

## Characteristic Findings of Bladder Function in SERCA2a-Transgenic Rats

### Hypothesis / aims of study

The contractile activity of smooth muscle depends on intracellular Ca<sup>2+</sup> concentration, which is regulated by the activities of channels, transporters and pumps at cell and organellar membranes. Sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA) 2 is responsible for lowering Ca<sup>2+</sup>, leading to relaxation of smooth muscle. Similar molecular mechanism to cardiac muscle seems to act in bladder smooth muscle. However, in cardiac muscle, SERCA2 down-regulation occurs in the rat hypertrophy model [1], whereas it was reported that the deletion of a pair of SERCA2 allele protected bladder against hypertrophy in a murine model of partial bladder outlet obstruction [2]. The aim of the present study was to reveal the role of SERCA2 in formation of bladder hypertrophy using female SERCA2a-transgenic rats (TG) and wild-type rats (WT).

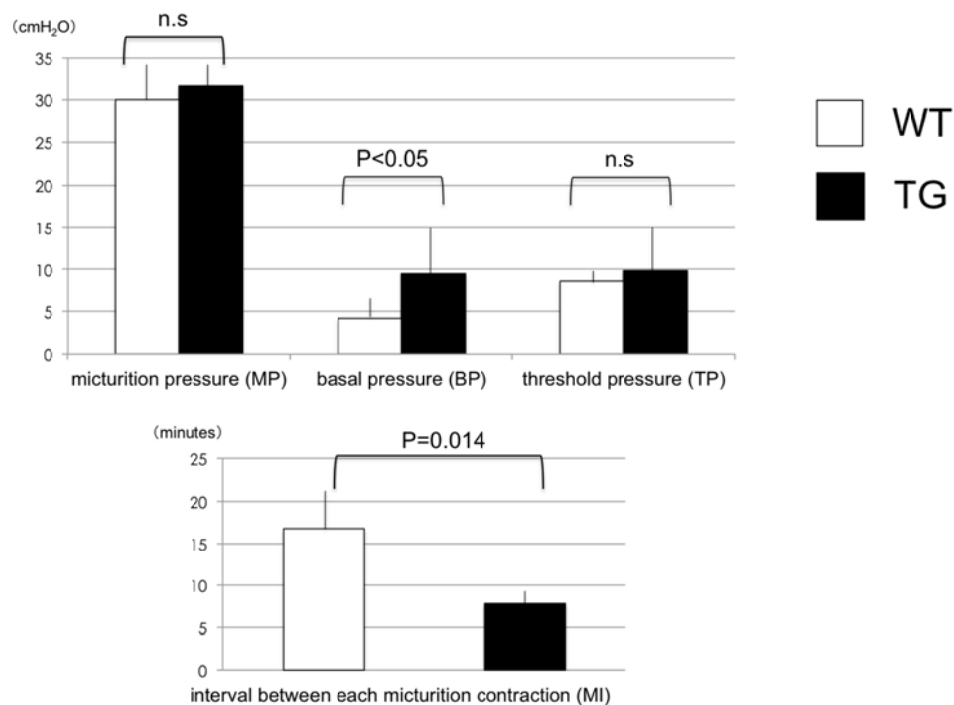
### Study design, materials and methods

A total of 15 female Wistar rats (TG:10; WT:5) were used in this study. Under halothane anesthesia, a polyethylene catheter (PE-50) with a cuff was implanted into the dome of bladder through an abdominal incision. Cystometry was performed in conscious conditions. Basal pressure (BP: the lowest pressure during filling), threshold pressure (TP: pressure just before micturition contraction), maximum pressure (MP: maximum pressure during micturition), and micturition interval (MI: interval between each micturition contraction) were measured. After cystometry the rats were sacrificed and the bladders were removed. Membrane proteins were used for Western blot analysis using a SERCA2 specific monoclonal antibody.

### Results

In cystometry, there were no significant difference in parameters between 10 TG and 5 WT groups. However, the bladders in 4 of 10 TG rats appeared to be hypertrophic and showed significantly shorter MI and significantly higher BP than other 6 TG and WT rats ( $P<0.05$ )(Fig. 1 and 2). In these 4 TG rats, the expression of SERCA2 protein was higher than other 6 TG rats.

