

COMBINATIONAL EFFECTS OF MUSCARINIC RECEPTOR INHIBITION AND B3-ADRENOCEPTOR SIMULATION ON NEUROGENIC BLADDER DYSFUNCTION IN RATS WITH SPINAL CORD INJURY (SCI)

Hypothesis / aims of study

Mirabegron, a β_3 -adrenoceptor agonist, is widely used as new medication for patients with overactive bladder (OAB) in addition to anticholinergic agents. Our previous study showed that mirabegron dramatically improved bladder dysfunction in patients with anticholinergic-resistant neurogenic OAB [1]. In this study, we investigated the effects of combined therapy with an anticholinergic agent and a β_3 -adrenoceptor agonist on bladder dysfunction and proliferation-related molecule expression in rats with spinal cord injury (SCI).

Study design, materials and methods

The spinal cord was transected at the level of T8-9 in female Sprague-Dawley rats, which were divided into four groups; A: Vehicle, B: 10mg/kg/day of oxybutynin, C: 10mg/kg/day of mirabegron, and D: combined administration of oxybutynin and mirabegron. Drugs were administered by oral gavage from 2 to 4 weeks after spinal cord transection. We evaluated urodynamic parameters during awake cystometry and the mRNA expression of collagen, HIF1- α , TGF- β 1 and bFGF as well as collagen/elastin levels of the bladder in each group.

Results

The intercontraction intervals (ICI), voided volume (VV) and bladder capacity were significantly increased in the group D (combination therapy) compared to the other 3 groups whereas the monotherapy groups B and C did not significantly alter these parameters compared to the vehicle-treated group A (Figures 1). The significant increase in bladder compliance was also seen in the group D vs the group A. The group B showed a tendency of bladder compliance increase compared to the group A, but the difference was not statistically significant. In addition, the time to the first non-voiding contraction (NVC) was significantly prolonged in groups B (oxybutynin therapy) and D, but not in the group C, vs. the group A. The NVC integral for 3 minutes before voiding contractions was decreased in all three treated groups with the significant reduction in the group D compared to the group A. In addition, when compared to the group A, PVR was decreased in the group C (mirabegron therapy) whereas the oxybutynin (group B) or combination therapy (group D) increased PVR with the significant PVR increase in the group D vs. the group C.

The expression of mRNA (Figure 2), type 3 collagen (1.5-fold), HIF-1 α (8.1-fold), TGF- β 1 (5.5-fold) and bFGF (2.9-fold) were increased in vehicle-treated SCI rats (group A) compared to normal (spinal intact) rats. In all three treated groups (B-D), the expression of HIF1- α and TGF- β 1 was decreased compared to the group A. The expression of type 3 collagen and bFGF was decreased in groups B and D. The elastin concentration of groups B and D and total elastin amount of the group D were significantly increased compared to the group A.

Interpretation of results

The combination therapy of an anticholinergic agent and a β_3 -adrenoceptor agonist can significantly increase ICI, VV and bladder capacity, improve bladder compliance and decrease the magnitude of NVCs in SCI rats whereas either of the monotherapies cannot. The combination therapy also reduced the gene expression of some factors involved in tissue remodeling in the bladder, indicating the anti-fibrotic effects of anticholinergics and β_3 -adrenoceptor agonists. Furthermore, HIF-1 α , a transcription factor upregulated under hypoxia, was increased in rats with SCI and then normalized after treatment, suggesting that bladder hypoxia is involved in neurogenic bladder dysfunction such as detrusor overactivity, low bladder compliance and/or bladder remodeling. The bladder elastin concentration was increased in the oxybutynin only and combination groups, suggesting that elastogenesis after the combined therapy could be involved in the improvement of bladder compliance, which was significantly decreased after SCI and then increased by the combination treatment.

Concluding message

Combination therapy of an anticholinergic and a β_3 -adrenoceptor agonist elevated the bladder elastin level, reduced NVCs and increased bladder compliance more effectively compared to the monotherapy in SCI rats. Thus, the combination therapy could be more effective for the treatment of neurogenic bladder dysfunction as well as bladder remodeling such as tissue fibrosis.

