 16%; fat: 55%). Lean and obese mice were orally treated with BAY 60-2770 (1 mg/kg/day, given as daily gavage

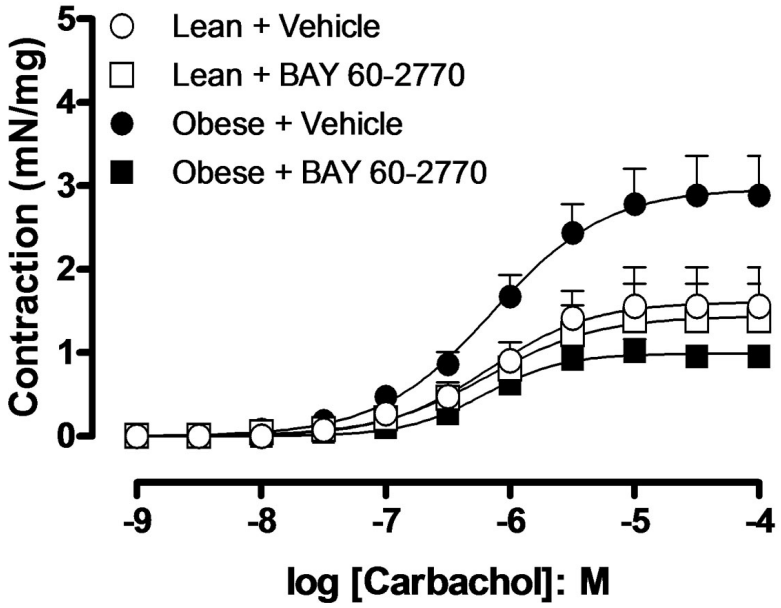

Figure 1 Concentration response curve to cabachol (0.001-100 μM) in isolated bladder from lean and obese mice that received or not BAY 60-2770 (1 mg/Kg, 2 weeks). Data represent mean ± S.E.M.

* Correspondence: denucci@gilbertodenucci.com
[1]Department of Pharmacology, State University of Campinas (UNICAMP), Brazil
Full list of author information is available at the end of the article

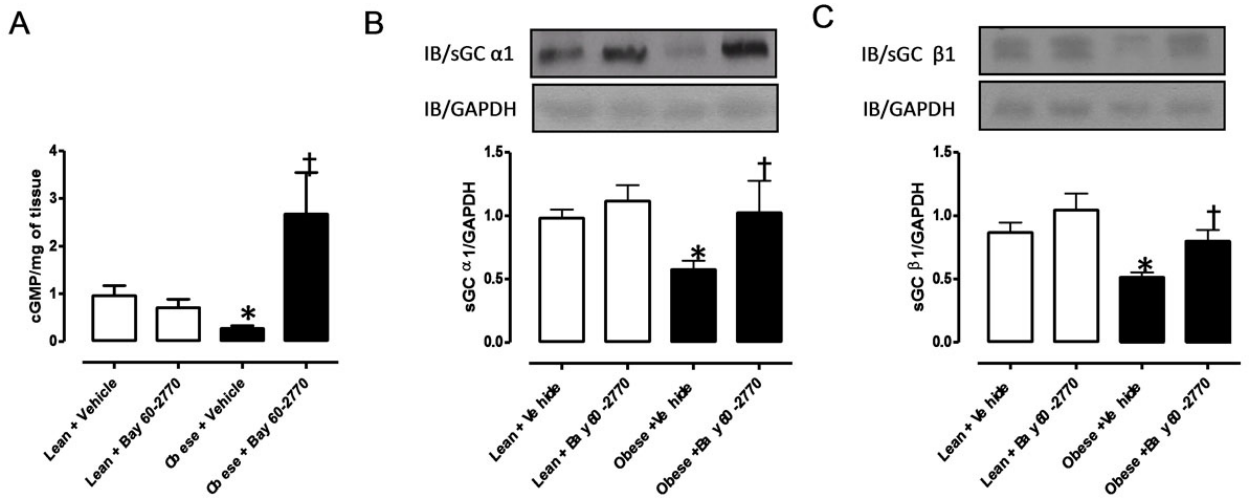

Figure 2 Effect of chronic treatment with BAY 60-2770 (1 mg/kg, 2 weeks) on cGMP levels (A) and protein expression of α_1 (B) and β_1 (C) subunits of sGC in bladders from lean + vehicle, lean + BAY 60-2770, obese + vehicle and obese + BAY 60-2770 groups. Data are presented as mean ± SEM. ★p <0.05 in comparison with lean + vehicle group; †p <0.05 in comparison to obese + vehicle group.

from the 10th to the 12th week) or its vehicle (Transcutol®: Cremophor®:water, 1:2:7, v/v/v). Concentration-response curves to full agonist carbachol (CCh, 0.001-100 μM) were obtained. The values of potency (pEC_{50}) and maximal responses (E_{max}) were calculated. The cGMP levels and Western blotting for α_1 and β_1-subunit of sGC in the bladder tissues were also determined.

Results

Contractile response to the muscarinic agonist carbachol was greater (p<0.05, n=5) in bladder from the obese in comparison with lean group. Long-term treatment with BAY 60-2770 normalized the enhanced contractile responses of the obese group, driving it to control levels (p<0.05; figure 1). The cGMP levels in the bladder tissues from obese group were significantly lower in comparison with lean mice (0.27 ± 0.04 and 0.95 ± 0.14 pmol/mg tissue, respectively, p<0.05, n=5). Treatment with BAY 60-2770 generated a 10-fold increase (p<0.01) in the bladder cGMP levels of obese mice, without affecting the levels in the lean group (Figure 2A). Protein expression of α_1 and β_1 subunits of sGC was decreased by 41% and 43% (p<0.05) in bladder tissues of obese animals, respectively. However, oral treatment with BAY 60-2770 restored the protein levels of α_1 and β_1 subunits to that of lean group (Figure 2B and 2C).

Conclusion

Chronic treatment with BAY 60-2770 results in amelioration of bladder dysfunction in high-fat obese mice.

Authors' details
[1]Department of Pharmacology, State University of Campinas (UNICAMP), Brazil. [2]Institute of Biomedical Sciences, University of Sao Paulo (USP), Brazil.

Published: 29 August 2013

References

1. Leiria LO, Sollon C, Calixto MC, Lintomen L, Mónica FZ, Anhê GF, De Nucci G, Zanesco A, Grant AD, Antunes E: **Role of PKC and CaV1.2 in detrusor overactivity in a model of obesity associated with insulin resistance in mice.** *PLoS One* 2012, **7**:e48507.
2. Leiria LO, Sollon C, Báu FR, Mónica FZ, D Ancona CL, De Nucci G, Grant AD, Anhê GF, Antunes E: **Insulin relaxes human and mice bladder via PI3K/AKT/eNOS pathway activation in mucosal cells: UPR-dependent insulin resistance as a cause of obesity-associated overactive bladder.** *J Physiol* 2013, **591**:2259-2273.

doi:10.1186/2050-6511-14-S1-P18
Cite this article as: de Nucci *et al.*: The soluble guanylyl cyclase activator BAY 60-2770 ameliorates detrusor dysfunction in obese mice. *BMC Pharmacology and Toxicology* 2013 **14**(Suppl 1):P18.