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INTRATHECAL ADMINISTRATION OF EP1 ANTAGONIST REDUCES BLADDER HYPERACTIVITY IN CYSTITIS MODEL RATS

Hypothesis / aims of study

Previous reports have suggested that prostanoids are involved in the control of bladder function under normal and pathological conditions, including detrusor overactivity and overactive bladder. Prostanoid receptors (EP receptors) are found on the urothelium, in detrusor muscle and intramural ganglia. It is suggested that the effects of prostaglandin E2 (PGE2) on bladder function are mediated through EP1 receptor. However there are few reports about the spinal mechanism of PGE2 and EP1 receptor in the control of bladder function. We studied the effects of intrathecal administration of PGE2 and EP1 antagonist on bladder function in rats.

Study design, materials and methods

Female Wistar rats (194 ~ 234 g) were anaesthetized for surgical placement of cystostomy and intrathecal silicone catheter. At first, PGE2 (ONO-01676; 50 pg, 5 ng and 500 ng) was intrathecally (i.t.) administered in normal rats (n=12). As the next step, we administered EP1 antagonist (ONO-8711; 50, 80 and 100 μ g) i.t. in sham control rats (intraperitoneal injection of saline, n=6) and cystitis model rats induced by a single intraperitoneal injection of cyclophosphamide (300 mg/kg, n=9). We evaluated voiding pressure and voided volume per micturition using a conscious-filling cystometry. Cystometry in cystitis model rats was performed 48 hours after cyclophosphamide injection. Saline was infused at a constant rate (10 ml/hr for PGE2 administration study and 6 ml/hr for EP1 antagonist administration study).

Results

In normal rats, i.t. administration of PGE2 at the dose of 500 ng significantly increased voiding pressure compared to saline administration (9.9 ± 2.9 vs. 13.6 ± 6.3 cmH_2O, $p<0.05$), while voided volume per micturition was not significantly different (Figure 1). Voided volume per micturition in cystitis model rats was significantly smaller than that in sham control rats (1.1 ± 0.36 ml vs. 0.40 ± 0.20 ml, $p<0.005$). Compared to saline, i.t. administration of EP1 antagonist at the dose of 100 μ g in cystitis model rats significantly decreased voiding pressure (12.6 ± 5.4 vs. 8.0 ± 2.7 cmH_2O, $p<0.05$) and increased voided volume per micturition (0.40 ± 0.20 vs. 0.53 ± 0.28 ml, $p<0.05$). In contrast, i.t. administration of EP1 antagonist in sham control rats did not change voiding pressure or voided volume per micturition (Figure 2).

Interpretation of results

As i.t. administration of PGE2 in normal rats caused a significant change in voiding pressure, there seem to be EP receptors influencing bladder function in the spinal cord. In cystitis model rats voiding pressure was decreased and voided volume per micturition was increased by i.t. administration of EP1 antagonist. These data suggest that the effects of i.t. administration of PGE2 on bladder function are probably mediated through EP1 receptor and that i.t. administration of EP1 antagonist could reduce bladder hyperactivity in cystitis model rats.

Concluding message

EP1 receptor in the spinal cord is involved in the pathophysiology of bladder hyperactivity in cystitis model rats. I.t. administration of EP1 antagonist might have a therapeutic applicability to bladder hyperactivity associated with interstitial cystitis.

Figure 1. Effect of i.t. administration of PGE2 (50 pg, 5 ng and 500 ng) on voiding pressure and voided volume per micturition in 12 normal rats. *p<0.05 vs. saline

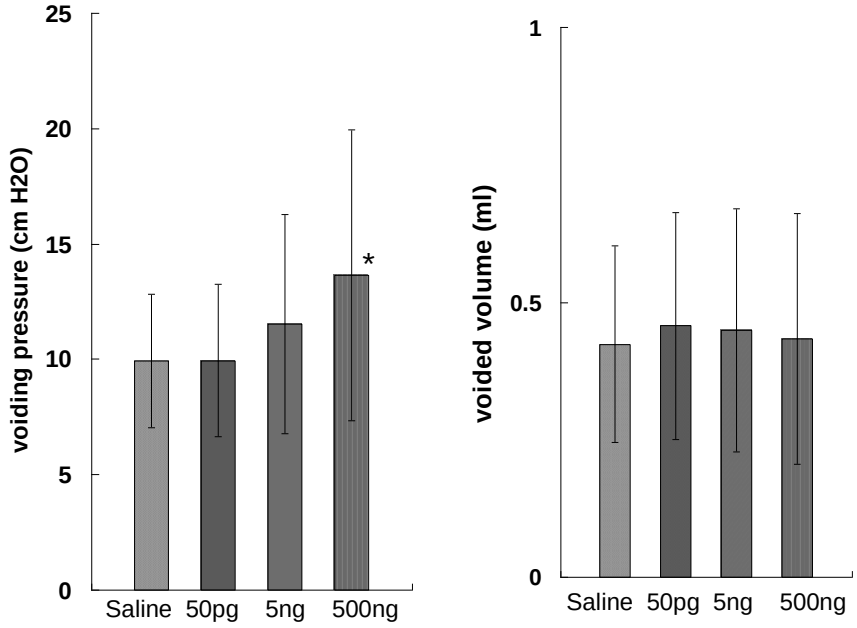
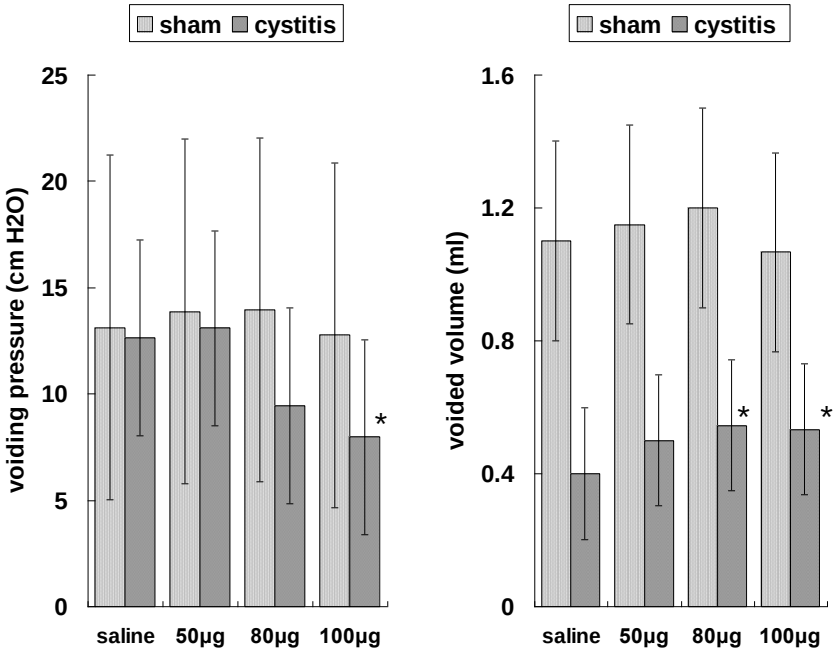


Figure 2. Effect of i.t. administration of EP1 antagonist (50, 80 and 100 μ g) on voiding pressure and voided volume per micturition in 6 sham control rats and 9 cystitis model rats. *p<0.05 vs. saline



Specify source of funding or grant	**Ono Pharmaceuticals**
Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**The ethical committee of Asahikawa Medical college**