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INHIBITION OF PIEZO1 IN BLADDER UROTHELIUM: A POTENTIAL THERAPY FOR OVERACTIVE BLADDER

Hypothesis / aims of study

We have previously reported on Piezo1 expression and its function as a mechanosensitive ion channel in mouse bladder urothelium (ICS 2012). To date, the expression of Piezo1 in the human bladder urothelium was unknown, and we validated the expression by using quantitative RT-PCR and immunostaining. We hypothesized that inhibition of Piezo1 affects bladder function, and therefore, targeting Piezo1 may become a potential new therapy for an overactive bladder. In this study, we investigated the effect of GsMTx4, Piezo1 inhibitor, in mouse by using metabolic cages for the experiment.

Study design, materials and methods

(1) Wild-type (C57BL/6Cr) mice were used. All experiments were performed using 8–12-week-old male mice. (2) Human bladder specimens were harvested from 29 patients with prostate cancer or benign prostatic hyperplasia who had undergone operations. (3) Quantitative RT-PCR: mRNA was extracted from human bladder urothelium, and expression of the Piezo1 gene was confirmed using the Smart Cycler System. (4) Immunohistostaining: expression of the Piezo1 protein in human bladder specimens was confirmed using an anti-Piezo1 antibody. (5) Analysis of voluntary voiding behavior was carried out using a mouse metabolic cage: mice were housed singly in metabolic cages, which had been improved for precise collection of voided urine in a soundproof windbreak room at 25°C. Mice were treated with GsMTx4 (1350 µg/kg) or vehicle (500 µL saline) via intraperitoneal injections. The following parameters were evaluated: water intake (µL/12 h), urine volume (µL/12 h), urine volume/voided urine (µL), and voiding frequency (number of times/12 h).

Results

(1) Piezo1 mRNA was expressed in the human bladder urothelium. (2) Immunohistochemical analysis revealed that Piezo1 was expressed in all layers of the human bladder urothelium, which confirmed the expression of Piezo1 in the human bladder urothelium. (3) The metabolic cage analysis revealed that the voiding frequency and average urine volume/voided urine in period 2 (post-treatment) were almost similar to that in period 1 (pre-treatment) (6.9 ± 0.86 vs. 6.8 ± 0.92 times, n.s.; 293.9 ± 58.6 vs. 313.0 ± 57.3 µL, n.s., respectively) in control mice. In contrast, the voiding frequency was significantly lower during period 2 than in period 1 (7.0 ± 0.90 vs. 4.3 ± 0.61 times, $p < 0.01$) and the average urine volume/voided urine during period 2 significantly increased than that in period 1 (299.8 ± 45.1 µL vs. 439.7 ± 49.8 µL, $p < 0.05$ in GsMTx4-treated mice).

Interpretation of results

We confirmed the expression of Piezo1 in the human bladder urothelium., hence verifying that Piezo1 is expressed not only in mouse urothelium, but also in the human urothelium. The mouse metabolic cage experiment showed that administration of GsMTx4 decreased urinary frequency and increased urine volume/voided urine in mice, despite there being no changes in water intake and total urine volume, thereby suggesting that Piezo1 is involved in mouse bladder function. This indicates that if GsMTx4 were to be used as a therapeutic agent in humans, it could be effective in alleviating urine storage disorders.

Concluding message

It is possible that the specific inhibition of urothelial Piezo1, such as through treatment with GsMTx4, would likely become a new therapy for an overactive bladder.

Disclosures

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