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Nanri M[1], Ogawa M[1], Sakakibara H[1], Kirimoto T[1], Kiniwa M[1], Yamaguchi O[2]
1. Taiho Pharmaceutical Co., Ltd., 2. Department of Urology, Fukushima Medical University School of Medicine

IS IT POSSIBLE TO INDUCE URINARY FREQUENCY BY STIMULATING THE EPITHELIAL SODIUM CHANNEL?

Hypothesis / aims of study

Excitement of the sensory nervous system may be cited as one of the pathogeneic mechanisms for overactive bladder. ATP and ACh, that are released by the bladder epithelium due to urine accumulation-induced extension simulation, have been reported to act on sensory nerve endings to conduct centripetal neurotransmission [1]. The release of ATP due to the extension stimulation of the urinary bladder requires the presence of a mechanosensor that is sensitive to mechanical stimulation in the bladder epithelium. The epithelial sodium channel (ENaC) has been reported to express in overactive bladder in humans, and ENaC inhibitors to inhibit ATP release due to the extension stimulation of the urinary bladder and to suppress micturition reflex [2]. This fact leads to consider that ENaC on the urinary tract epithelium plays a role as a mechanosensor and induces urinary frequency through ATP release. However, no research has yet been conducted to examine the actions of Na^+ on bladder function. In this study, we injected the NaCl solutions of different concentrations into the urinary bladder of dogs under conscious and unrestricted conditions and verified the effects of Na^+ on symptoms of micturition. In considering the involvement of osmotic pressure, furthermore, we also examined the effects of mannitol and glucose of same osmotic concentrations.

Study design, materials and methods

Under conscious and unrestricted conditions, beagle dogs were used to continuously inject the solutions of NaCl (0.9, 1.8, 2.7, 3.6, and 4.5 %) and the mannitol and glucose solutions of same osmotic pressures (5.2, 9.4, 13.2, 17.0, and 19.9 %) into the urinary bladder; changes in micturition were thus determined. Furthermore, the intravesical injection of each solution was initiated at 20 hours before measurement onset to examine micturition parameters (number of micturitions, micturition interval, single voided volume, urine flow rate, and maximum bladder contraction pressure) for subsequent 4 hours.

Results

Osmotic pressures at respective concentrations were 287, 576, 873, 1163, and 1470 mosm in increasing order of concentration. The number of micturitions increased, micturition interval shortened, and single voided volume reduced in an NaCl concentration-dependent manner. However, high NaCl concentrations showed little effects on urinary flow rate and maximum bladder contraction pressure. All animals in the 4.5 % NaCl injection group showed hematuria. However, the return to 2-day spontaneous micturition recovered the normal pattern of micturition in all animals, thus verifying that the animals were in a reversible condition of urinary frequency. The intravesical injection of amiloride, an ENac inhibitor, suppressed this micturition reflex. On the other hand, only the injection groups of the 5.2 % mannitol and glucose solutions showing the same osmotic pressure as that of the 0.9 % NaCl solution exhibited urinary frequency. However, urinary frequency was not observed at concentrations greater than 5.2 %; inversely, the number of micturitions tended to decrease.

Interpretation of results

The intravesical injection of high-concentration NaCl solutions to dogs induced urinary frequency in a Na^+ concentration-dependent manner. We had predicted that a high osmotic pressure would stimulate the interstitial bladder wall, allowing the entry of Na^+ that activates smooth muscle of the urinary bladder and the urinary tract epithelium. However, high osmotic pressures induced by mannitol and glucose did not induce urinary frequency. Therefore, micturition reflex was evidenced not to occur only due to a high osmotic pressure. Furthermore, urinary frequency was improved by amiloride. Therefore, the reflex was verified to be mediated by ENac in the bladder epithelium. The results from this study lead us to consider that the action of Na^+ on ENac in the bladder epithelium binds epithelium-released ATP to the P_2X_3 receptor, thus activating centripetal sensory neurons and leading to micturition reflex. A high osmotic pressure and a high concentration of Na^+ occur also in the concentrated urine; therefore, these changes potentially occur also in humans. Furthermore, the urinary bladder is considered readily influenced by Na^+ because much ENac expresses under the conditions of overactive bladder.

Concluding message

We expect that further advancement of this study will elucidate the ENac-mediated mechanism of micturition.
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References

1. Urology (2006) 67; 425-430
2. Urology (2004) 64; 1255-1260

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