Hypothesis / Aims of study

A class of agents called sGC stimulators and activators has been studied for improving enzymatic conversion of GTP to cyclic GMP, and promoting smooth muscle relaxation [1]. The sGC stimulator BAY 41-2272 is to effective in producing cavernosal relaxations in rabbits and human [2], and could be used to ameliorate bladder function when urethral obstructive process is present. This study aimed to evaluate bladder function in mice with BOO treated chronically with BAY 41-2272.

Study design, materials and methods

All animal procedures were approved by the Ethical Principles in Animal Research. C57BL/6 male mice were anesthetized with xilazine and ketamine for surgical procedure. BOO was performed using nylon ligature in the bladder neck. Four groups with 6 to 9 animals per group were obtained: Sham + vehicle, Sham + BAY, BOO + vehicle and BOO + BAY. Vehicle and BAY 41-2272 (1.3 mg/ml, approximately 10 mg/Kg) were given by gavage (0.2 ml/animal) from 3 to 5 weeks after surgery. At 5 weeks, in vivo and in vitro studies were performed: continuous cystometry, bladder weight to body weight ratio and tissue bath studies (contractility was evaluated by concentration-response curves to carbachol, KCl and electrical-field stimulation, and relaxant responses were obtained using the β2-agonist mirabegron).

Results

BOO+vehicle animals had increased bladder mass when compared to Sham+vehicle (Figure 1). BOO+BAY treated mice had less non-voiding contractions and fewer micturition frequency when compared to BOO+vehicle. Compliance was also augmented in BOO+BAY mice in relation to the other groups (Figure 2). As shown in Figure 3, tissue bath protocols revealed that BOO+BAY mice had lower contractile response to CCh when compared to BOO+vehicle (E_max: 0.82 ± 0.06 and 1.78 ± 0.18 mN, respectively), but no differences were seen for EFS. BOO+BAY mice had lower contractile responses to KCl when compared to Sham+BAY (E_max: 0.9 ± 0.07 and 1.451 ± 0.2 mN, respectively). Mirabegron produced lower bladder relaxations in BOO+vehicle compared to Sham+vehicle and BOO+BAY (E_max: 49.0 ± 5.1, 85.5 ± 8.8 and 88.3 ± 4.2%, respectively).

Interpretation of Results

BAY 41-2272 had a protective effect in BOO mice, since it prevented development of hyperactive bladder, suggesting that direct stimulation of sGC in a NO-independent manner by BAY 41-2272 counteracts the bladder dysfunction in BOO mice.

Concluding Message

BAY 41-2272 ameliorates bladder function in obstructed mice, and the decrease in NO bioavailability in bladder could be responsible for detrusor hyperactivity.

References