(Fig.1) WT(n=5) vs. TG(n=4)



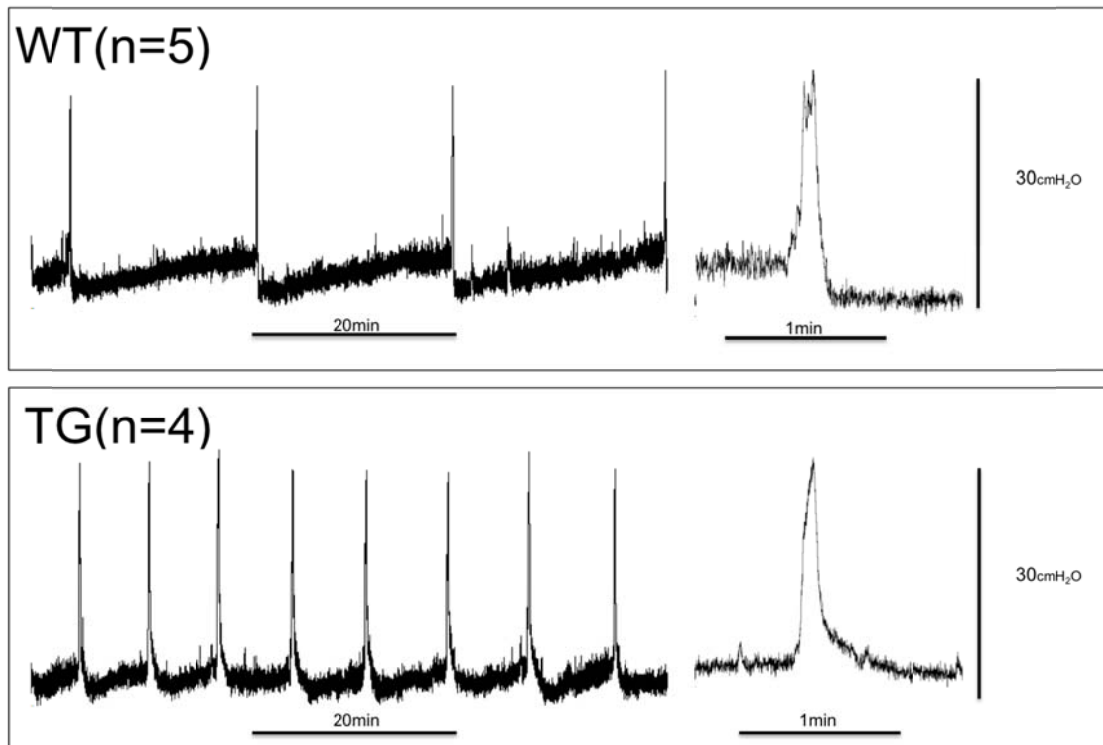
### Interpretation of results

The amount of SERCA2 protein supposed to be dependent on homo or hetero condition of SERCA2 gene in TG group. The SERCA2a-rich bladder showed lower compliance and detrusor overactivity while non-SERCA2a-rich bladder did not, suggesting that the SERCA2-rich bladder functionally resembles hypertrophic bladder. The SERCA2a-rich bladder showed higher vesical pressure after micturition because the relaxation function of bladder may have been impaired, resulting in increased micturition frequency.

### Concluding message

Overexpression of SERCA2 in bladder affected bladder function, inducing lower compliance and detrusor overactivity. The functional changes partially resembled hypertrophic bladder induced by its outlet obstruction. The intervention in SERCA2-related pathway can be a novel treatment for bladder hypertrophy if we could demonstrate that overexpression of SERCA2 accelerates formation of bladder hypertrophy induced by partial outlet obstruction.

## (Fig.2) Typical charts of cystometry



### References

1. Aoyagi T et al. The sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA2) gene promoter activity is decreased in response to severe left ventricular pressure-overload hypertrophy in rat hearts. *J Mol Cell Cardiol.* 1999 Apr;31(4):919-26.
2. Jenny Lassmann et al. Deletion of one SERCA2 allele confers protection against bladder wall hypertrophy in a murine model of partial bladder outlet obstruction. *Am J Physiol Regul Integr Comp Physiol* 294: R58–R65, 2008.

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<b>Is this a clinical trial?</b>	<b>No</b>
<b>What were the subjects in the study?</b>	<b>ANIMAL</b>
<b>Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?</b>	<b>Yes</b>
<b>Name of ethics committee</b>	<b>the animal care of use committee of Nara Medical University</b>