

RELAXANT EFFECTS OF COMBINATION TREATMENT WITH FESOTERODINE AND MIRABEGRON: AN IN-VITRO STUDY USING DETRUSOR STRIPS FROM THE STROKE MODEL AND PELVIC CONGESTION MODEL IN RATS

Hypothesis / aims of study

Medicines with different mode of actions (MOA) such as antimuscarinics and β_3 agonist, are available for recent OAB treatment. The combination treatment with these medicines may have the potential to provide benefits for the non-responder or suboptimal responder patients to the mono-therapy. Fesoterodine therapy has shown significant benefits on urge urinary incontinence (UUI) in many studies, including the study in vulnerable elderly patients. As the prevalence of OAB increases with age, basic data on combination therapy of fesoterodine with mirabegron may be useful to provide insights for the future treatments for OAB. Fesoterodine is converted to 5-hydroxymethyl tolterodine (5-HMT) immediately after the oral administration. Therefore, *in-vitro* functional studies were conducted to compare the effects of 5-HMT and mirabegron used independently and when combined, by using two disease models, i.e., stroke model (neurogenic model) and pelvic congestion model (non-neurogenic model) in rats. Both models express urinary frequency and up-regulations of M_2 and M_3 receptors.

Study design, materials and methods

Female Sprague-Dawley rats (body weight: 250-300 g) were used in this study. Stroke model and pelvic congestion model were developed according to a published method. The detrusor and urethra were separated and cut to strips from each model. The strips were mounted in 5 mL organ baths containing Krebs solution which was maintained at 37°C and continuously gassed with 95% O₂ and 5%CO₂. The strips were stretched to a passive tension of 4 mN and allowed to equilibrate for 45-60 min. The independent and combinatory effects of 5-HMT and mirabegron on the bladder strips contracted by carbachol (CCh, 3X10⁻⁶M) or electrical field stimulation (EFS, 1Hz) were evaluated. Treatment concentrations of 5-HMT and mirabegron were set by about 10-15 % inhibition of bladder strip contraction by CCh stimulation. Dunnett's test was used for multiple comparisons with the combination group.

Results

The relaxant effects of 5-HMT (10⁻⁹M) and mirabegron (10⁻⁷M) on both CCh- or EFS-induced contraction in bladder strips were examined in rat models with stroke and pelvic congestion. The combination of 5-HMT and mirabegron showed an additive relaxant effect and it was statistically significant compared to the effects of each mono-therapy in EFS-induced contractions in both models (P<0.05, Figure 1). Similarly, the additive effect by the combination of 5-HMT and mirabegron was also exerted in CCh-induced contractions in both models, while the effect was not as prominent as in the EFS-induced contractions (Figure 2). There was a statistical significance between mirabegron and combination (P<0.05, Figure 2) but not between 5-HMT and combination (P≥0.05, Figure 2).

