

POSTER PRESENTATION

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

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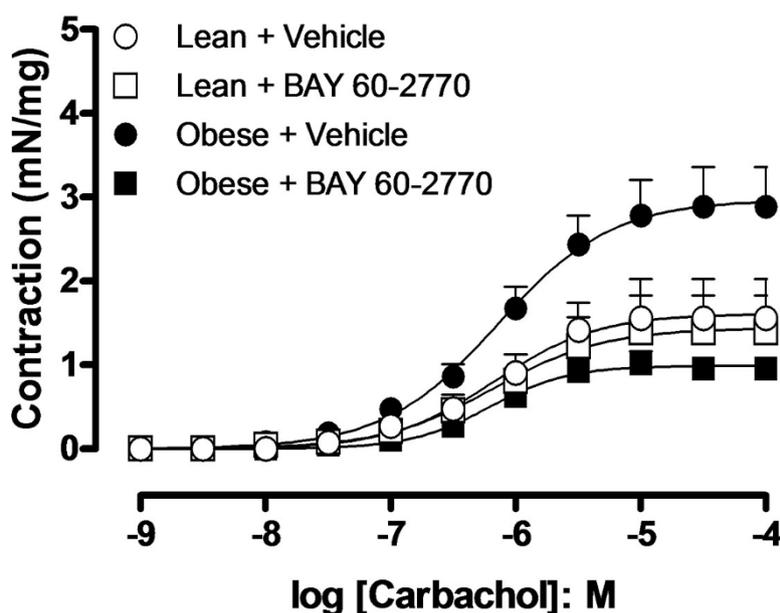
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## Background

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

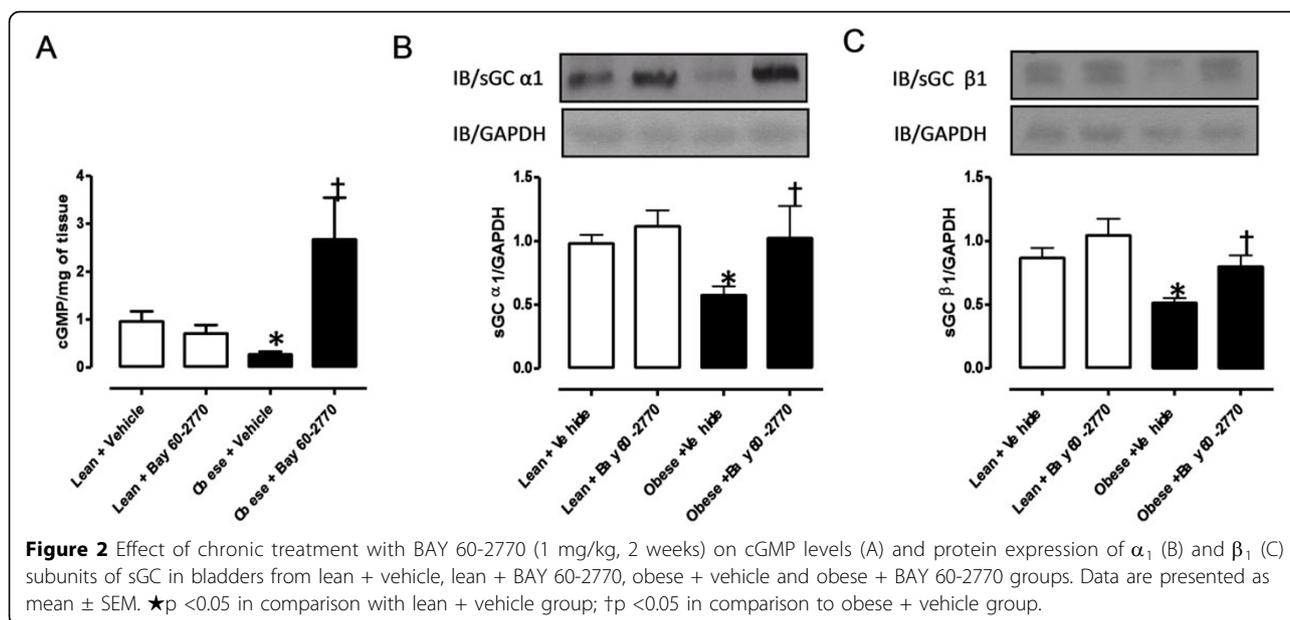


**Figure 1** Concentration response curve to carbachol (0.001-100  $\mu$ M) in isolated bladder from lean and obese mice that received or not BAY 60-2770 (1 mg/Kg, 2 weeks). Data represent mean  $\pm$  S.E.M.

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from the 10<sup>th</sup> to the 12<sup>th</sup> week) or its vehicle (Transcutol<sup>®</sup>: Cremophor<sup>®</sup>:water, 1:2:7, v/v/v). Concentration-response curves to full agonist carbachol (CCh, 0.001-100  $\mu$ M) were obtained. The values of potency ( $pEC_{50}$ ) and maximal responses ( $E_{max}$ ) were calculated. The cGMP levels and Western blotting for  $\alpha_1$  and  $\beta_1$ -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 ( $0.27 \pm 0.04$  and  $0.95 \pm 0.14$  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  $\alpha_1$  and  $\beta_1$  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  $\alpha_1$  and  $\beta_1$  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.

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