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EFFECTS OF ESTROGEN ON AGE-RELATED CHANGES IN MUSCARINIC RECEPTOR SUBTYPES, MUSCARINIC RESPONSIVENESS AND THE SENSORY NEURONS IN THE URINARY BLADDER OF FEMALE RATS

Hypothesis / aims of study
The aim of this study was to investigate the effect of estrogen on aged-related changes in bladder function.
Study design, materials and methods
A total of 36 female Wistar rats were placed into 3 groups: a YR group, consisting of 3-month-old rats; an OR group, consisting of 13-month-old rats; and an OR+E group, consisting of 13-month-old rats with subcutaneous treatment of estradiol for 6 weeks. The following were evaluated: (i) micturition behaviour, (ii) responsiveness to muscarine as measured by cystometrogram, (iii) mRNA expression of the muscarinic receptor subtypes in the detrusor muscle, measured by RT-PCR, and (iv) immunoreactivity of $P2X_3$ in DRG (L6-S1).
Results
The urodynamic data showed that the muscarinic responsiveness in terms of maximum detrusor pressure (Pdet,max) of the OR+E group was improved compared to that of the OR group (Figure 1). As shown in Table 1, maximal micturition volume significantly increased in the OR+E group. Intravenous administration of muscarine significantly decreased the intercontraction interval (ICI) during continuous cystometrograms in the OR and OR+E groups (Figure 1). Moreover, the expression of M_2 receptor mRNA also significantly increased in these groups compared to the YR group (Table 2). Table 3 shows that estrogen treatment significantly induced the up-regulation of $P2X_3$ in DRG.

Table 1 Comparison of micturition behaviour in the experimental rats

	YR	OR	OR+E
Average micturition volume (ml)	0.8 ± 0.1	0.9 ± 0.1	1.3 ± 0.2
Maximal micturition volume (ml)	2.1 ± 0.3	1.8 ± 0.2	2.8 ± 0.4$^{\#}$

Table 2 Expression of muscarinic M_2 and M_3 receptor mRNAs in the bladder dome

	YR	OR	OR+E
M_2/β-actin (x 10^{-2})	0.33 ± 0.09	1.20 ± 0.47*	0.74 ± 0.20*
M_3/β-actin (x 10^{-2})	64.0 ± 14.8	69.1 ± 17.5	108.8 ± 32.5

Table 3 Proportion of immunoreactivity for P2X3 in dorsal root ganglia (L6~S1)

	YR	OR	OR+E
$P2X_3$ (%)	27.9 ± 1.2	31.2 ± 2.9	40.9 ± 2.6$^{*,\#}$

Each value represents the mean ± SEM. *: $p < 0.05$ compared with group YR.
$^{\#}$: $p < 0.05$ compared with group OR.

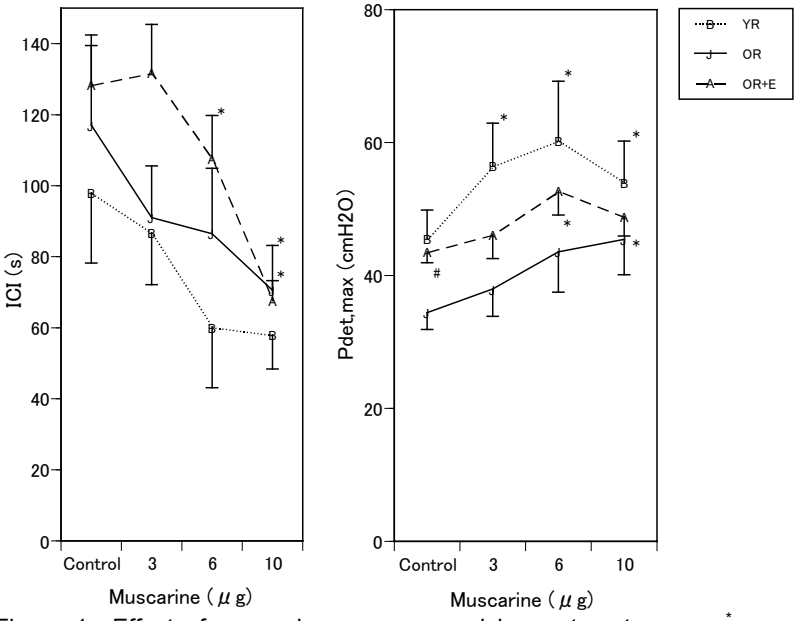

Figure 1 Effect of muscarine as measured by cystometrogram. *: $p < 0.05$ compared with Control. $^{\#}$: $p < 0.05$ compared with group OR.

Interpretation of results
Our findings indicate that estrogen maintained the detrusor contractile response to muscarine in old female rats. Previous studies have reported that estrogen increases the response of the detrusor to muscarinic agents *in vitro* [1], and that estrogen induces the functional hypertrophy of the detrusor muscle [2]. Thus, we speculate that estrogen resulted in the increase of force generation stimulated by muscarinic agents. On the other hand, the increase of M_2 receptors with age may be one of the factors which induced the decreased ICI by muscarine in the old female rats. These changes were not improved by estrogen treatment. Although an increase in maximal micturition volume by

estrogen was seen, the up-regulation of $P2X_3$ in DRG may possibly indicate the estrogen-induced hypersensitivity of the bladder.

Concluding message

These results suggest that aging has adverse effects on urinary bladder, and that estrogen treatment for 6 weeks improves detrusor contractility but has little effect to the storage phase of the micturition cycle.

References

1. J Urol (1992) **148**; 915-919.
2. J Urol (2002) **168**; 1265-1268.

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