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URODYNAMIC EFFECT OF INTRAVESICAL AND INTRATHECAL ADMINISTRATION OF SELECTIVE E-SERIES PROSTAGLANDIN 4 RECEPTOR ANTAGONIST, ONO-AE3-208, ON CYCLOPHOSPHAMIDE INDUCED CYSTITIS RATS

Hypothesis / aims of study
Prostaglandin is synthesized from arachidonic acid via the COX pathway in response to various physiological and pathological stimuli. Of the prostaglandins, prostaglandin E2 (PGE2) is known to be increased in urine of patients with lower urinary tract (LUT) dysfunction including interstitial cystitis/bladder pain syndrome (IC/BPS) and overactive bladder (OAB). There have also been several studies that examined the roles of PGE2 or E-series prostaglandin (EP) receptors using cystitis model animals to explore the PGE2-EP mechanism underlying IC/BPS pathogenesis. We also previously reported in rats with cyclophosphamide (CYP) induced cystitis that intrathecal administration of a selective EP1 receptor antagonist inhibited urinary frequency [1] and that intravenous and intravesical administration of an EP4 antagonist increased intercontraction intervals (ICI) in filling cystometry [2]. In this study, we further investigated the effects of intrathecal administration of a selective EP4 receptor antagonist, ONO-AE3-208, on bladder activity and compared the results with those of the intravesical treatment in CYP-induced cystitis rats in order to determine the site(s) of action of EP4 receptor activation that is involved in cystitis-induced bladder dysfunction.

Study design, materials and methods
All experimental procedures were performed on female Sprague-Dawley rats (200-230g).Cystitis was induced by a single intraperitoneal injection of cyclophosphamide (200mg/kg) and at the same time a cystostomy catheter (PE-50) was placed into the bladder from the bladder dome. Forty-eight hours later, conscious-filling cystometry was performed with an infusion speed of 0.08ml/min. Study 1: Continuous infusion cystometry was performed to examine the effect of intravesical administration of a selective EP 4 receptor antagonist (ONO-AE3-208; 30μM). Study 2: ONO-AE3-208 was administrated intrathecally (10μg and 50μg) via a catheter inserted into the intrathecal space at the L6-S1 spinal cord level. Urodynamic parameters including micturition pressure (MT), ICI, voided volume (VV) and postvoid residual (PVR) were assessed before and after intravesical or intrathecal administration of ONO-AE3-208.

Results
Study 1: Cystitis rats (N=8) showed a shorter ICI (114±17 sec vs 186±11 sec) and small bladder capacity (VV+PVR) (0.15±0.02 ml vs 0.33±0.02 ml) compared with control rats (N=7). In cystitis rats, but not in control rats, continuous intravesical application of ONO-AE3-208 significantly increased ICI from 114±17 sec to 156±6 sec (37% increase) (Figure 1) and bladder volume from 0.15±0.02 ml to 0.22±0.03 ml (55% increase) (Figure 1).
Study 2: At 50 μg dose of ONO-AE3-208 (N=5), ICI was significantly increased from 215±59 sec to 235±61 sec) (13% increase) (Figure 2), while of the drug at 10 μg did not change ICI. Bladder capacity was not significantly changed at either dose (0.24±0.06, 0.27±0.05 and 0.29±0.08 ml after vehicle, 10μg and 50μg of ONO-AE3-208, respectively).
Other parameters including MT were not altered by either treatment route in Studies 1 & 2.

Interpretation of results
ONO-AE3-208, a selective EP4 receptor antagonist, reduced bladder overactivity as evidenced by prolonged ICI after intravesically and intrathecally application of the drug, indicating that both bladder and lumbosacral spinal cord are sites of action of EP1 receptor activation that induces bladder overactivity. Also, because EP4 receptor blockade increased ICI without affecting MT, EP4 receptor activation is likely to be involved in modulation of the afferent limb, but not the efferent limb, of the micturition reflex. In addition, the improvement ratio of ICI by intravesical administration of ONO-AE3-208 was greater than that by intrathecal administration. Therefore, EP4 receptors in the bladder might play a more significant role in cystitis-induced bladder overactivity, when compared to those in the spinal cord.

Concluding message
Because intravesical or intrathecal administration of EP4 receptor antagonist effectively reduced cystitis-induced bladder overactivity in a rat model, blockade of EP4 receptors at bladder and spinal cord levels could have a therapeutic potential for reducing bladder symptoms in patients with IC/BPS.

Figure 1

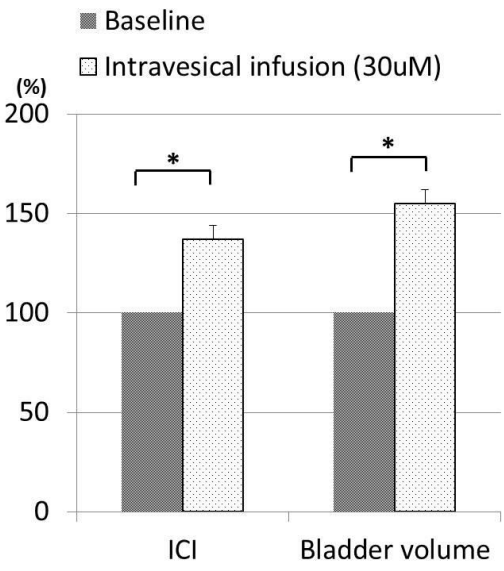
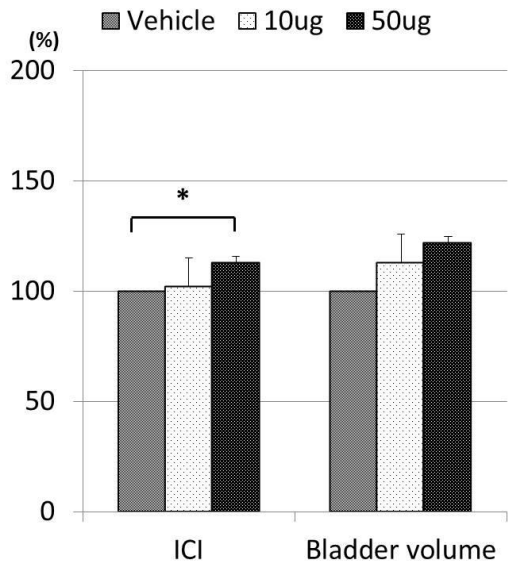


Figure 2



* P<0.05

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Disclosures

Funding: National Institutes of Health (Grants DK088836); Department of Defense (W81XWH-12-1-0565) **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** University of Pittsburgh Institutional Animal Care and Use Committee