Figure 1

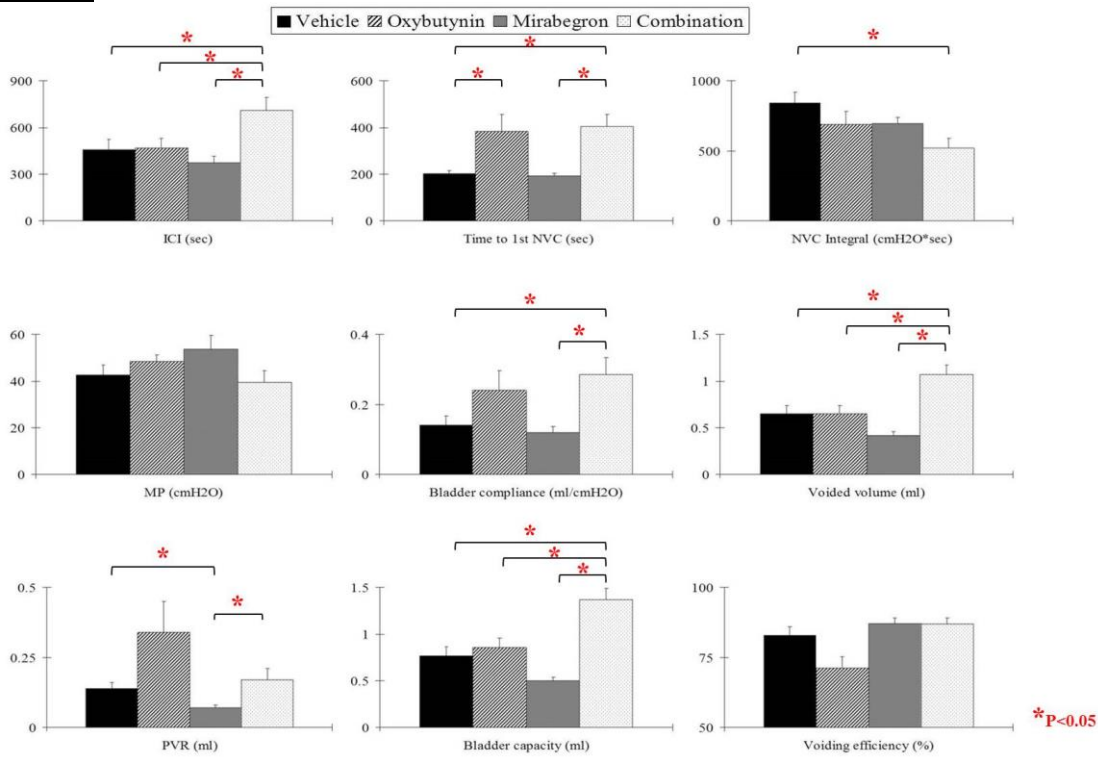
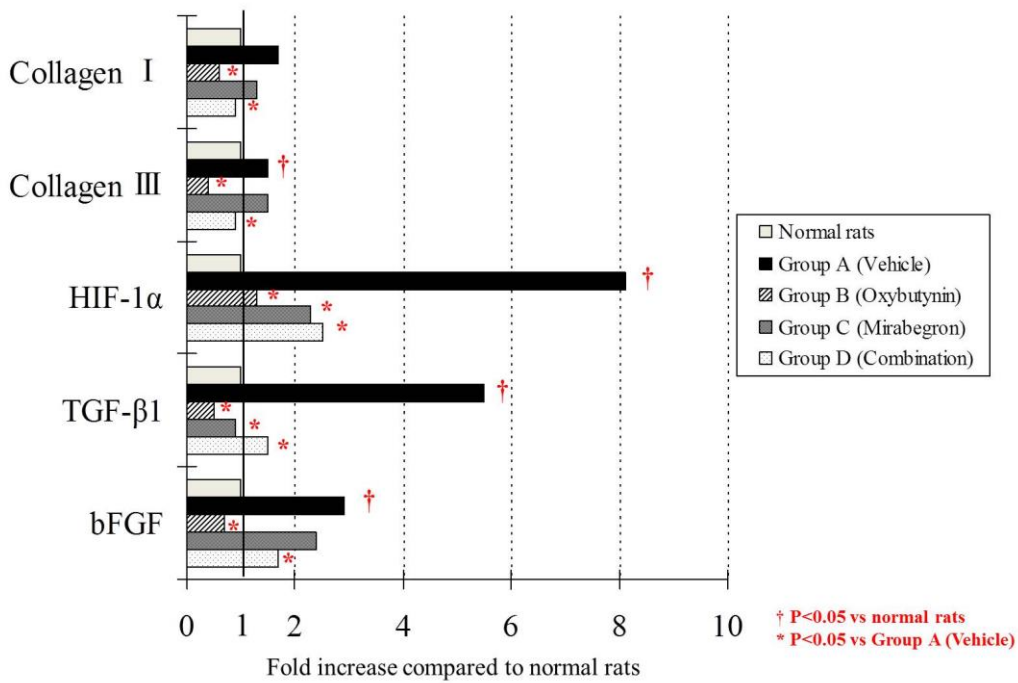


Figure 2



References

1. Wada N et al. Act Urol Jpn 2015; 61: 7-11

Disclosures

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