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TRK-380, A NOVEL B3 ADRENOCEPTOR (AR) AGONIST, DECREASES VOIDING FREQUENCY IN RATS WITH FORMALIN-INDUCED POLLAKIURIA AND SUPPRESSES THE NON-VOIDING CONTRACTIONS(NVCS) IN BLADDER OUTLET OBSTRUCTION (BOO)

Hypothesis / aims of study

It has been reported that β_3-ARs potentially play an important role in urine storage due to the relaxation of bladder in humans (1); therefore, β_3-AR agonist is considered to be a candidate drug for the treatment of overactive bladder (OAB). In rats as well as dogs and humans, β-ARs (β_3-ARs and β_2-ARs) also play an important role in the relaxation of bladder (2). The aim of this study is to clarify the effects of TRK-380, a selective β_3-AR agonist, on natural voiding behaviors in rats with formalin-induced pollakiuria or bladder outlet obstruction (BOO) in order to evaluate its therapeutic efficacy for OAB.

Study design, materials and methods

In a natural voiding behavioral study, female SD rats were intravesically pre-treated with 2.5% (0.2 mL for 2 min) formalin under isoflurane anesthesia. Next day, TRK-380 (7.5, 15, and 30 mg/kg, p.o.) or tolterodine (3.25, 7.5, and 15 mg/kg, p.o.), an anti-cholinergic drug, was administered and their voiding behavior was monitored with an acquisition system connected to a balance. In the study with BOO rats, the urethra was partially obstructed with a 4-0 nylon suture in the presence of a tungsten rod (O.D.: 1 mm) placed alongside the urethra in female SD rats. Six weeks later, cystometry was performed during intravesical infusion of saline (10 mL/hr) in the conscious condition. After stable voiding intervals were obtained, TRK-380 (1 and 3 mg/kg, iv) or oxybutynin (0.3-3 mg/kg, iv), an anti-cholinergic drug, was administered to BOO rats, and then the effects of drugs on the number of non-voiding contractions (NVC, > 4 cm H_2O) and on the micturition pressure were investigated.

Results

In the voiding behavioral study, rats pre-treated with intravesical infusion of formalin showed a significant increase in voiding frequency compared to the vehicle-treated group, which was dose-dependently and significantly attenuated by TRK-380 within 1 hour after oral administration (Fig. 1). In the study with BOO rats, TRK-380 significantly decreased the number of NVC during cystometry (Fig. 2a). On the other hand, micturition pressure was unaffected with the TRK-380 treatment (Fig. 2b). Oxybutynin did not decrease the number of NVCs, but significantly attenuated the micturition pressure.

Interpretation of results

TRK-380 is shown to induce decreased voiding frequency in rats with formalin-induced pollakiuria and suppression of the NVCs in BOO rats, which are possibly caused by its relaxing effects on detrusor smooth muscle via β_3-ARs.

Concluding message

These data suggest that TRK-380 is able to ameliorate storage symptoms in patients with OAB. Especially, the present results of TRK-380 in the BOO model showing the reduction of NVCs without affecting micturition pressure are important because the use of anti-cholinergic drugs for the treatment of OAB is limited in patients with obstructive symptoms due to BPH. Therefore TRK-380 might be a promising drug for the treatment of OAB symptoms including those associated with BPH.

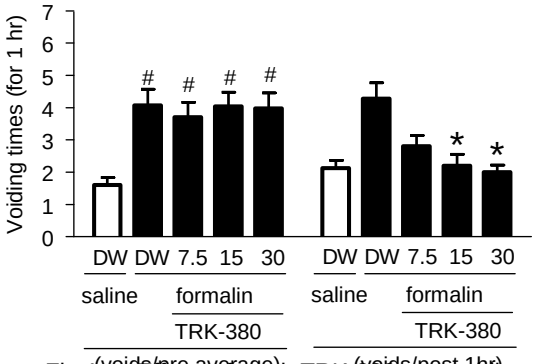

Fig.1 Effect of oral TRK-380 on voiding behaviors in rats with formalin-induced pollakiuria (N=15).

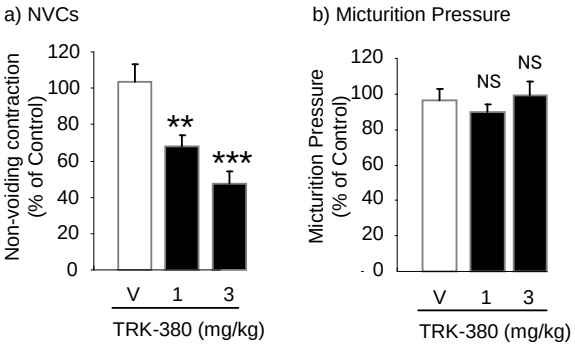

Fig.2 Effect of intravenous TRK-380 on NVCs (a) and micturition pressure (b) in BOO rats (N=6-8).

References
1. Takeda M. et al., J Pharmacol Exp Ther (1999) 288: 1367-73
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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
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