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NRF2 ACTIVATION ATTENUATES ISCHEMIA-INDUCED DETRUSOR OVERACTIVITY BY DOWNREGULATING ASSOCIATED ENDOPLASMIC RETICULUM STRESS, AUTOPHAGY, AND APOPTOSIS IN RAT BLADDER

Hypothesis / aims of study

Atherosclerosis-associated pelvic ischemia has been reported to be a risk factor for bladder dysfunction and subsequent lower urinary tract symptoms (LUTS) in the elderly population. However, the molecular mechanisms of this association remain unclear. We hypothesized that stress-induced cellular responses might play a role in the pathogenesis of ischemia-induced bladder dysfunction.

Study design, materials and methods

In the present study, the animal model of bladder ischemia was induced by bilateral partial arterial occlusion (BPAO) in rats. We utilized a transcystometric model to measure micturition alterations in the bladder in response to BPAO. The rats were divided into 4 groups: sham control, 2 weeks of ischemia (2WBI), 4 weeks of ischemia (4WBI), and 4WBI with treatment.

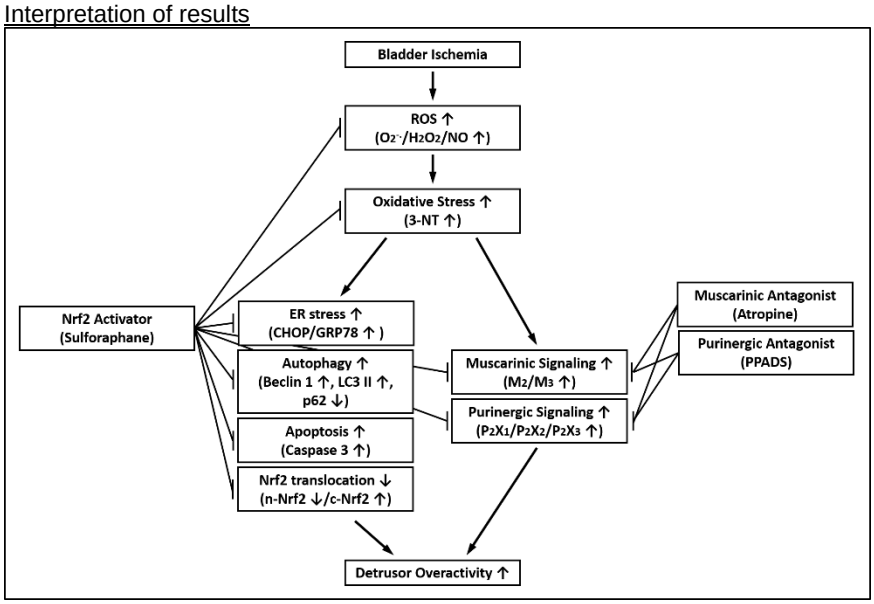
The presence of cellular reactions in response to ischemia including endoplasmic reticulum (ER) stress (78 kDa glucose-regulated protein, GRP78 and C/EBP-homologous protein, CHOP), autophagy (Beclin-1, p62 and LC3 II), apoptosis (caspase 3) and the Kelch-like ECH-associated protein 1–nuclear factor erythroid-2-related factor 2 (Keap1–Nrf2) pathways, as well as the changes in muscarinic (M_2 and M_3) and purinergic (P_2X_1, P_2X_2, and P_2X_3) receptors in bladder smooth muscle layer tissues were analyzed by Western blot and immunohistochemical staining.

To investigate the drugs' effects on BPAO-induced detrusor overactivity (DO), the 4WBI group was treated daily with the selective purinergic P_2X antagonist (PPADS), muscarinic antagonist (atropine) and Nrf2 activator (sulforaphane).

Results

We found that BPAO significantly induced the presence of DO and upregulated the expression of several molecular reactions, including biomarkers in ER stress (GRP78 and CHOP), autophagy (Beclin-1, p62 and LC3 II) and apoptosis (caspase 3). BPAO also disturbed the Keap1–Nrf2 pathways. These responses might collectively alter muscarinic and purinergic signaling and contribute to the presence of DO in the ischemic bladder. Therapeutically, treatment with neither a muscarinic nor purinergic receptor antagonist restored bladder function. Interestingly, activation of the Nrf2 pathway by sulforaphane effectively attenuated the cellular responses and ameliorated ischemia-induced bladder dysfunction.

Interpretation of results



Concluding message

In conclusion, the present study found that BPAO significantly induced the presence of GRP78/CHOP-mediated ER stress, Beclin-1/p62/LC3 II-mediated autophagy, caspase 3-mediated apoptosis, and Keap1-Nrf2 signaling disturbances in the bladder. These responses possibly lead to alterations in bladder neurotransmission and contribute to the development of ischemia-induced DO. Treatment with the Nrf2 activator SR but not a muscarinic or purinergic antagonist effectively ameliorated ischemia-induced bladder dysfunction.

References

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Disclosures

Funding: None **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Wistar rats **Ethics Committee:** All of the animal surgical and experimental procedures were approved by the Institutional Animal Care and Use Committee of National Taiwan University, College of Medicine and College of Public Health (approval no. 20090278), and were performed in accordance with the guidelines of the National Science Council of the Republic of China (NSC 1997).