

## EFFECTS OF LONG-TERM ESTROGEN TREATMENT ON THE CONTRACTILE RESPONSE TO MUSCARINE AND MUSCARINIC RECEPTOR SUBTYPES IN THE BLADDER OF THE OLD FEMALE RATS

### Hypothesis / aims of study

The role of estrogen treatment in the management of urinary incontinence remains controversial. In addition, estrogen-induced changes in muscarinic receptor subtypes have not been reported. The aim of this study was to examine the effects of long-term estrogen treatment on the contractile response to muscarine and muscarinic receptor subtypes in the bladders of old female rats.

### Study design, materials and methods

Thirteen-month-old female Wistar rats were divided into two groups. Rats in the ET group (n=8) underwent treatment with estradiol for 12 weeks whereas rats in the control group (n=8) underwent no treatment. The following were evaluated: (i) micturition behaviour with normal water or water plus 5% sucrose, (ii) the effect of intravenous administration of muscarine as measured by cystometrogram, and (iii) mRNA expression of muscarinic receptor subtypes in the detrusor muscle, measured by real-time polymerase chain reaction.

### Results

Our data in monitoring micturition behaviour showed that estrogen treatment induced a significant increase in the maximum micturition volume in the ET group (Table 1). Moreover, the average micturition volume also significantly increased under the condition of polyuria. The urodynamic results in the figure show that administration of muscarine significantly increased the maximum detrusor pressure (P<sub>det,max</sub>) in the ET group while there was no significant change in the control group. Furthermore, M<sub>3</sub> receptor mRNA expression in the detrusor muscle was significantly lower in the ET group than in the control group (Table 2).

Table 1 Comparison of micturition behaviour

Drinking water	Water		Water plus 5% sucrose	
	Control	ET	Control	ET
Urine production (ml/day)	18.3 ± 2.2	20.4 ± 2.6	117.2 ± 1.9	117.7 ± 7.6
Micturition frequency (per day)	20.2 ± 3.1	15.6 ± 1.7	99.5 ± 7.2	72.8 ± 2.2*
Average micturition volume (ml)	0.9 ± 0.1	1.3 ± 0.2	1.2 ± 0.1	1.6 ± 0.1*
Maximal micturition volume (ml)	2.0 ± 0.1	3.1 ± 0.4*	2.7 ± 0.2	3.8 ± 0.3*

Table 2 Expression of muscarinic M<sub>2</sub> and M<sub>3</sub> receptor mRNAs in the bladder dome

	Control	ET
M <sub>2</sub> /β-actin (x 10 <sup>-2</sup> )	2.7 ± 1.0	2.4 ± 0.5
M <sub>3</sub> /β-actin (x 10 <sup>-2</sup> )	79.3 ± 14.5	23.5 ± 6.8*

Each value represents the mean ± SEM. \* : p < 0.05 compared with Control.

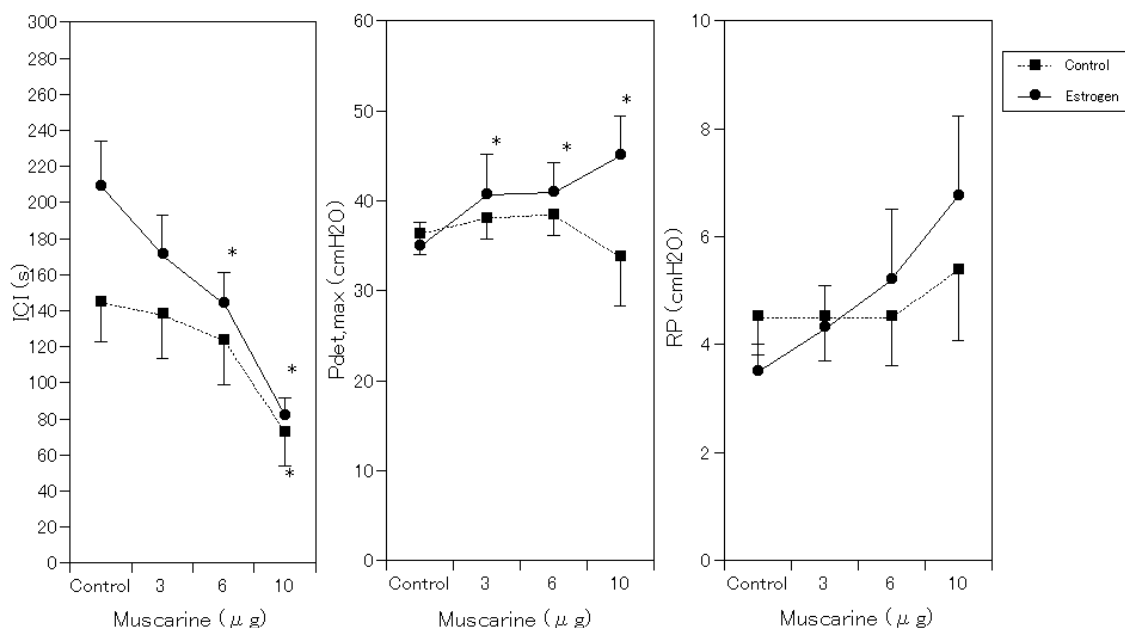


Figure: Effect of muscarine on the cystometrogram. Each value represents the mean ± SEM.

ICI: Intercontraction interval, RP: the post-contraction resting pressure. \* : p < 0.05 compared with Control.

### Interpretation of results

In general, the condition of polyuria may make the bladder feel "more sensitive". Thus, this condition might help to clarify the changes in micturition characteristics with estrogen treatment. We speculated that estrogen might increase

the bladder capacity by raising the sensory threshold of the bladder. A decrease in M<sub>3</sub> receptors due to estrogen might be another factor in the increased bladder capacity. In addition, our data showed that estrogen maintained detrusor contractility by muscarinic stimulation.

Concluding message

These findings indicate that long-term treatment by estrogen may have therapeutic benefits for urge incontinence in women.

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**ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by institutional Animal Care and Use Committee of Tottori University**