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HIGH SALT LOADING INDUCES URINARY STORAGE DYSFUNCTION VIA UPREGULATION OF EPITHELIAL SODIUM CHANNEL-ALPHA IN DAHL SALT-SENSITIVE RATS

Hypothesis / aims of study

Hypertension is known as one of the risk factors for nocturia and/or urinary frequency. Urinary storage dysfunction has been also identified in animal models of salt-sensitive hypertension, such as Dahl salt-sensitive (DS) rats [1]. However, the mechanisms underlying storage dysfunction induced by high salt loading are unknown. In this study, we focused on the epithelial sodium channel (ENaC), which acts as a mechanosensor in the bladder epithelium [2]. ENaC is expressed in the kidneys and upregulated by high salt loading [3]. Thus, we investigated whether high salt intake alters the expression of ENaC in the bladder and affects bladder function.

Study design, materials and methods

Six-week-old male Dahl salt-resistant (DR) and DS rats were fed a high-salt diet (8% NaCl, w/w) for one week. Then, heart rate, blood pressure, and body weight were measured, and cystometry was performed under intrabladder infusion of saline (80 µl/min), followed by infusion of amiloride, an ENaC inhibitor, in saline at the same speed. Localization and expression levels of ENaC-α protein in the bladder were evaluated by immunohistochemistry and western blot analysis. The two-sided Student's t-test was used to evaluate differences between the DS and DR rats, while the paired t-test was used to compare pre- and post-intervention differences.

Results

There was no difference in bladder-to-body weight ratio between DR and DS rats. Systolic and diastolic blood pressures were significantly higher in DS rats than in DR rats after treatment. The intercontraction intervals (ICI) were significantly shorter in the DS group than in DR group during saline infusion (Figure 1A,B). Subsequent infusion of amiloride significantly prolonged ICI in DS group, while no intragroup difference in ICI was observed in the DR group (Figure 1A,B). No intra- or intergroup differences in maximum intravesical pressure were observed (Figure 1A,C). Protein expression levels of ENaC-α in the bladder were significantly higher in the DS group than in the DR group. ENaC-α protein was localized at the bladder epithelium in both groups similarly.

Interpretation of results

High salt intake induced storage dysfunction with the upregulation of ENaC-α in the bladder epithelium in DS rats. This storage dysfunction was inhibited by infusion of amiloride, an ENaC-α inhibitor, suggesting that high salt induced storage dysfunction via ENaC-α. Amiloride did not change the intercontraction intervals and the expression of ENaC-α in DR rats treated with high salt. The data also suggested that overexpression of ENaC-α is involved in storage dysfunction in salt-sensitive rats.

Concluding message

High salt intake is considered to cause urinary storage dysfunction via the upregulation of ENaC-α in the bladder epithelium in rats with salt-sensitive hypertension, suggesting that ENaC-α might be a candidate therapeutic target for this pathological condition.

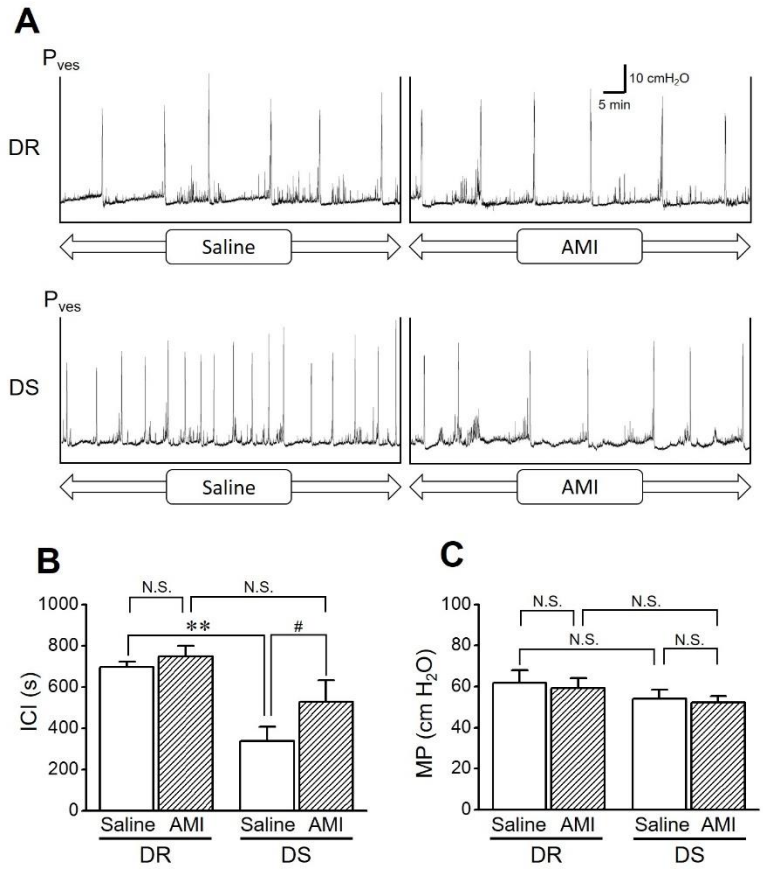

Figure 1 Cystometrography results. A) Representative cystometrograms of DS and DR rats after infusion of saline and amiloride (AMI). B) Intercontraction intervals in DS and DR rats after infusion of saline and amiloride. C) Maximum intravesical pressure in DS and DR rats after infusion of saline and amiloride. n = 5 in each group. **P < 0.01 vs. DR rats. #P < 0.01 vs. saline. N.S., not significant. Pves, intravesical pressure.

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Disclosures
Funding: none **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** The Animal Care and Use Committee of Nagoya City University