Comparison of the effects of mirabegron, a novel \( \beta_3 \)-adrenoceptor agonist, with the anticholinergic agent, oxybutynin, on primary bladder afferent activity and bladder microcontractions in rats

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**INTRODUCTION**

- Mirabegron, a \( \beta_3 \)-adrenoceptor agonist, has proved its efficacy and safety in overactive bladder (OAB) patients in several randomised control trials.
- Mirabegron was launched as a new OAB drug in Japan in 2011.
- A previous study demonstrated that the \( \beta_1 \)-adrenoceptor agonist CL316,243 reduced bladder non-voiding contractions in rats with bladder outlet obstruction\(^3\).
- Another study suggested that mirabegron can suppress the mechanosensitive bladder afferent activities during bladder filling in normal rats\(^4\).

**OBJECTIVES**

- To determine the direct effects of mirabegron on single unit afferent nerve fibre activities (SAAs) of the primary bladder mechanosensitive afferent nerves and bladder microcontractions.
- To compare these effects with the anticholinergic agent, oxybutynin, in rats.

**METHODS**

**Study design**

- The experiment set-up of this study is shown in Figure 1.
- Female Sprague-Dawley rats were used.
- The anaesthesia was used urethane (1.5 g/kg intraperitonally).
- The left pelvic nerve was put on an electrode for electrical stimulation.
- A catheter (PE-50) was inserted into the bladder.

**Measurement**

- The bladder was emptied and saline instilled at a rate of 0.08 ml/min until the intravesical pressure reached 30 cmH\(_2\)O. The bladder was kept under an isovolumetric condition and allowed to stabilise for 5 minutes, after which the vehicle was administered intravenously (IV) and the recording was performed after a further 5 minutes.
- A similar procedure was repeated with IV administration of mirabegron (0.3 or 1 mg/kg) or oxybutynin (1 mg/kg) instead of vehicle.

**RESULTS**

- The number of microcontractions was significantly decreased after mirabegron administration at both the 0.3 and 1.0 mg/kg doses, although the bladder pressure was also decreased at 1.0 mg/kg (Figures 2 and 3A,B).
- However, these parameters did not change significantly with oxybutynin administration (Figure 3A,B).
- 47 single afferent fibres (A\(-\)fibres: n=31, CV: 4.21 ± 0.45 m/sec; C\(-\)fibres: n=16, CV: 1.55 ± 0.07 m/sec) were isolated from 40 rats.
- SAAs of A\(-\)fibres were significantly decreased with mirabegron administration at both the 0.3 and 1 mg/kg dose levels, whereas SAAs of C\(-\)fibres were significantly decreased only at the 1 mg/kg dose (Figures 2 and 3C,D).
- Oxybutynin did not significantly alter either A\(-\) or C\(-\) fibre SAAs (Figure 3C,D).

**CONCLUSIONS**

- The present study shows that the \( \beta_3 \)-adrenoceptor agonist, mirabegron, can inhibit both the bladder microcontractions and A\(-\) fibre activity at doses that do not decrease the bladder pressure. This suggests that the microcontractions may link to the A\(-\)fibre SAAs, and that mirabegron inhibits the SAAs through the suppression of the microcontractions.
- The microcontractions observed in the present study are of myogenic origin as no reflex arc though the L6 dorsal roots was preserved in the present experiment set-up.
- At higher doses, which also decreased the bladder pressure, mirabegron inhibited both A\(-\) fibre and C\(-\) fibre activities. These effects were not observed with oxybutynin.

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**REFERENCES**


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