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Kitta T[1], Tanaka H[1], Mitsui T[1], Kannno Y[1], Moriya K[1], Nonomura K[1], Yoshimura N[2]
1. *Department of Renal and Genitourinary Surgery, Graduate School of Medicine, Hokkaido University,* ***2.*** *Department of Urology, University of Pittsburgh School of Medicine*

DIFFERENTIAL EFFECTS OF AGING AND HORMONE DEFICIENCY ON URETHRAL CONTINENCE REFLEX DURING SNEEZING IN RATS

Hypothesis / aims of study

Stress urinary incontinence (SUI) is common in elderly, post-menopause women, suggesting that aging and estrogen deficiency contribute to its etiology. However, limited information is available for detailed pathophysiological effects of these etiological factors on urethral function. The present study therefore examined how aging and estrogen deficiency induced by ovariectomy (OVX) affect the urethral continence mechanism that prevents sneeze-induced SUI functionally and histologically in rats.

Study design, materials and methods

Young (3m) and aged (12m) female Sprague-Dawley rats underwent bilateral OVX or sham operation. After 3 or 6 weeks, urethral responses and immunohistochemical analyses were performed. (Figure 1)

Urethral responses were measured using a microtransducer-tipped catheter inserted to the middle urethra from the urethral orifice. The amplitude of urethral responses during sneezing (A-URS) and urethral baseline pressure (UBP) was evaluated. Sneeze was induced by a rat whisker inserted into the nostril. Apoptotic cells in tissue sections were detected by the TUNEL (TdT-mediated dUTP nick end labelling) method. The percentage of TUNEL positive cells were calculated and used as the apoptotic index (AI).

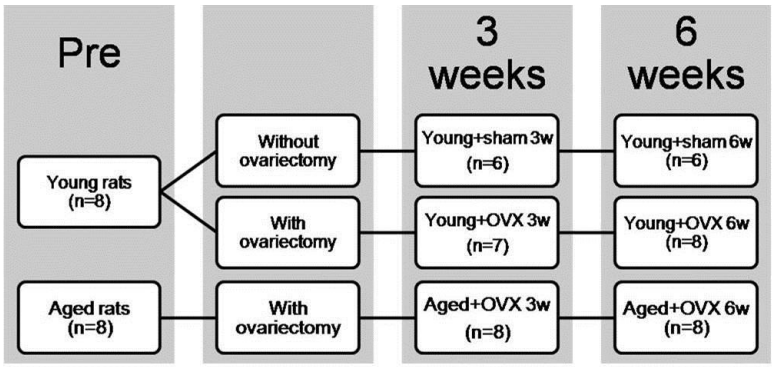

Figure.1 Study design

Results

In aged rats, UBP, but not A-URS, was significantly decreased than in young rats. In 3-week OVX rats, A-URS was significantly decreased compared to sham rats in both young and aged groups, and the OVX-induced reduction in A-URS was more pronounced in aged vs. young rats. Neither young, 3-week OVX nor sham rats leaked during sneezing. However, SUI occurred in 2 of 8 aged rats with 3-week OVX (Tables 1 & 2). After 6 weeks of OVX, sneeze-induced SUI was observed in 5 out of 8 young rats and 6 out of 8 aged rats (Table 2).

AI was significantly increased in urethral smooth muscles in aged rats; however, AI in the mucosa and striated muscle ware not significantly changed. In OVX rats, AI was increased only in the mucosa. (Figure 2)

Interpretation of results

The current results indicate that: (1) aging is more likely to impair smooth muscle function (represented by UBP) although degeneration of striated muscle occurs in aged rats based on the AI data, (2) despite the absence of overt incontinence during sneezing, A-URS was already decreased at an early stage (3 weeks) of OVX in young rats and (3) although any changes in AI of striated muscle were not detected, AI of the mucosa was significantly increased after ovariectomy. Mucosal apoptosis may indicate the impairment of urethral mucosa coaptation and/or decrease vascularity and tone.

Table 1

Urethral functions of various groups of rats

A-URS			
	Young		Aged
	Sham	OVX	OVX
Pre	29.0 ± 3.3		29.5 ± 3.9
3weeks	33.1 ± 3.6	23.5 ± 1.7*	16.2 ± 1.8†#
6weeks	31.4 ± 2.8	14.6 ± 1.9*	14.0 ± 2.6†#

UBP			
	Young		Aged
	Sham	OVX	OVX
Pre	26.7 ± 1.7		18.3 ± 1.9†
3weeks	27.0 ± 0.8	21.7 ± 2.0	19.6 ± 1.0†
6weeks	27.0 ± 1.2	14.6 ± 0.9*	15.7 ± 1.4†

All values are expressed in cmH_2O. $^{*}P<0.05$ $^{**}P<0.01$ compared with control values in each group of either sham operate (Sham) or ovariectomized (OVX) rats. Compared with same timeline group. †$P<0.05$ compared with the same timeline Sham group. #$P<0.05$ compared with the same timeline OVX group.

Table 2

The number of SUI rat and Sneeze-LPP (MEAN ± SEM cmH_2O) of various groups of rats

	Pre		3 weeks	6 weeks
Young	0/8	Sham	0/6	0/6
		OVX	0/7	5/8 (71.5 ± 8.2cmH_2O)
Aged	0/8	OVX	2/8 (76.9 ± 10.2cmH_2O)	6/8 (82.9 ± 5.9cmH_2O)

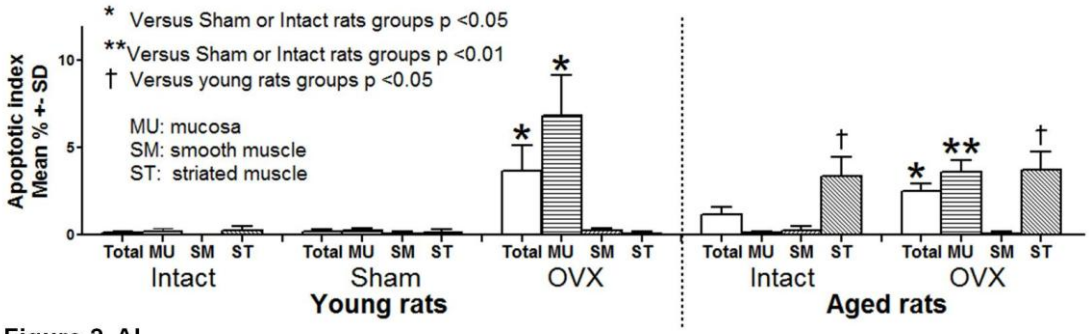

Figure.2 AI

Concluding message

Our data indicate that aging and estrogen deficiency have different effects on urethral function. Furthermore, both factors act as a precipitating cause to accelerate the disease process of SUI.

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**University of Pittsburgh Institutional Animal Care and Use Committee**