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DIFFERENCES IN THE ACTIONS OF THE M3-ANTAGONIST TOLTERODINE AND THE BETA 3 ADRENOCEPTOR AGONIST MIRABEGRON ON NON-VOIDING ACTIVITY IN RATS WITH PARTIAL OUTFLOW OBSTRUCTION

Hypothesis / aims of study

Non-voiding activity (NVA) during the filling phase represents the motor component of the motor/sensory system in the bladder wall [1]. Muscarinic receptor antagonists and beta$_3$ adrenergic receptor agonists are effective in the treatment of overactive bladder. How they do this is controversial. The aims of the present study were (i) to establish that the anticholinergic drug tolterodine and the beta$_3$ adrenergic agonist mirabegron modulate NVA and (ii) to identify differences in the way these disparate drugs exert its therapeutic effect.

Study design, materials and methods

The study used an established model, the partially bladder outlet obstructed rat [2]. Briefly, rats were anesthetized with isoflurane (3%) and urethral obstruction was produced by a urethral ligature (partial bladder outflow obstruction (pBOO)). Sham operated animals underwent the same surgery, but without a ligature, and were used as controls. After six weeks, urethral ligatures were removed and catheters were implanted into the bladder for infusion and pressure measurement and in the jugular vein for drug administration. Cystometry was performed in conscious rats 48 hours later using infusion rates of 10 ml/hr (pBOO) and 1-3 ml/hr (sham). Drug or vehicle was administered intravenously. Standard voiding parameters and frequency and amplitude of NVA were measured. Differences were assessed using Student t-test or one way Anova.

Results

Examples of recordings from pBOO animals, illustrating the effects of tolterodine and mirabegron, are shown in Figure 1 A(a) and B(a), respectively. Four consecutive filling cycles are shown, two control and two in the presence of drug. Voiding contractions are clearly seen and pronounced NVA is apparent during the filling phase of control cycles. Data from 48 rats, determining void frequency (○), void amplitude (●) and threshold (△), in the presence of different concentrations of tolterodine and mirabegron are shown in Figure 2 A and B respectively. The dose dependent decrease on the voiding contraction by tolterodine and the absence of an effect of mirabegron is clear.

Both compounds affect NVA. However, detailed examination of the NVA at high-resolution revealed differences (Figure 2 A (b) and (c) and 2 B (b) and (c)). Tolterodine reduced both the amplitude and frequency of the NVA while mirabegron affected primarily frequency with little effect on amplitude. A detailed analysis, focusing on the final 200 seconds of the filling phase (defined as p3 [3]) for the whole data set, is shown in Figure 2 C and D.

Interpretation of results

It is well known that, anticholinergic drugs can reduce voiding contractions, an effect which can lead to urinary retention. However, mirabegron does not have this action in the dose range studied. The analysis of NVA demonstrates that anti-muscarinics and □$_3$ adrenoceptor agonists both reduce NVA. Intriguingly, there is a differential effect, with tolterodine affecting amplitude and frequency while mirabegron affecting only frequency. Therefore, both types of drug have the capacity to reduce bladder sensations by reducing the 'afferent noise' generated by the motor/sensory system in the bladder [1]. One way to interpret these findings is to suggest that both tolterodine and mirabegron appear to act on the mechanisms involved in the generation and modulation of the NVA, a 'pacemaker' like mechanism. This suggests that the 'pacemaker' has an excitatory cholinergic input and an inhibitory adrenergic input. In conclusion, mirabegron is a good candidate for the treatment of sensory disorders of bladder dysfunction with the specific advantage that it may avoid complications such as retention.

