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## EFFECT OF TRK-380, A NOVEL B<sub>3</sub>-ADRENOCEPTOR (AR) AGONIST, ON CARBACHOL-INDUCED BLADDER CONTRACTIONS IN ANESTHETIZED DOGS

### Hypothesis / aims of study

Previous reports on mRNA expression and functional studies have suggested that  $\beta_3$ -ARs potentially play an important role in the relaxation of human bladder (1, 2); therefore, its agonist is considered to be a candidate drug for the treatment of overactive bladder (OAB). In dogs similar to humans,  $\beta_3$ -ARs are also considered to play a pivotal role in the relaxation of detrusor from the functional stand points (3). The aim of this study is to clarify the effect of TRK-380, a selective  $\beta_3$ -AR agonist, on bladder functions in dogs in order to estimate its therapeutic potential for OAB.

### Study design, materials and methods

In pentobarbital-anesthetized dogs (male beagle), the elevation of intravesical pressure was induced by carbachol (CCh, 3  $\mu$ g/kg, iv) after the bladder was filled to its capacity with saline through a transurethral catheter. After stabilization of the bladder contraction by CCh, TRK-380 (0.125 and 0.25 mg/kg) was intraduodenally administered to the dog, and subsequently CCh was intravenously applied to the dog at 115 min after its administration. Percentage changes of the response induced by each CCh over the pre-value were calculated using an area under the curve (AUC) for 10 min after each CCh application. In an organ bath assay, the detrusor strips of dogs (male beagle) were mounted in 10 mL organ bath filled with Krebs-Henseleit solution, which was gassed with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. The preparations were equilibrated for at least 60 min after the establishment of an initial tension of 0.5 g; each compound was then added cumulatively to the organ bath and concentration-response curves were obtained. The maximal response induced by forskolin (10  $\mu$ M) was expressed as 100 % relaxation. pEC<sub>50</sub> value of each compound was calculated from its concentration-response curve.

### Results

Intraduodenal administration of TRK-380 significantly and dose-dependently suppressed bladder contractions induced by CCh in anesthetized dogs (Fig. 2). In the organ bath assay with isolated bladder strips, TRK-380 showed a concentration-dependent relaxing effect on the resting tension with pEC<sub>50</sub> of 6.92 $\pm$ 0.11, which was similar to the value obtained in human detrusor strips (pEC<sub>50</sub>: 7.33 $\pm$ 0.10 in house data).

### Interpretation of results

TRK-380 induced attenuation of bladder contractions induced by CCh in dogs, which is possibly caused by its relaxing effects on detrusor smooth muscle via  $\beta_3$ -ARs.

### Concluding message

These data suggest that TRK-380 may induce relaxation of the bladder via  $\beta_3$ -ARs and an increase in bladder capacity in humans, thereby resulting in amelioration of OAB symptoms because TRK-380 showed the relaxing effects on the canine detrusor whose function and distribution of  $\beta_3$ -AR are similar to those of the human detrusor.

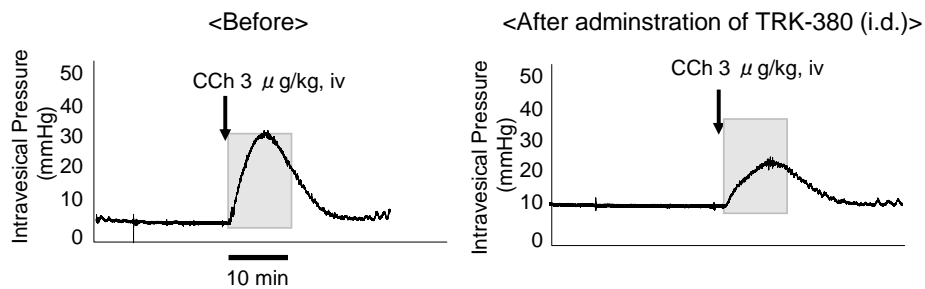


Fig. 1 Typical trace of the effect of TRK-380 on CCh-induced bladder contraction in an anesthetized dog

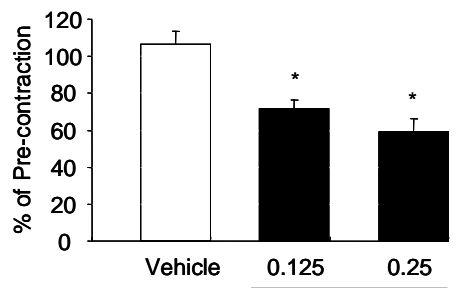


Fig. 2 Effect of TRK-380 on CCh-induced bladder contraction in anesthetized dogs (N=5)

**References**

1. Nomiya et al., J Urol (2003) 170: 649-53
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<b>What were the subjects in the study?</b>	<b>ANIMAL</b>
<b>Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?</b>	<b>Yes</b>
<b>Name of ethics committee</b>	<b>The ethical committee of Research &amp; Development Division, Toray Industries, Inc.</b>