311

Wada N[1], Kadekawa K[2], Majima T[2], Shimizu T[2], Tyagi P[2], Kakizaki H[3], Yoshimura N[2]
1. *Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, Department of Renal and Urological Surgery, Asahikawa Medical University, Japan,* ***2.*** *Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania,* ***3.*** *Department of Renal and Urological Surgery, Asahikawa Medical University, Japan*

URODYNAMIC EFFECTS OF INTRAVENOUS AND INTRATHECAL ADMINISTRATION OF E-SERIES PROSTAGLANDIN 1 RECEPTOR ANTAGONIST ON DETRUSOR OVERACTIVITY IN RATS WITH SPINAL CORD INJURY

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 overactive bladder (OAB). There have also been several basic research studies that examined the roles of PGE2 or E-series prostaglandin (EP) receptors in the control of LUT function using normal animals or animal models of cystitis or outflow obstruction. We previously reported that blockade of the spinal EP1 receptor improved urinary frequency in cystitis rats [1]. Also, previous studies using animal models of spinal cord injury (SCI) showed increase of PGE2 release from bladder muscle strips, implying that PGE2 contributes to LUT dysfunction. However, there are a few studies that examined the effect of selective EP receptor agonists or antagonists on bladder dysfunction in SCI model animals. In this study, we therefore examined the effect of an EP1 antagonist on bladder activity using SCI rats.

Study design, materials and methods

Spinal cord was transected at the level of T9-T10 in female Sprague-Dawley rats (200-250g). The bladder of spinalized rats was emptied by abdominal compression twice daily until reflex voiding recovered. Six weeks later, a cystostomy catheter (PE-50) and an intravenous catheter (PE-10) or an intrathecal catheter (PE-10; L6-S1 spinal cord level) were placed. In conscious-filling cystomery, SC51089, an EP1 antagonist, was given intravenously at doses of 0.1 and 1.0mg/kg (Study 1) and intrathecally at doses of 0.1 and 1.0 μg (Study 2). We assessed the change of urodynamic parameters including maximal micturition pressure (MT), the intercontraction interval (ICI), time to the first non-voiding contraction (NVC), NVC integral of a 2-minutes period before the voiding contraction, voided volume (VV) and postvoid residual (PVR). NVC was defined as more than 8 cmH_2O increases in intravesical pressure above the baseline.

Results

Study 1: Compared to vehicle administration, both doses of intravenous administration of EP1 antagonist significantly prolonged the time to the first NVC (58% increase at dose of 1.0mg/kg intravenously, N=10, Figure1 and 2), while other parameters such as MT, ICI, the NVC integral or bladder capacity (VV+PVR) were not significantly changed. When the changes in NVC integral were evaluated, 5 out of 10 rats showed a decrease in the NVC integral after intravenous administration of EP1 antagonist (from 1399±170 to 851±217 cm H2O*s) whereas, in the remaining 5 rats, the NVC integral was not decreased after intravenous administration of EP1 antagonist. In 5 rats whose NVC integral was decreased, mean NVC integral at baseline before drug application was significantly larger (1399±170 vs 728±53 cm H2O*s) than that of other 5 rats.
Study 2: Compared to vehicle administration, 1.0 μg of intrathecal administration of EP1 antagonist significantly prolonged the time to the first NVC (15% increase at dose of 1.0 μg intrathecally, N=10) whereas other parameters such as MT, ICI, NVC integral or bladder capacity (VV+PVR) were not significantly changed.

Interpretation of results

Blockade of EP1 receptors prolonged the time to the first NVC, but did not affect the NVC integral or bladder capacity when all SCI rats were included for analysis. It is known that, in SCI rats, NVCs and voiding bladder contraction are dependent upon activation of C-fiber and Aδ-fiber afferent pathways, respectively [2]. Therefore, the present study implies that PGE2-induced EP1 receptor activation is involved in the initiation of C-fiber excitation to elicit NVCs in SCI rats. In addition, because EP1 receptor blockade was also effective to reduce the NVC integral in SCI rats whose baseline NVC integral was larger than that in the unresponsive group of rats, EP1 receptor activation may also be involved in the maintenance of C-fiber activation when the PGE2-EP1 receptor mechanism is enhanced to induce severe detrusor overactivity as indicated by large NVCs after SCI. Furthermore, the lumbosacral spinal cord is considered as a site of action of EP1 receptor antagonist because intravenous and intrathecal application of EP1 antagonist similarly increased the time to the first NVC in SCI rats.

