They investigated the dual mechanism of action of mirabegron on urethral smooth muscle.

**Methods:** Functional assays were carried out in mouse urethra rings, and rat vas deferens, prostate, aorta, and spleen. β3-AR expression (mRNA and immunohistochemistry) and cyclic AMP levels were determined in mouse urethra. Competition assays for the specific binding of [3H]Prazosin to membrane preparations of HEK 293 cells expressing each of the human α1-AR subtypes were performed.

**Results:** Mirabegron (1 nM-100 µM) produced concentration-dependent urethral relaxations that were right shifted by the selective β3-AR antagonist L 748,337, but unaffected by β1- and β2-AR antagonists (atenolol and ICI 118,551, respectively). The non-selective β-AR agonist isoprenaline produced biphasic relaxant responses that were turned into a monophasic concentration-response curve in presence of L 748,337. Mirabegron-induced relaxations were enhanced by the phosphodiesterase-4 inhibitor rolipram, and associated with β3-AR-stimulated cAMP synthesis. Mirabegron (1 to 100 µM) also produced rightward displacements in urethral contractions induced by phenylephrine. Schild regression analysis revealed that mirabegron behaves as a competitive antagonist of α1-AR in urethra, vas deferens and prostate (α1A-AR, pA2 ≅ 5.6) and aorta (α1D-AR, pA2 ≅ 5.6), but not in spleen (α1B-AR). The affinities estimated for mirabegron in functional assays were consistent with those estimated in radioligand binding with human recombinant α1A- and α1D-ARs (pKi ≅ 5.6). RT-PCR and immunohistochemistry confirmed the presence of β3-AR in mouse urethra.

**Conclusion:** The effects of mirabegron in mouse urethra smooth muscle are the result of β3-AR agonism together with α1A / α1D-AR antagonism. The combination of both of these pharmacological actions may contribute to the efficacy of mirabegron in treating OAB-associated with BOO.
References: