

## KEEP ON TRIPPING: ALSO TRPM4 PLAYS A FUNCTIONAL ROLE IN THE LOWER URINARY TRACT OF THE RAT

### Hypothesis / aims of study

Many different Transient Receptor Potential (TRP) channels are expressed in the lower urinary tract (LUT) and some of them, under which TRPV1, TRPV4, TRPA1 and TRPM8, have been shown to have a functional role in LUT physiology and to be promising drug target candidates for LUT dysfunction.

Although the TRP Melastatin 4 channel (TRPM4) has been shown to be abundantly expressed in urothelium and detrusor smooth muscle and to play a role in detrusor muscle contractility, its *in vivo* functional role has until now not yet been elucidated.

This study utilizes TRPM4 knock out rats and wild type littermate controls in combination with the most specific TRPM4 antagonist available, 9-Phenanol, to study the functional role of TRPM4 in the LUT of the rat.

### Study design, materials and methods

Experiments were conducted on 11 weeks old female *TrpM4*<sup>-/-</sup> (n=6) and *TrpM4*<sup>+/+</sup> (n=6) littermate rats. After urethane anaesthesia a catheter was inserted into the bladder. The catheter was connected to a syringe pump and a pressure transducer to infuse the bladder and record intravesical pressure. Cystometrograms (CMG) recordings were registered during infusion of vehicle (1% DMSO) and 500  $\mu$ M 9-Phenanol (in 1% DMSO), a TRPM4 antagonist.

### Results

In *TrpM4*<sup>-/-</sup> rats the voiding interval was significantly increased when compared to littermate controls (1,58 vs. 2,56 min, p=0,03). There was a trend towards larger voided volumes in *TrpM4*<sup>-/-</sup> rats (0,227 vs. 0,307 ml, p=0,08). Baseline pressure (8,07 vs. 7,44 cmH<sub>2</sub>O, p=0,72) and amplitude of voiding contraction (58,51 vs. 55,58 cmH<sub>2</sub>O, p=0,73), however, were not different.

Infusion of 500  $\mu$ M 9-Phenanol (in 1% DMSO) resulted in an increase of voiding interval which was more pronounced in the *TrpM4*<sup>+/+</sup> rats compared to *TrpM4*<sup>-/-</sup> rats, respectively 49% increase (p<0,05) vs. 19% increase (p>0,05). Amplitude of voiding contraction decreased equally in *TrpM4*<sup>+/+</sup> and *TrpM4*<sup>-/-</sup> rats, respectively 41% and 35% (both p<0,01).

### Interpretation of results

Voiding interval in *TrpM4*<sup>-/-</sup> rats is significantly increased compared to *TrpM4*<sup>+/+</sup> littermate controls. These data suggest that TRPM4 might play a functional role in the sensory signal transduction cascade in the LUT of the rat. In despite of its previously suggested role in detrusor smooth muscle contractility, no differences were found in baseline pressure and amplitude of voiding contraction.

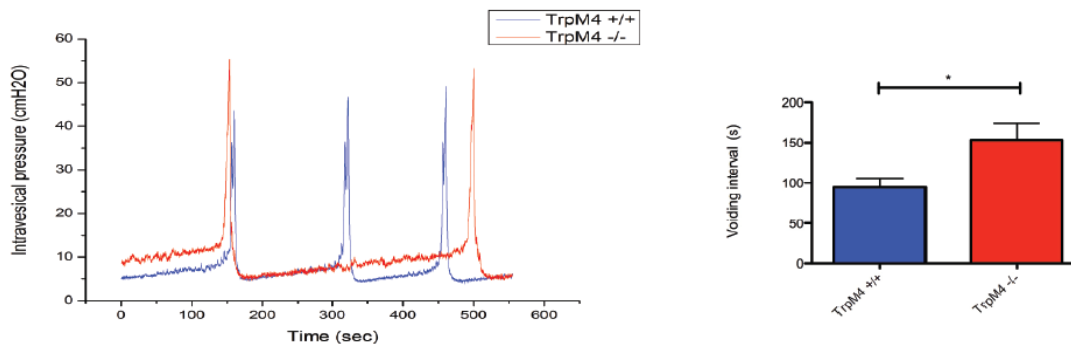
Intravesical infusion of 500  $\mu$ M 9-Phenanol, a TRPM4 antagonist, results in an increase of the voiding interval and a strong decrease of the amplitude of voiding contraction in both *TrpM4*<sup>+/+</sup> and *TrpM4*<sup>-/-</sup> rats. This indicates that, at least in this dose, other mechanisms than TRPM4 inhibition are involved.

### Concluding message

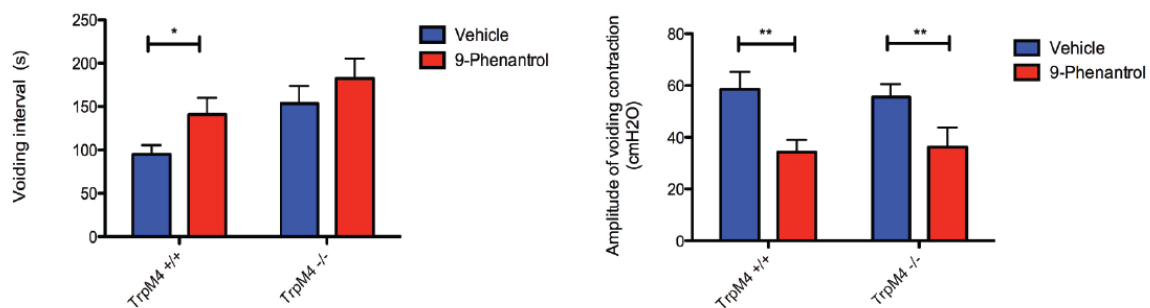
The present study demonstrates that rats lacking the TRPM4 protein have increased voiding intervals, suggesting a functional role for TRPM4 in the LUT of the rat.

The TRPM4 antagonist, 9-Phenanol, increases voiding interval and decreases amplitude of voiding contractions in both *TrpM4*<sup>+/+</sup> and *TrpM4*<sup>-/-</sup> rats, which indicates that other mechanisms than merely TRPM4 inhibition are involved.

### A. Representative CMG traces (vehicle) of *TrpM4*<sup>-/-</sup> and *TrpM4*<sup>+/+</sup> rats



**B. Graph summary of intravesical effect of 500  $\mu$ M 9-Phenantrol on voiding parameters**



**Disclosures**

**Funding:** KU Leuven **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Ethical Committee for Animal Experimentation, KU Leuven