

## MODULATION OF PGE<sub>2</sub>-AUGMENTED NON-VOIDING ACTIVITY BY B<sub>3</sub>-ADRENOCEPTOR AGONIST MIRABEGRON IN CONSCIOUS RATS

### Hypothesis / aims of study

The  $\beta_3$ -adrenoceptor agonist mirabegron was shown to reduce symptoms of urge and frequency in patients with overactive bladders (OAB). However, at organ bath concentrations corresponding to plasma levels at therapeutic doses, mirabegron has modest relaxant effects on the detrusor muscle. So it is hypothesized that mirabegron may have actions on other functional systems within the bladder. Studies in rat bladder outlet obstruction have shown that mirabegron decreases the frequency of non-voiding activity (NVA), which is indicative for a mechanism reducing afferent signaling [1]. One possibility is that mirabegron decreases the sensory outflow from the bladder and inhibits the generation or transduction of sensations that initiate voiding. Intra-vesical infusion of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) has been shown to increase voiding frequency in man and rats [2]. The underlying mechanism(s) are not fully understood but may involve an increase in bladder sensations possibly via augmenting motor/sensory noise. The present study was done to examine the hypotheses (i) that PGE<sub>2</sub> increases NVA (the motor component of the motor/sensory system) during iso-volumetric condition and (ii) that the  $\beta_3$ -adrenoceptor agonist mirabegron is able to reduce this augmented motor activity.

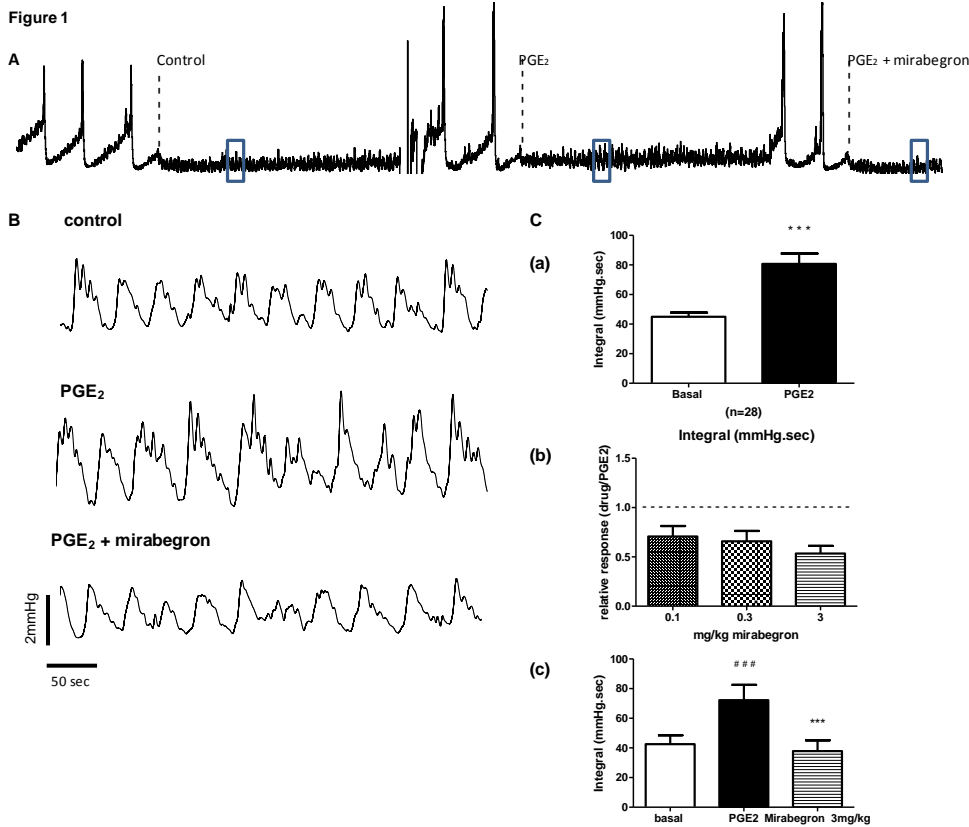
### Study design, materials and methods

Female Sprague-Dawley rats (225-250g, n=28) were anesthetized with Isoflurane (1.5%) and the jugular vein and the urinary bladder catheterized for i.v. drug administration and intra-vesical pressure recording, respectively. Two days after surgery, cystometry was performed in conscious animals. In order to study non-voiding activity recordings were made under iso-volumetric conditions. The bladder was infused with saline (1 or 6mL/hr). Control-filling cycles were recorded and the bladder volume triggering voiding was measured (threshold volume). During a filling cycle bladders were filled until 60% of threshold volume was reached. NVA was then recorded for a period of 10-20 minutes. This procedure was done with saline infusion into the bladder (control), saline with PGE<sub>2</sub> (100  $\mu$ M) and saline with PGE<sub>2</sub> (100  $\mu$ M) after i.v. administration of vehicle or mirabegron (0.1, 0.3 and 3 mg/kg). Cystometric sections (60 sec) were recorded at each condition for analysis of NVA integral (mmHg.sec). Mean values  $\pm$  SD were determined and statistical analysis was performed using paired Student *t*-test for single test comparison and one-way ANOVA followed by Newman-Keuls for multiple comparison ( $p < 0.05$  was set as level of significance). NVA integrals were calculated using Chart 7 (ADInstruments).

### Results

Figure 1A shows an entire experiment illustrating iso-volumetric periods of recording in control, PGE<sub>2</sub> and PGE<sub>2</sub> with 3 mg/kg i.v. of mirabegron. During each phase a section of record is shown on an expanded time base (Figure 1B). In the control condition the NVA consisted of small irregular contractions. After PGE<sub>2</sub> infusion the transient activity increased. Mirabegron 3mg/kg i.v. clearly reversed the PGE<sub>2</sub>-augmented NVA to basal levels.

Figure 1C panel (a) summarizes data from 28 animals illustrating the effect of PGE<sub>2</sub> on integral of non-voiding activity compared to the basal levels. PGE<sub>2</sub> increased significantly the integral ( $80.71 \pm 37.06$  vs  $45 \pm 14.95$ ;  $p < 0.001$  vs basal, paired Student's *t*-test). Figure 1C panel (b) shows the effects of mirabegron at 0.1, 0.3 and 3 mg/kg i.v.. The effects of drug were calculated relative to values in the presence of PGE<sub>2</sub> alone. Figure 1C panel (c) the highest dose mirabegron reduced significantly the integral of PGE<sub>2</sub>-augmented NVA ( $37.84 \pm 17.92$  vs  $72.19 \pm 25.45$ ,  $p < 0.001$ ; Newman-Keuls test). No effect of Vehicle on PGE<sub>2</sub>-augmented NVA was shown.



### Interpretation of results

Intra-vesical PGE<sub>2</sub> increases non-voiding activity during iso-volumetric condition in rats and so may increase bladder sensation. Mirabegron reduces this PGE<sub>2</sub>-augmented activity.

### Concluding hypothesis

β<sub>3</sub>-adrenoceptor agonists modulate the motor/sensory system of the bladder wall. This reduction in afferent/sensory outflow from the bladder may represent a therapeutic mode of action of this class of drugs.

### References

- Gillespie et al. (2012). Modulation of non-voiding activity by the muscarinic antagonist tolterodine and the β<sub>3</sub>-adrenoceptor agonist mirabegron in conscious rat with partial outflow obstruction. BJU 110, E132-E142.
- Schröder A. et al. (2004). Detrusor responses to prostaglandin E<sub>2</sub> and bladder outlet obstruction in wild-type and EP1 receptor knock-out mice.

### Disclosures

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