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EFFECTS OF PROSTAGLANDIN E_2 RECEPTORS ANTAGONIST IN OVERACTIVE BLADDER IN THE CHRONIC SPINAL RATS

Aims of Study

Injury to the spinal cord can lead to hyperreflexic bladder because of the emergence of a spinal micturition reflex pathway. Recent studies have shown that various factors contribute to the increased excitability into the bladder afferent neurons in the spinal rats (1). While, it has been reported that prostaglandins (PGs) act as local modulators of reflex micturition in the pathophysiological condition (2). Furthermore, it has been reported that the increased local stretch of the mouse bladder induced an expression of cyclooxygenase-2, which was the rate limiting enzyme in PG biosynthesis. Molecular biological studies revealed that PGE_2 receptors consisted of 4 subtypes (EP-1~ EP-4), and it has been reported that EP-1 subtype may contribute to smooth muscle contractions (3). Therefore, in the present study, we have evaluated the synthesis of PGE_2 from bladder and the effects of PGE_2 (EP-1 subtype) receptors antagonist on bladder overactivity in the chronic spinal rats.

Methods

Spinal cord was transected at the level of Th 8-9 in adults female Sprague-Dawley rats. The bladders were evacuated by Crede maneuver two times daily. After 8 weeks, the rats were implanted with femoral vein and bladder dome tubing before filling cystometry. PGE_2 receptors antagonist (ONO-8711; 1.0-10 mg/kg, i.v.) or saline solution was administrated 20 min before filing cystometry in both spinal and sham operated control rats. The micturition volume, micturition pressure, residual urine, , number and amplitude of hyperreflexic contractions were recorded. Furthermore, the amounts of PGE_2 released from bladder smooth muscle strips obtained from the control and chronic spinal rats were measured by radioimmunoassay.

Results

The amount of PGE_2 released from bladder strips was significantly greater in the spinal rats than in the control rats. In the spinal rats, micturition volume was significantly decreased, and the residual urine, the number and amplitude of hypereflexic contractions were increased. The administration of PGE_2 receptors antagonist caused significant decreases in the residual urine and the number and amplitude of hyperreflexic contraction in the spinal rats. The micturition volume was significantly increased in the spinal rats after administration of PGE_2 receptors antagonists. While, PGE_2 receptors antagonist did not cause significant change in the micturition pressure in both spinal and control rats.

Table: Comparison and the effects of PGE_2 receptors antagonist on cystometric parameters in the control and chronic spinal rats

	Control	Spinal rats (before PGE_2)	Spinal rats (after PGE_2; 5 mg/kg i.v.)
Micturition volume: ml	0.47±0.05	0.22±0.03	0.38±0.07*
Residual volume: ml	0.45±0.09	0.81±0.12	0.43±0.12*
Hyperreflexic contraction			
Number between micturition	—	4.56±1.35	2.15±0.65*
Max. amplitude: cmH_20	—	16.5±2.6	5.5±0.7*
Micturition pressure: cmH_20	34.0±1.2	22.2±2.5	18.8±1.7

values are mean ± S.E.M of the results from 7 separate experiments. * Significantly different from comparable values for spinal rats (before PGE_2) ($P<0.05$).

Conclusions

The present data suggest that the increased level of PGE_2 in the bladder contributes to the detrusor hyperreflexia in the chronic spinal rats, and that PGE_2 receptors antagonist reduced the hyperreflexia without decrease in the micturition pressure. This may lead to a new therapeutic potential using PGE_2 receptors antagonist for overactive bladder.

References

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Title (type in CAPITAL LETTERS, leave one blank line before the text)
CYSTOMETRIC STUDIES IN CONSCIOUS P2X3 KNOCKOUT MICE REVEAL URINARY BLADDER HYPOREFLXIA

Aims of Study:

P2X3 is a ligand-gated channel expressed by small-diameter sensory neurons and is present in nerve bundles within detrusor muscle layers (1, 2). Endogenous ATP, released during bladder distension, may be responsible for 50-75% of the afferent nerve response to filling (3). In this study, urodynamic studies in conscious P2X3 knockout ($P2X3^{-/-}$) mice were conducted to investigate the role of P2X3 receptors in urine storage and voiding reflexes.

Methods:

Adult (5-6 months) male and female C57BL/6 (n=7), 129Sv (n=6), $P2X3^{-/-}$ (n=8) and $P2X3^{+/+}$ (n=8) as well as young (2 months) male $P2X3^{-/-}$ (n=6) and $P2X3^{+/+}$ (n=6) mice were studied. Cystometry was conducted 7 days after surgical placement and exteriorization of a urinary bladder catheter. Each mouse was placed in a metabolic cage, and saline was infused into the bladder (3ml/h). Urinary bladder pressures, void intervals, and void volumes were recorded using a Grass polygraph.

Results:

$P2X3^{-/-}$ mice had significantly increased urinary bladder capacity and decreased micturition frequency compared to $P2X3^{+/+}$ mice (Figure 1). There were no significant cystometric differences between male and female $P2X3^{-/-}$ mice. Mean void volumes (ml) were 0.41±0.04 and 0.23±0.02 and void intervals (min) were 9.0±0.8 and 5.3±0.3 in $P2X3^{-/-}$ and $P2X3^{+/+}$ mice, respectively ($p<0.01$, Figure 2). Similar results were obtained when $P2X3^{-/-}$mice were compared to C57BL/6 and 129Sv parental strains ($p<0.01$, Figure 2). Baseline, threshold, and micturition pressures were not significantly different between $P2X3^{-/-}$ and $P2X3^{+/+}$ mice. There were also no significant cystometric differences between young $P2X3^{-/-}$ and $P2X3^{+/+}$ mice.