

POSTER PRESENTATION

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

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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

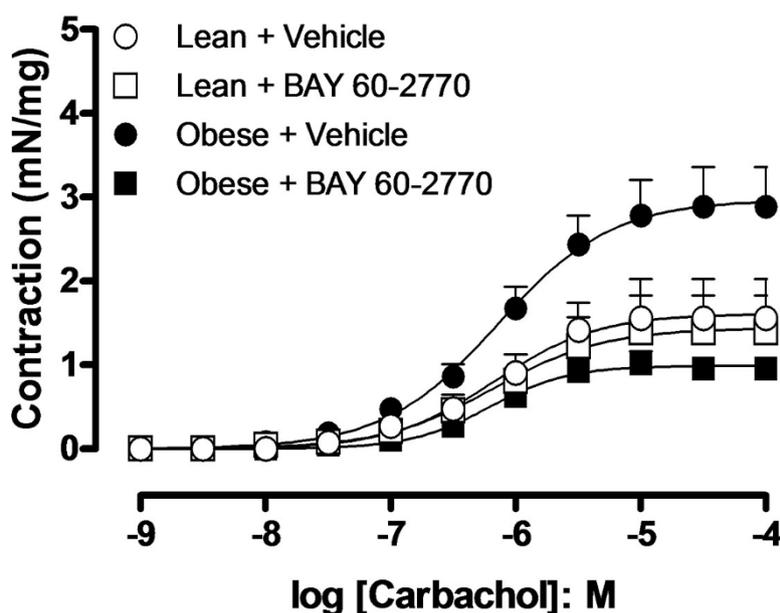
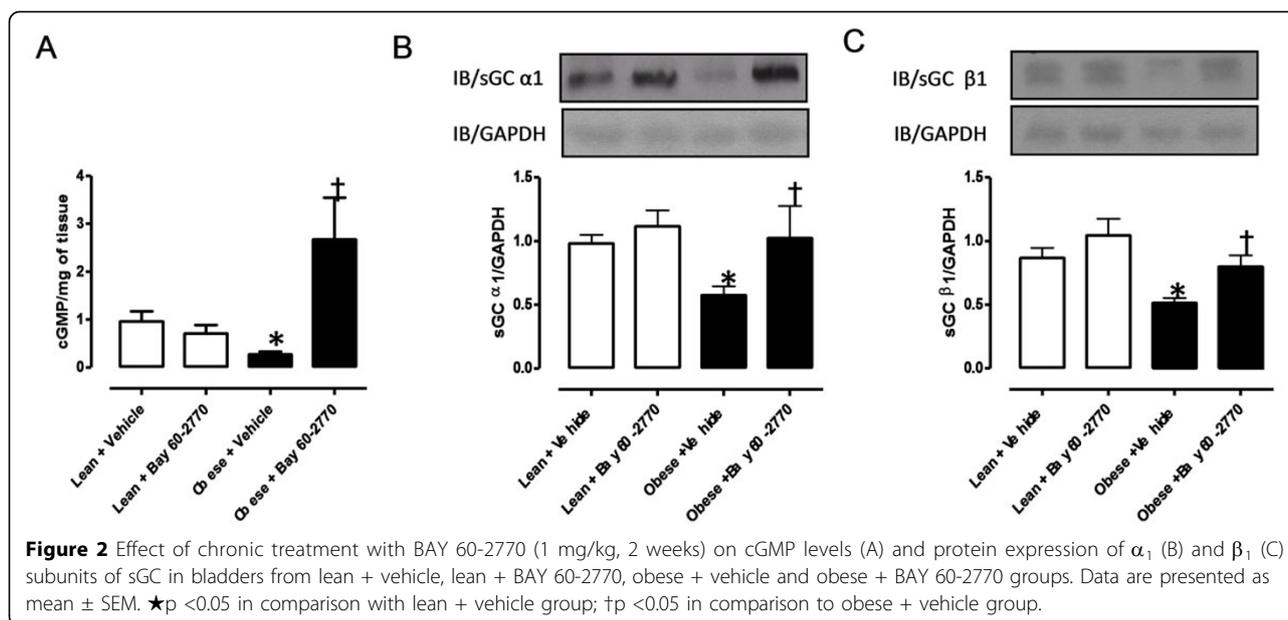


Figure 1 Concentration response curve to carbachol (0.001-100 μ M) in isolated bladder from lean and obese mice that received or not BAY 60-2770 (1 mg/Kg, 2 weeks). Data represent mean \pm S.E.M.

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from the 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 μ M) 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.

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