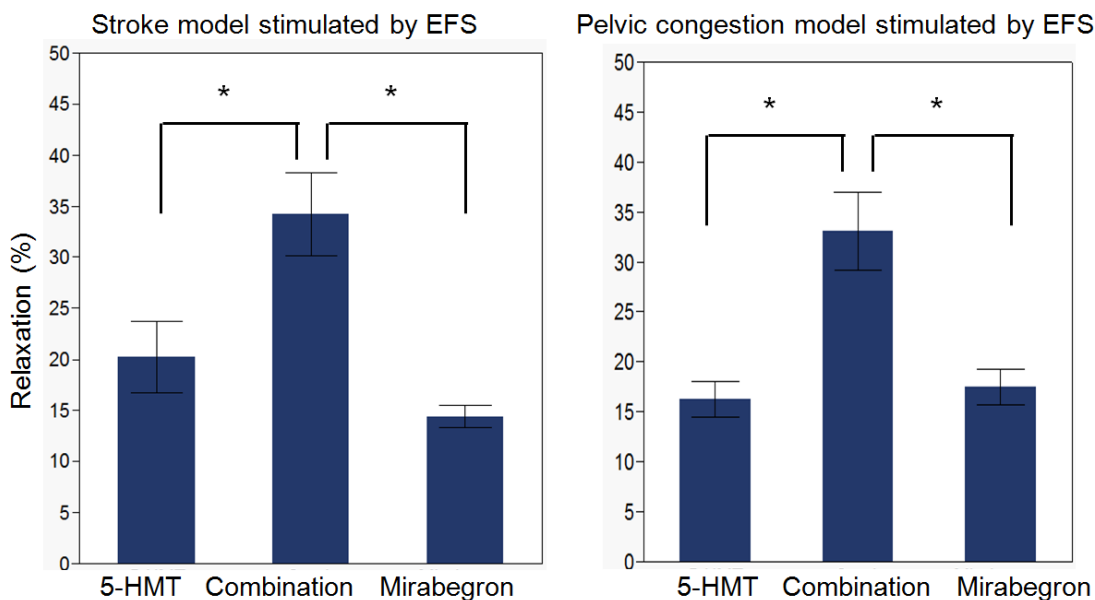
Interpretation of results

Additive relaxant effects of 5-HMT and mirabegron were observed in the EFS- and CCh-induced contractions of bladder strips from rat models of stroke and pelvic congestion. The underlying mechanism causing the contractile responses through CCh and EFS may be different. The endogenous ATP may be released by EFS but not by CCh. The additive relaxant effect of combination treatment might differ by the cause (ex: pelvic organ prolapse, etc.) of OAB.

Concluding message

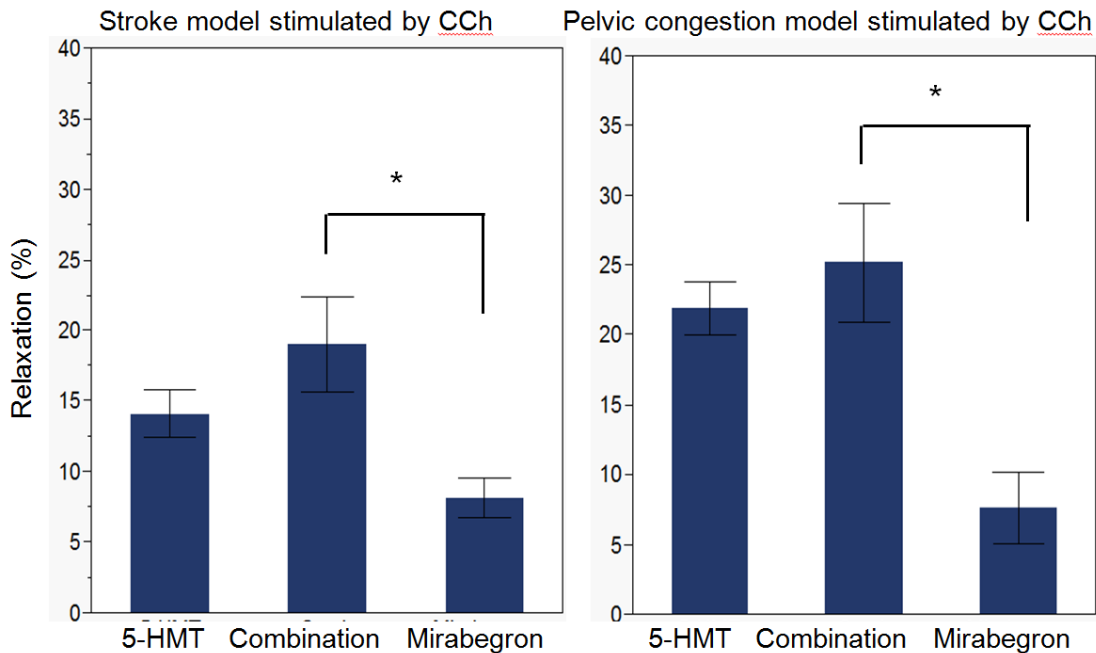
The combination treatment with fesoterodine and mirabegron has a potential to be a good therapeutic alternative in the non-responder or suboptimal responder patients to mono-therapy of OAB.

Figure1. Relaxant effect of combination of 5-HMT and mirabegron on EFS-induced contractions



*: Dunnett's test $P < 0.05$; data are given as means \pm SE

Figure2. Relaxant effect of combination of 5-HMT and mirabegron on CCh-induced contractions



$P < 0.05$; data are given as means \pm SE

*: Dunnett's test

Disclosures

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