

EFFECTS OF MIRABEGRON (YM178), A NOVEL BETA3-ADRENOCEPTOR AGONIST, ON THE PRIMARY BLADDER AFFERENT ACTIVITY OF THE RAT

Hypothesis / aims of study

It has been suggested that β 3-adrenoceptor (β 3-AR) agonists affect not only the efferent but also the afferent pathways innervating the bladder. In addition, a previous report demonstrated that CL316,243, a relatively selective β 3-AR agonist in the rat, can inhibit A δ -fibers of the primary mechanosensitive bladder afferents in the rat (1). Recently, clinical proof of concept study (BLOSSOM) shows a novel β 3-AR agonist, mirabegron (YM178), is effective and well tolerated in the treatment of symptoms of overactive bladder (OAB), thus this drug has a great potential in the treatment of OAB in the quite near future (2). We investigated direct effects of this novel β 3-AR agonist on single unit afferent nerve fiber activities (SAAs) of the primary bladder afferent nerves in rats.

Study design, materials and methods

Female Sprague-Dawley rats were used. Under intraperitoneal urethane anesthesia (1.5 g/kg), through a laminectomy, bilateral L6 dorsal roots were cut, and 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 (Figure 1). Nerves of which conduction velocity (CV) is more than 2.5 m/sec were determined as A δ -fibers and those with less than 2.5 m/sec as C-fibers (3). At the beginning of the experiments, the afferent activity measurements with constant bladder filling (at 0.08 ml/min until the intravesical pressure reached 30cmH₂O) were repeated three times and the third measurement served as the control observation. Then, mirabegron was administered intravenously at three doses, 0.1, 0.3 and 1 mg/kg cumulatively, and SAAs during cystometry with saline-instillation were studied after each mirabegron-administration. The SAA was expressed as a percentage of baseline activity, integrated for the whole filling phase, which is based on pressure and volume.

Results

13 single afferent fibers (A δ -fibers: n=6, CV: 7.29 \pm 1.96 m/sec, C-fibers: n=7 CV: 1.77 \pm 0.17 m/sec) were isolated from 10 rats. After mirabegron-administration, bladder compliance did not significantly change from the base-line value although it tended to be increased (data not shown). The SAAs of both A δ - and C-fibers significantly decreased after mirabegron-administration in a dose-dependent manner, which was more remarkable for A δ -fibers than C-fibers (Figures 2 and 3). Moreover, the inhibition of SAAs appeared to synchronize with the decrease in fluctuation on bladder pressure, although it was difficult to quantify as the numeric values.

Interpretation of results

The results of the present study indicate that mirabegron, the novel β 3-AR agonist, can inhibit mechano-sensitive A δ -fibers and C-fibers primarily originating from the rat bladder. The mechanism of mirabegron's action may be due to an action on a part of urothelial-afferent transduction system or a direct action on afferent nerves themselves as the bladder compliance was not significantly increased. However, it cannot be excluded that the reduction of bladder microcontractions, as a myogenic factor enhancing afferent activities, contributes to the inhibition of the SAAs, since no reflex arc though the L6 dorsal roots worked in the present experimental set-up.

Concluding message

The present results clearly demonstrate that the novel β 3-AR agonist, mirabegron, can inhibit both A δ -fibers and C-fibers of the primary bladder afferents in the rat. These findings may give us a new insight into possible mechanisms of action when we use β 3-AR agonists in the treatment of OAB.

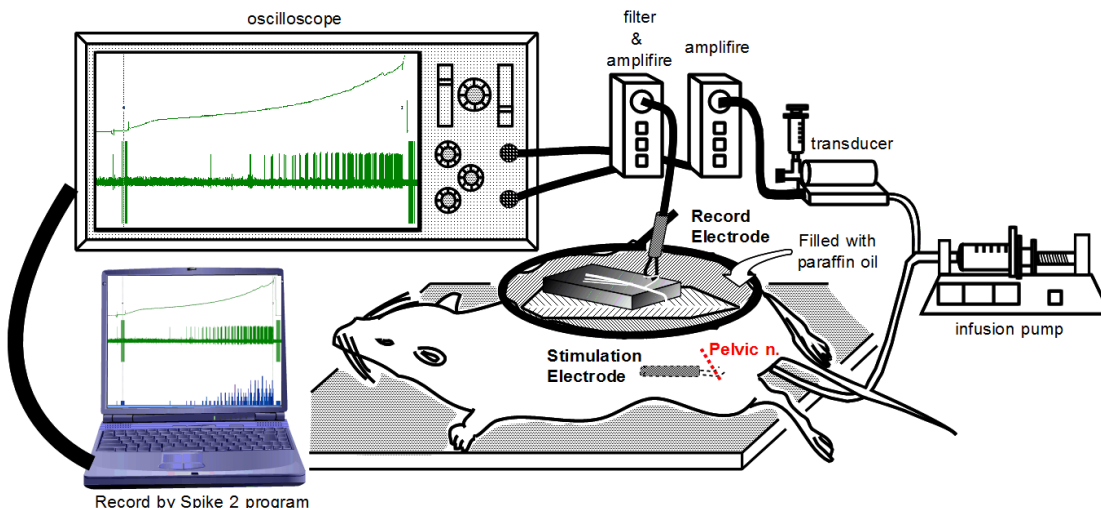


Figure 1. Diagram of the experimental set-up.

