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INDUCTION OF HYPOXIA GENES EXPRESSION IN VOIDING DYSFUNCTION FROM LONG TERM BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study
Hypoxic changes of the bladder induced by long term bladder outlet obstruction (BOO) could be the cause of bladder dysfunction. Increased bladder thickness and low oxygen conditions activate the hypoxia signaling pathway primarily via the hypoxia inducible factor (HIF) transcription factor as the response to BOO. Hypoxia inducible target genes mediate multiple biological functions such as angiogenesis, hematopoiesis, maintenance of vascular tone to provide and supply tissues with blood and oxygen. Therefore, we designed this study to investigate to obtain an expression profile of hypoxia related genes in voiding dysfunction from long term bladder outlet obstruction.

Study design, materials and methods
Fifteen 6-week old female Sprague-Dawley rats were divided into 3 groups, 5 rats each, group 1: control, group 2: sham operation, group 3: BOO for 8 weeks and bladder dysfunction with the volume of residual urine more than 4 ml. Eight weeks after the onset of BOO, cystometric evaluation was performed, and bladder tissues were processed for PCR array. The first strand cDNA synthesis was performed with 2 μg of total RNA. Each array consists of 84 genes known to be involved in the hypoxic response, cell differentiation, and metabolism, as well as 12 sequences to control for loading and cDNA quality. Genes were considered to be up-regulated or down-regulated.

Results
In group 3, BOO induced the thickened bladder wall and bladder dysfunction compared with control and sham operation group. 8 genes were at least 2-fold up-regulated, and 3 genes were at least 2-fold down-regulated in BOO, compared with Sham group. The up-regulated genes (fold change) by BOO belong to Blm (5.2), Cdkn2a (11.0), Erg1 (4.2), F10 (30.1), Hmox1 (6.1), Lox (6.0), Mmp9 (74.7), Serpine1 (11.0) and the down-regulated gene belong to Hif3a (-39.6), Lgfbp3 (-7.0) and Per1 (-5.1). HIF and Co-transcription factors included Hif3a and Per1. Other HIF1 interactor included Cdkn2a. Angiogenesis included Erg1, Mmp9, Serpine1, Lox and Hmox1. Coagulation included F10 and Serpine1. Lgfbp3 included regulation of cell proliferation. Genes were influenced each other through TGFβ1, TNF and TP53.
Interpretation of results
This results demonstrated that angiogenesis genes were enhanced in voiding dysfunction from long term BOO.

Concluding message
The gene expression profiles could explain changes of hypoxia in voiding dysfunction from long term BOO.

Disclosures
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