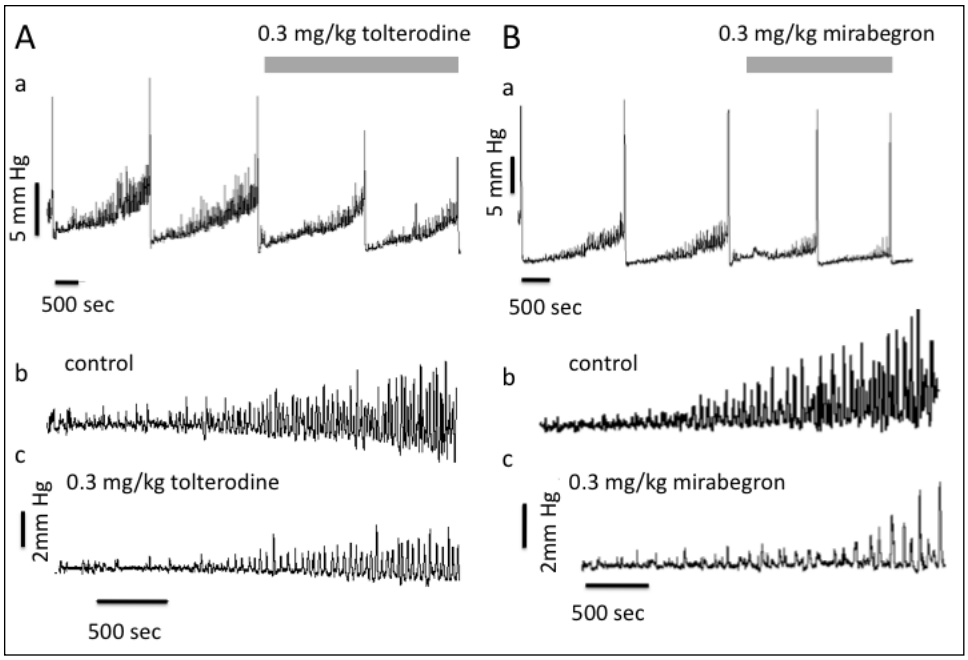

Figure 1 The effects of tolterodine (A) and mirabegron (B) on bladder activity in the conscious rats with partial bladder outflow obstruction (pBOO). In each panel (a) shows 4 filling cycles: 2 control and 2 in the presence of drug. (b) and (c) show the NVA isolated from the whole record, on an expanded scale. Calibration bars show time in seconds and pressure in mm Hg.

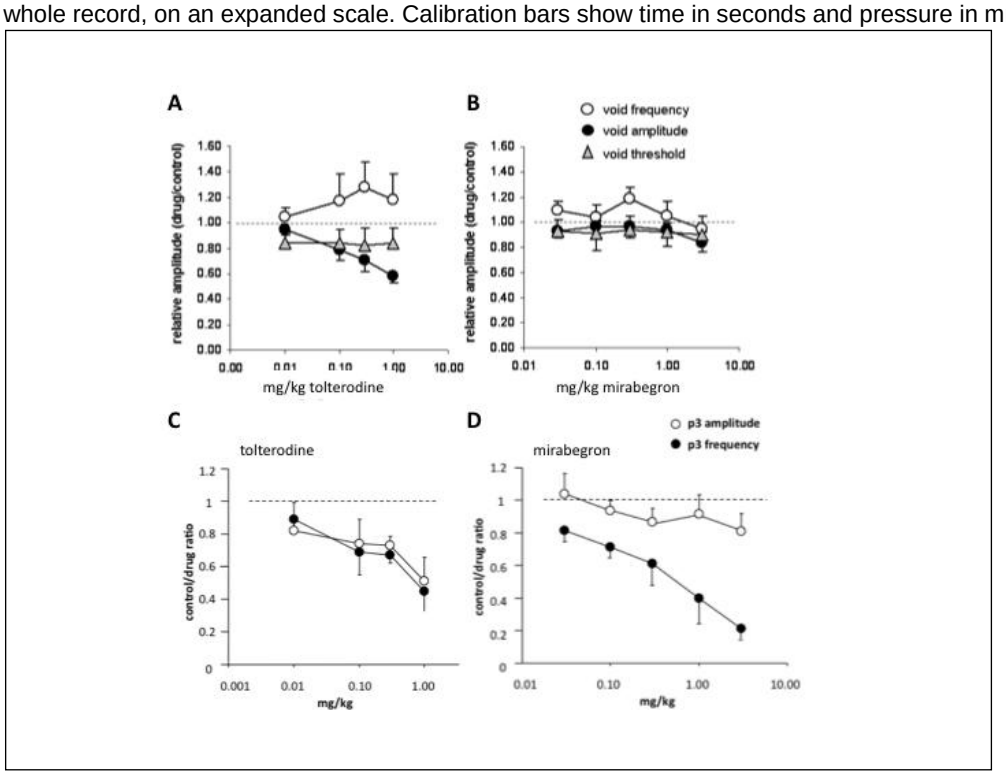

Figure 2 Data combined from different animals illustrating the effects of different doses of tolterodine and mirabegron. A and B show the effects of the drugs on voiding parameters (void frequency (○), void amplitude (●) and threshold (△)) while C and D illustrate the effects of the drugs on the amplitude (●) and frequency (○) of the NVA in pBOO rats. Data shown are mean ± 1 S.D.

References
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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**All experimental protocols were carried out in accordance with the European Community Council Directive 86/609/EEC. They were performed in accordance with French legislation cpncerning the protection of laboratory animals.**