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COMPARISON OF THE EFFECTS OF MIRABEGRON, A NOVEL BETA3-ADRENOCEPTOR AGONIST, WITH THE ANTICHOLINERGIC AGENT, OXYBUTININ, ON PRIMARY BLADDER AFFERENT ACTIVITY AND BLADDER MICROCONTRACTIONS IN RATS

Hypothesis / aims of study

Mirabegron, which has been approved in Japan, is the first β3-adrenoceptor (β3-AR) agonist for the treatment of overactive bladder (OAB). A previous study demonstrated that the β3-AR agonist, CL316,243, reduced bladder non-voiding contractions (NVCs) in the rat bladder outlet obstructed model (1). Another study suggests that mirabegron can suppress the mechanosensitive bladder afferent activities during bladder filling in the normal rat (2). The current study determined the direct effects of the mirabegron on single unit afferent nerve fiber activities (SAAs) of the primary bladder mechanosensitive afferent nerves and bladder microcontractions and compared those effects with the anticholinergic agent, oxybutinin, in the rat.

Study design, materials and methods

Female Sprague-Dawley rats were anesthetized (urethane, 1.2 g/kg, i.p.) and bilateral transaction of the L6 dorsal roots were made via a laminectomy. The fine filaments were dissected from the left L6 dorsal roots and placed across a bipolar electrode for monitoring SAAs. Nerve fibers primarily originating from the bladder were identified by electrical stimulation of the left pelvic nerve and by bladder distension. Nerves with conduction velocities (CV) more than 2.5 m/sec were designated as Aδ-fibers and those with CV less than 2.5 m/sec as C-fibers. The bladder was then emptied and saline instilled at a rate of 0.08 ml/min until the intravesical pressure reached 30cmH_2O. The bladder was kept under an isovolumetric condition, allowed to stabilize for 5 minutes, after which, vehicle was administrated intravenously (iv) and the recording was performed 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. The bladder pressure, number of microcontractions (> 1.5 cmH_2O) and SAAs were analysed for 3 minutes before and after each-administration.

Results

The number of microcontractions was significantly decreased after mirabegron-administration at both 0.3 and 1.0 mg/kg, although the bladder pressure was also decreased at 1.0 mg/kg (Figures 1 and 2A, B, D and E). On the other hand, these parameters did not change significantly with oxybutynin-administration (Figure 2C and F). A total of 47 single afferent fibers (Aδ-fibers: n=21, CV: 4.21 ± 0.45 m/sec, C-fibers: n=26, CV: 1.55 ± 0.07 m/sec) were isolated from 40 rats. SAAs of Aδ-fibers were significantly decreased with mirabegron-administration at both the 0.3 and 1 mg/kg dose levels, whereas SAAs of C-fibers were significantly decreased only at 1 mg/kg (Figures 1 and 2G, H, J and K). Oxybutynin did not significantly alter either Aδ- or C-fiber-SAAs (Figure 2I and L).

Interpretation of results

The present study shows that the β3-AR agonist, mirabegron, can inhibit both the bladder microcontractions and Aδ-fiber activity at doses that do not decrease the bladder pressure. This suggests that the microcontractions may link to the Aδ-fiber-SAAs, and 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 experimental set-up. At higher doses, which also decreased the bladder pressure, mirabegon inhibited C-fiber activity. These effects were not observed with oxybutynin.

Concluding message

The present study demonstrates that mirabegron can inhibit the single unit bladder afferent activity, especially of Aδ-fibers rather than C-fibers, which is associated with the suppression of the bladder microcontrations. This finding gives us a new insight into possible mechanisms of action for β3-AR agonists in the treatment of OAB.