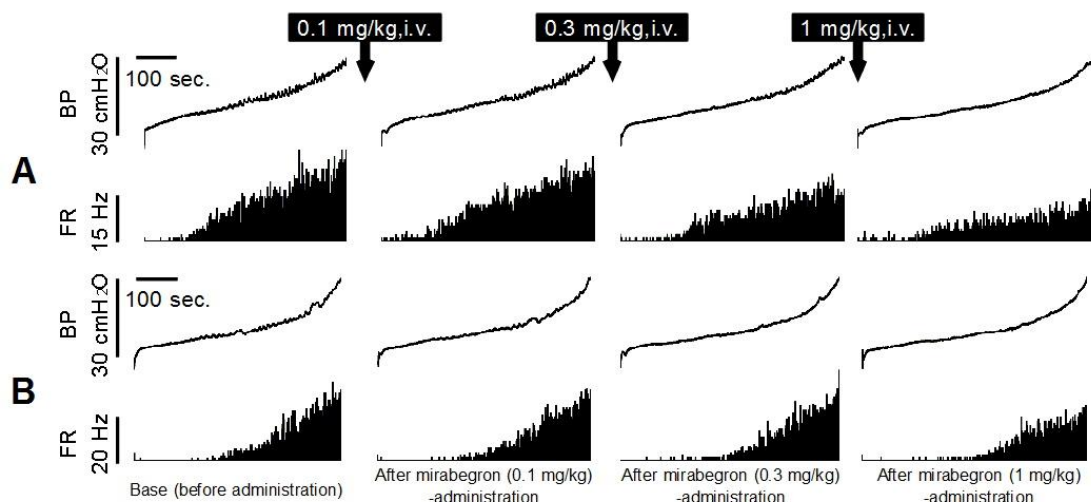


Figure 2. Bladder pressure (BP) and firing rate (FR) of A δ -fiber (A) and C-fiber (B) during bladder filling with saline before (Base) and after mirabegron-administrations.

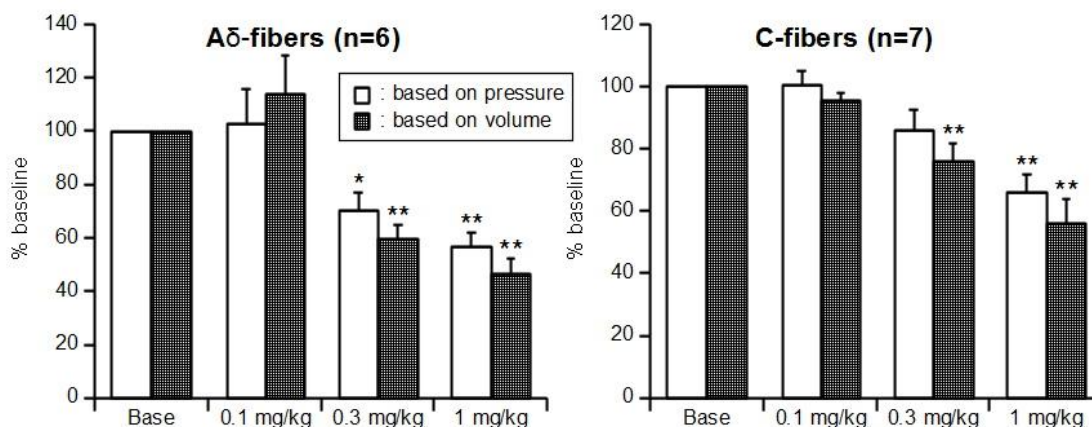


Figure 3. Responses to intravenous administration of mirabegron of the A δ -fibers (left) and C-fibers (right) integrated during the whole filling phase. The values are expressed as a percentage of base-line activity (mean \pm S.E.M.). * P <0.05, ** P <0.01: significant difference from Base (two-way ANOVA followed by Tukey's test).

References

1. Neurourol Urodyn. 2010; 29(5):771-6
2. Eur Urol suppl 2008; 7(3): 239
3. J Neurophysiol 1994; 72: 2420

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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	Animal Ethics Committee, The University of Tokyo Graduate School of Medicine