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EFFECTS OF DESENSITIZATION OF CAPSAICIN-SENSITIVE AFFERENTS ON BLADDER OVERACTIVITY INDUCED BY INTRAVESICAL ATP AND ACETIC ACID IN CONSCIOUS RATS

Aims of Study

Recent studies using knockout mice provide evidence for a major role of urothelially released adenosine triphosphate (ATP) acting via P2X3 receptors on a subpopulation of pelvic afferent nerves in mechanoafferent transduction in the bladder [1,2]. In addition, elevated urine ATP levels and increased stretch-activated ATP-release from bladder urothelial cells in patients with interstitial cystitis have been reported [3]. The urinary bladder is rich in capsaicin-sensitive afferent fibers that detect the presence of irritant chemicals via a specific capsaicin receptor VR1 (vanilloid receptor-1) and in turn trigger reflex bladder activity [4]. However, it has not been determined whether or not the subpopulation of afferent nerves that contribute to this purinergic mechanoafferent transduction involves capsaicin-sensitive afferent fibers. In the present study, we investigated the effect of intravesical instillation of ATP, capsaicin and acetic acid on bladder function in conscious rats, and also examined whether desensitization of capsaicin-sensitive nerve fibers by systemic resiniferatoxin (RTX) pretreatment can counteract the possible effects of these intravesically applied drugs.

Methods

Female Sprage-Dawley rats, weighing 220-250g, were used. A polyethylene catheter was implanted into the bladder through the dome. Cystometric investigations were performed without any anesthesia 2 days after bladder catheter implantation to obtain base-line values. Room-temperature saline was instilled into the bladder at a rate of 10ml/h by a syringe infusion pump. Intravesical pressure and micturition volumes were continuously recorded. When the base-line cystometric investigations were finished, all the animals were randomly divided into two groups. One group of rats received RTX (0.3mg/kg) by subcutaneous injection. The other group of rats received only vehicle injection. Twenty-four hours after the RTX- or vehicle-treatment, cystometric investigations were again performed. Immediately after three reproducible micturition cycles were recorded with saline instillation, saline containing ATP (100 microM), capsaicin (30 microM), or acetic acid (pH=4.0) was instilled intravesically by changing the syringe of the infusion pump. The doses used were defined in a pilot study. The following cystometric parameters were investigated: basal pressure, threshold pressure, micturition pressure, voiding interval, micturition volume, residual volume, and bladder capacity. The results are given as mean values±standard error of the mean. Students paired t-test was used for comparisons before and after RTX (or vehicle) treatment and each intravesical drug administration. One-way factorial ANOVA was used for comparisons of drug effects between RTX- and vehicle-pretreated rats. It was followed by Scheffe's F-test. A probability level of <5% was accepted as significant.

Results

Twenty-four hours after RTX administration, there were statistically significant increases in threshold pressure, voiding interval, micturition volume and bladder capacity, compared with those cystometric parameters in the same rat before RTX administration. Its vehicle had no effects on any of the cystometric parameters. Table 1 shows summarized results of each intravesical drug instillation. In vehicle-pretreated rats, intravesical instillation of capsaicin (30 microM), as well as acetic acid (pH 4.0), led to significant decreases in voiding interval, micturition volume, and bladder capacity. However, in RTX-pretreated rats, neither capsaicin nor acetic acid affected any parameters. The difference in each of these parameter changes between the RTX- and vehicle-pretreated groups was statistically significant. On the other hand, intravesical ATP (100 microM) led to significant decreases in voiding interval and micturition volume not only in vehicle-pretreated animals but also in RTX-pretreated animals: There was no significant difference between the two groups of animals in changes in each parameter.

Conclusions

ATP instilled intravesically caused a decrease in volume threshold for micturition without affecting pressure threshold or micturition pressure, supporting the view that increased extracellular ATP may have a role in mechanoafferent transduction in the bladder. The present results with systemic RTX pre-treatment suggest that this ATP-induced facilitation of the micturition reflex may be mediated via other than capsaicin-sensitive afferent nerves.

References

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Table 1 Effects of intravesical administration of capsaicin (30micro , n=6), acetic acid (pH=4.0, n=6), and ATP (100microM, n=6) on cystometric parameters in vehicle- and RTX-pretreated rats

	B.P.	T.P.	M.P.	V.I.	M.V.	R.V.	B.C.
Capsaicin (vehicle)							
before	9.5±2.1	14.8±3.8	64.5±10.5	6.20±0.76	0.97±0.17	0.34±0.33	1.09±0.19
after	12.3±6.2	14.5±7.0	71.3±15.4	3.12±1.04**	0.46±0.13**	0.31±0.23	0.61±0.25**
Capsaicin (RTX)							
before	7.5±2.8	24.5±4.8	50.2±13.1	8.71±1.84	1.36±0.32	0.19±0.12	1.55±0.30
after	9.1±1.8	22.8±6.2	51.4±14.4	8.59±2.75††	1.41±0.38†	0.39±0.21	1.7±0.19††
Acetic Acid (vehicle)							
before	8.3±2.0	15.1±3.4	48.7±8.5	6.48±0.95	0.99±0.07	0.24±0.14	1.22±0.17
after	13.2±4.9*	17.7±3.5	66.4±2.0**	2.48±1.06**	0.46±0.17**	0.22±0.12	0.68±0.26**
Acetic Acid (RTX)							
before	6.7±3.1	26.8±7.3	50.5±14.5	10.74±0.93	1.63±0.12	0.34±0.17	1.96±0.28
after	8.1±3.4	21.3±12.7	49.6±8.8††	8.94±2.52†	1.43±0.43	0.33±0.21	1.7±0.36†
ATP (vehicle)							
before	8.7±1.6	13.2±2.5	60.7±10.3	5.90±1.85	0.93±0.33	0.18±0.13	1.11±0.25
after	9.6±2.8	12.9±3.0	68.0±13.9	3.74±1.43*	0.55±0.21*	0.24±0.17	0.76±0.27
ATP (RTX)							
before	6.8±1.5	28.5±5.7	54.5±16.1	10.02±2.19	1.55±0.32	0.29±0.17	1.81±0.47
after	9.4±2.1	21.3±7.4	65.0±17.5	6.71±1.72**	0.96±0.31*	0.38±0.31	1.35±0.29**

B.P.: Basal Pressure (cmH_2O); **T.P**.: Threshold Pressure (cmH_2O); **M.P.**: Micturition Pressure (cmH_2O); **V.I.**: Voiding Interval (minute); **M.V.**: Micturition Volume (ml); **R.V.**: Residual Volume (ml); **B.C.**: Bladder Capacity (ml)

Results are expressed as mean±standard error of the mean before and after administration. *p<0.05, **p<0.01(paired Student's two-tailed test), and between vehicle-pretreated rats and RTX-pretreated rats †p<0.05, ††p<0.01, †††p<0.001 (ANOVA followed by Scheffe's F-test)