

THE ROLE OF NRF2 IN THE PATHOGENESIS OF ISCHEMIA-INDUCED BLADDER OVERACTIVITY

Hypothesis / aims of study

Pelvic ischemia induces bladder overactivity by stimulating the bladder and its afferent nerve. Nuclear erythroid related factor 2 (Nrf2) protects cells from oxidative stress; however, its role in the pathogenesis of ischemic bladder overactivity is unknown. The current study examined the relationship between Nrf2 expression and bladder overactivity using a pelvic ischemia mouse model.

Study design, materials and methods

C57BL/6 mice were divided into six groups: normal, mild ischemia, severe ischemia, normal + sulforaphane, mild ischemia + sulforaphane, and severe ischemia + sulforaphane. Pelvic ischemia was induced by L-NAME added to the drinking water (0.3 g/L or 1.0 g/L) from day 1 to 7. Sulforaphane was also given in drinking water from day 0 to 7. On day 7, blood flow in the capillary vessels on the bladder surface was measured using a CCD camera, cystometrogram was performed in the awake condition (infusion speed; 0.5 mL/h), and the bladder was excised for histological evaluation.

Results

Immunohistochemical staining showed that Nrf2 was mainly expressed in the urothelium and was translocated from the cytoplasm to the nucleus in the ischemia groups. Sulforaphane increased Nrf2 expression. The bladder microcirculation was disturbed in the ischemia groups (Figure 1). Cystometrogram demonstrated that the intercontraction intervals were shorter in the ischemia groups in a dose-dependent manner. Sulforaphane prolonged the micturition intervals in the ischemia groups (Figure 2).

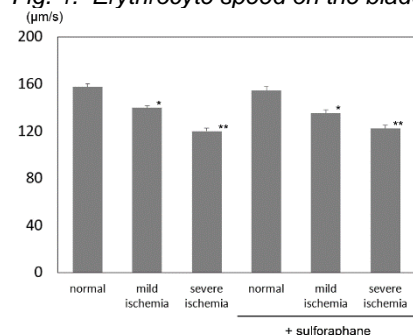
Interpretation of results

Activation of the Nrf2 signaling pathway, which leads to the upregulation of antioxidative genes has been reported to protect neurons against neurodegenerative diseases, promote myocyte differentiation and muscular contractile and metabolic properties in a diabetic muscle atrophy model, and protect various cells from apoptosis. The current study demonstrated that Nrf2 translocated from the cytoplasm to the nucleus in the pelvic ischemia groups. We interpret this as a response to protect organs from ischemic injury. Meanwhile, the Nrf2 upregulation induced by the administration of sulforaphane suppressed bladder overactivity. These results suggest that Nrf2 could be a therapeutic target for ischemia-induced overactive bladder.

Concluding message

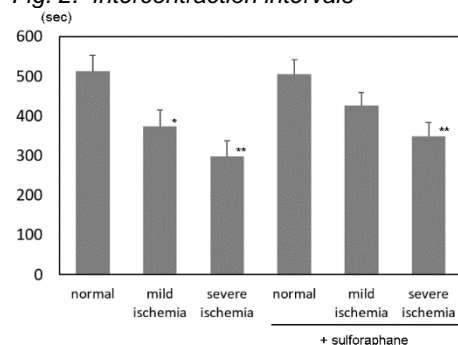
Pelvic ischemia induced bladder overactivity and translocation of Nrf2 to the nucleus. Upregulation of Nrf2 suppressed ischemia-induced bladder overactivity.

Fig. 1. Erythrocyte speed on the bladder surface



*, $p < 0.05$ and **, $p < 0.01$ compared to the normal group

Fig. 2. Intercontraction intervals



*, $p < 0.05$ and **, $p < 0.01$ compared to the normal group

Disclosures

Funding: Nagoya University Institutional Animal Care and Use Committee **Clinical Trial:** No **Subjects:** ANIMAL **Species:** mouse
Ethics Committee: Japanese Grants-in-Aid for Scientific Research