Concluding message

The PGE2-EP1 receptor system is involved in the emergence of detrusor overactivity as shown by increased NVCs after SCI. Thus, EP1 receptor antagonists could be effective for the treatment of OAB induced by neurogenic detrusor overactivity in pathological conditions such as SCI.

Figure 1 Change of the time to the first NVC and the NVC integral EP1 antagonist i.v. (N=10)

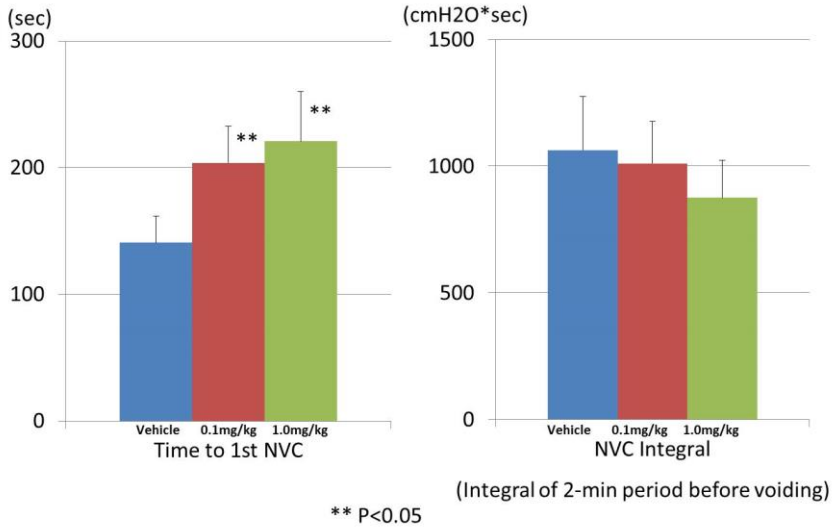
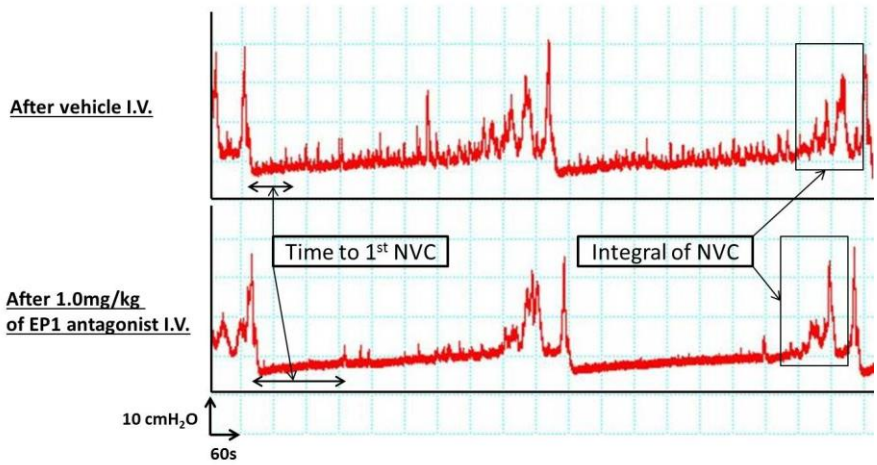


Figure 2 Cystometrogram before and after EP1 antagonist i.v.



References

1. . Wada N, Matsumoto S, Kita M, Watanabe M, Hashizume K, Kakizaki H. Effect of intrathecal administration of E-series prostaglandin 1 receptor antagonist in a cyclophosphamide-induced cystitis rat model. Int J Urol. 20: 235-40, 2013.
2. de Groat WC, Yoshimura N. Plasticity in reflex pathways to the lower urinary tract following spinal cord injury. Exp Neurol. 235: 123-32, 2012

Disclosures

Funding: National Institutes of Health (Grants DK088836 and P01DK093424) **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** University of Pittsburgh Institutional Animal Care and Use Committee