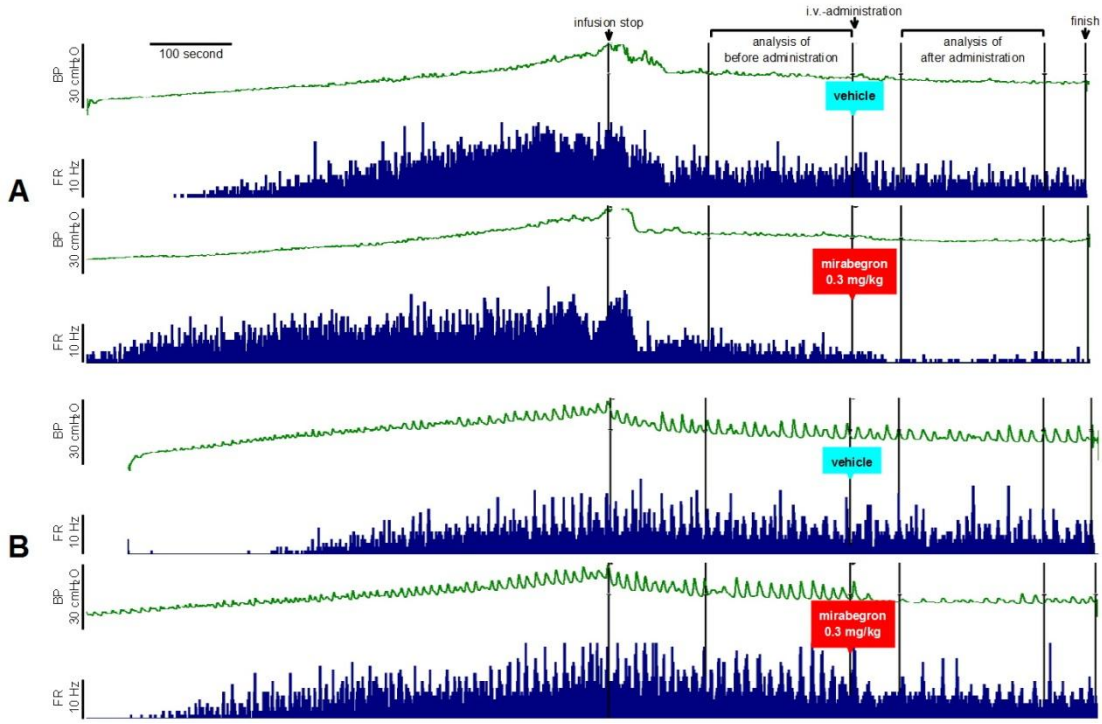

Figure 1. Typical bladder pressure (BP) and firing rate (FR) of Aδ-fiber (A) and C-fiber (B) afferent activity during isovolumetric condition before and after vehicle- or mirabegron (0.3 mg/kg)-administrations.

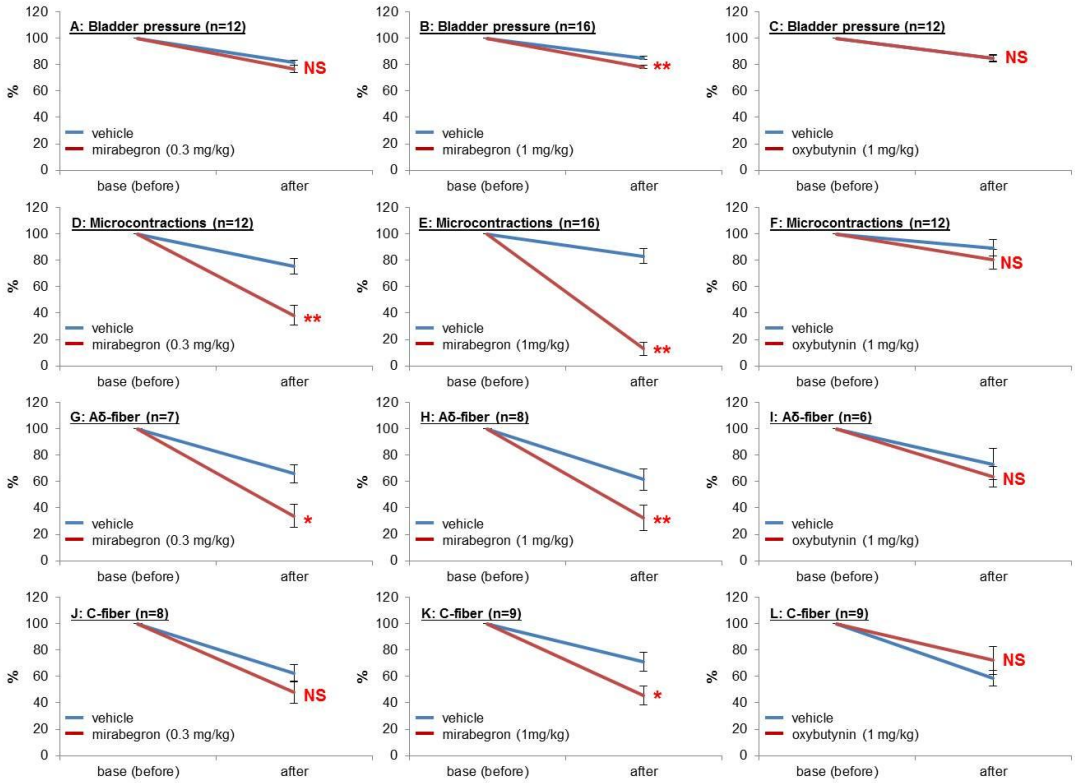

Figure 2. The relative comparison result of mean bladder pressure (A-C), number of microcontractions (D-F), and SAAs of both Aδ- (G-I) and C-fibers (J-L) before and after vehicle- or drug-administrations.
*P<0.05, **P<0.01, NS: significant differences or no significant difference between after vehicle- and drug-administration (unpaired Student's t-test).

References
1. J Urol. 2001; 166(3): 1142-7
2. Neurourol Urodyn. 2011; 30(6):1018-9 (abstract No. 154)

Disclosures

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