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# A NEXT GENERATION DRUG FOR OVERACTIVE BLADDER, TRK-130, ON PHASE-IIB CLINICAL TRIAL IN JAPAN; PRECLINICAL DATA OF POTENT PHARMACOLOGICAL EFFECTS BASED ON MODULATION OF NEUROTRANSMISSION.

Hypothesis / aims of study

It has been well-known that opioidergic modulation involves in the control of voiding pathway through spinal and supraspinal mechanism[1)]. Therefore, opioid receptor ligands have a potential for the drug of overactive bladder (OAB). The aim of this study is to clarify the effect of TRK-130, a novel mu opioid receptor (MOR) partial agonist which has been Phase IIb clinical trial in Japan, on the rhythmic bladder contraction and the voiding parameters in conscious or anesthetized animals in order to evaluate the therapeutic potential for OAB.

Study design, materials and methods

Binding affinities and agonistic activities for 3 opioid receptors were investigated by using CHO cells or HEK-293 cells stably expressed human opioid receptor respectively. In the assay of the agonistic activities for each opioid receptor, the inhibitory effects of the compounds on the forskolin-induced cAMP formation were evaluated. In order to evaluate whether TRK-130 possesses the direct effect on the bladder, the responses of the drug for the bladder contraction by the electrical field stimulation were observed. In the rhythmic bladder contraction study, animals were inserted the tube into the bladder to record the intravesical pressure under the anesthesia with the ligation of both urethra. The stable bladder contractions were induced by the consistent infusion of saline to the bladder and the effects of drugs were estimated as the change of shutdown time and the intravesical pressure before and after the application of them. In case of making the spinalised animals, the spinal cord of the animal at Th12 (12$^{th}$ thoracic vertebra) was cut under isoflurane anesthesia, and then they were used for above study after recovering. In the urodynamic study, the intravesically cannulated animals were used to record the intravesical pressure. After getting the stable duration of the bladder capacity, drug s were administered (iv) and observed the change of the urodynamic parameters. In a natural voiding behavioral study, animals were intravesically pre-treated with 2.5% formalin under ether anesthesia. 2 day later, the drug was administered and their voiding behavior was monitoring with an acquisition system connected to a balance.

Results

It was revealed that TRK-130 had higher affinity for human opioid mu receptor (Ki value: 0.268 nM) over other opioid receptors and partial agonistic activities for MOR (EC50 / Imax %: 2.39 nM / 66.1%). TRK-130 did not show the marked direct effect on the rat bladder contraction evoked the electrical-field stimulation up to 10 microM compared to oxybutynin, a typical anti-cholinergic. The administration of TRK-130 (0.001-0.01 mg/kg, iv) demonstrated the dose-dependent and significant suppression of the rhythmic bladder contraction, and its effect was antagonized by the treatment with naloxone, a typical opioid receptor antagonist. In spinalised animals, TRK-130 dose-dependently and significantly displayed the attenuation of the rhythmic bladder contraction, but its effect was weaker than that in the normal animals. In the cystometry experiment, TRK-130 (0.0025 mg/kg, iv) and oxybutynin (1 mg/kg, iv) both significantly increased bladder capacity to an equivalent extent in comparison to that of vehicle. Despite oxybutynin decreased the voiding parameters in relation to the evacuation of urine, but TRK-130 showed no such effects on those. In the voiding behavioral study, animals pretreated 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-130 (0.003 – 0.03 mg/kg, po). And reasonably, the averaged micturition volume was increased according to the application of TRK-130.

Interpretation of results

TRK-130 modulates the voiding responses through the activation of the MORs in central nervous system and the decreases of sensory inputs from the bladder without affecting the bladder contraction.

Concluding message

It has considered that TRK-130 is capable to ameliorate the storage symptoms in patients with OAB and interstitial cystitis . TRK-130 is an exactly first in class drug candidate for OAB treatment, which has been Ph-IIb clinical trial in Japan as an partial MOR agonist, but is free from the well-known common adverse effects (such as dependence) of MOR full agonists like morphine.

# REFERENCES INSIDE THE ABSTRACT ???

1) Durant PA and Yaksh T, Anesthesiology 68 (3), 325-334, 1988.

Table1 Agonistic activity of TRK-130 for each opioid receptor

| Test substance | μ-opioid receptor | | δ-opioid receptor | | κ-opioid receptor | |
|---|---|---|---|---|---|---|
| | EC50 (nmol/L) | Imax (%) | EC50 (nmol/L) | Imax (%) | EC50 (nmol/L) | Imax (%) |
| TRK-130 | 2.39 (1.85-3.09) | 66.1±3.9 | 26.1 (22.4-30.5) | 71.0±1.9 | 9.51 (8.40-10.8) | 62.6±1.3 |
| Morphine | 19.9 (18.4-21.5) | 100.0±1.0 | N.D. | N.D. | N.D. | N.D. |
| Buprenorphine | 4.49 (4.11-4.91) | 90.8±1.4 | 8.00 (6.59-9.68) | 62.2±2.4 | 2.08 (1.53-2.68) | 20.5±0.7 |
| DAMGO | 2.07 (1.92-2.23) | 100.0±0.9 | - | - | - | - |
| DPDPE | - | - | 0.527 (0.456-0.608) | 100.0±0.7 | - | - |
| U-69593 | - | - | - | - | 1.64 (1.55-1.73) | 100.0±0.4 |

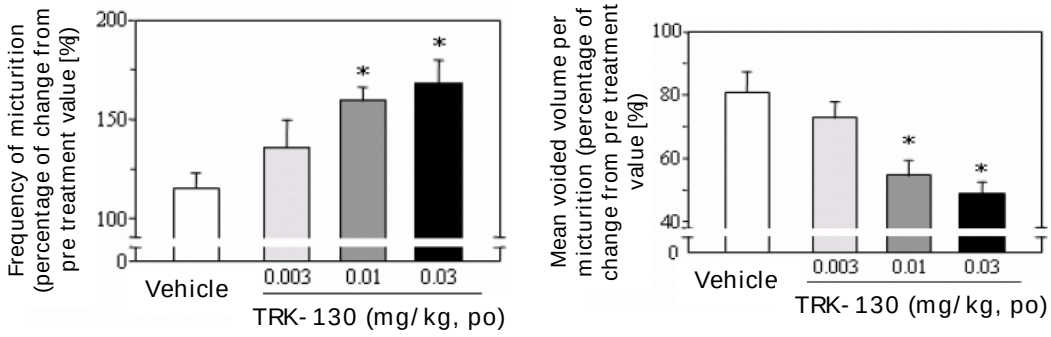


Fig.1 Effect of TRK-130 on the natural voiding behavior in guinea-pig

References

1. Durant PA and Yaksh T, Anesthesiology 68 (3), 325-334, 1988.

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|---|---|
| ***Specify source of funding or grant*** | **NONE** |
| ***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*** | **Guidelines for the care and use of laboratory animals in Toray Industries Inc.** |