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THE EFFECT OF A NOVEL EP2 AND EP3 RECEPTOR DUAL AGONIST, ONO-8055, ON A NEUROGENIC UNDERACTIVE BLADDER IN A RAT LUMBAR CANAL STENOSIS MODEL

Hypothesis / aims of study

In clinical settings, pharmacological management of an underactive bladder (UAB) with a high level of evidence has not been reported 1). Empirically, an alpha adrenoceptor antagonist or a cholinesterase inhibitor has been often used in UAB patients, and both the drugs showed modest efficacy in a rat lumbar canal stenosis (LCS) model 2). By the way, ONO-8055 is an EP2 and EP3 receptor dual agonist which induces urethral relaxation as well as detrusor contraction. Therefore, this compound would be a candidate for a therapeutic agent for UAB. In this study, we examined the lower urinary tract function of the rat LCS model with in vivo awake cystometry before and after taking ONO-8055. In addition, we measured intraurethral pressure in awake LCS rats in order to elucidate whether ONO-8055 had any effects on the urethral pressure.

Study design, materials and methods

Wistar rats (180 to 190 g) were employed in the present study. One small hole drilled at fifth lumbar vertebral arch, and a rectangular piece of silicone rubber was then placed into the L5 to L6 epidural space.
Experiment 1: Awake cystometry (CMG) was performed 2 weeks after surgery, with ONO-8055 (0.003, 0.01 and 0.03 mg/kg) being orally administered. To facilitate drug evaluation, LCS rats with the following lower urinary tract parameters were selected for this experiment : maximal cystometric capacity (MCC) >1.8 mL and voided volume (VV) <0.25 mL 2). The following cystometric parameters were investigated: baseline intravesical pressure (Pbase), threshold intravesical pressure (Pth), maximal intravesical pressure during voiding (Pmax), frequency of non-voiding contractions (NVCs), MCC, VV, postvoid residual urine volume (PVR), and RUR (%, PVR ÷ (VV +PVR) x 100). We compared these parameters between pre- and post-drug administration.
Experiment 2: We measured intraurethral perfusion pressure (Pura) via transvesically inserted intraurethral catheter for two hours after oral vehicle or ONO-8055 administration.

Results

Experiment 1: As shown in table1 and 2, ONO-8055 significantly decreased Pth, MCC, PVR, and RUR within the selected dose range. In addition, 0.01mg/kg of ONO-8055 significantly decreased Pmax, and 0.03mg of ONO-8055 significantly decreased Pmax and increased Pbase.
Experiment 2: As shown in figure, compared with pre-administration and vehicle administration, ONO-8055 significantly decreased Pura, although apparent dose-dependency could not be demonstrated.

Interpretation of results

ONO-8055 decreased PVR and RUR, probably through decreasing MCC. Unlike some parasympathomimetic drugs such as bethanechol chloride 3), this compound did not augment bladder tonus during the storage phase. These results suggested that this compound might affect bladder afferent system in a different manner. It was supposed that the decrease in Pmax probably resulted from the lowered Pura due to urethral relaxation. However, VV did not change because of insufficient potentiation of the bladder contractility with this compound in this severe UAB model.

Concluding message

A novel EP2 and EP3 receptor dual agonist, ONO-8055, may be therapeutically effective in neurogenic UAB.

Table 1. Storage phase cystometric parameters before and after ONO-8055 administration

Dose	Pbase mmHg	Pth mmHg	NVCs /min	MCC mL
0.003mg/kg (n=10)				
pre	2.52 ± 0.48	5.21 ± 0.46	0.13 ± 0.03	2.48 ± 0.17
post	2.72 ± 0.50	4.29 ± 0.47	0.14 ± 0.05	1.73 ± 0.25
p	n.s.	0.0016	n.s.	0.0019
0.01mg/kg (n=10)				
pre	3.00 ± 0.44	6.21 ± 0.52	0.06 ± 0.01	2.24 ± 0.14
post	3.04 ± 0.49	4.01 ± 0.50	0.07 ± 0.03	1.07 ± 0.17
p	n.s.	< 0.0001	n.s.	< 0.0001
0.03mg/kg (n=10)				
pre	2.79 ± 0.49	5.70 ± 0.52	0.13 ± 0.05	2.47 ± 0.12
post	3.06 ± 0.46	3.81 ± 0.52	0.12 ± 0.06	0.90 ± 0.19
p	0.0044	0.0002	n.s.	< 0.0001

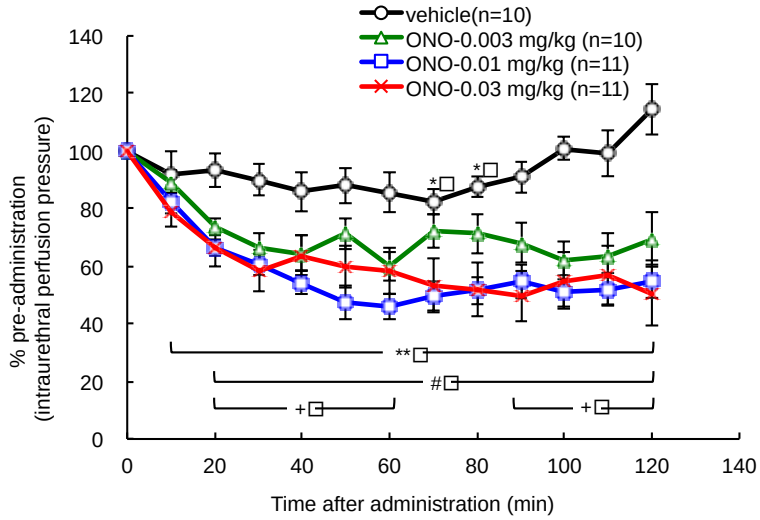
n.s.: not significant, data were shown as mean ± S.E.M.,
paired Student's t-test was used as a statistical analysis

Table 2. Voiding phase cystometric parameters before and after ONO-8055 administration

Dose	Pmax mmHg	VV mL	PVR mL	RUR %
0.003mg/kg (n=10)				
pre	8.59 ± 0.72	0.07 ± 0.01	2.41 ± 0.18	97.19 ± 0.53
post	8.31 ± 0.45	0.07 ± 0.01	1.66 ± 0.26	94.90 ± 0.99
p	n.s.	n.s.	0.0019	0.0350
0.01mg/kg (n=10)				
pre	9.05 ± 0.66	0.06 ± 0.01	2.18 ± 0.13	97.48 ± 0.38
post	6.84 ± 0.55	0.08 ± 0.01	0.99 ± 0.17	91.04 ± 2.06
p	0.0005	n.s.	< 0.0001	0.0065
0.03mg/kg (n=10)				
pre	8.99 ± 0.91	0.05 ± 0.01	2.42 ± 0.12	97.78 ± 0.45
post	7.06 ± 0.51	0.06 ± 0.01	0.84 ± 0.19	90.12 ± 2.91
p	0.0309	n.s.	< 0.0001	0.0187

n.s.: not significant, data were shown as mean ± S.E.M.,
paired Student's t-test was used as a statistical analysis

Figure. Effect of ONO-8055 on intraurethral perfusion pressure



*p < 0.05 vs. pre-administration, **p<0.05 vs. pre-administration (0.003 to 0.03 mg/kg), paired Student's t test, #p < 0.05 vs. vehicle (0.01 and 0.03 mg/kg), +p < 0.05 vs. vehicle (0.003mg/kg), unpaired Student's t test, bar indicated S.E.M.

References

1. BJU int 2007: 99: 749-752
2. Urology 2014: 85: 1248.e9-15

Disclosures

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