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OXIDATIVE STRESS-RESPONSIVE GENES REGULATE ULTRASTRUCTURAL CHANGES OF THE OVERACTIVE BLADDER

Hypothesis / aims of study: It has been shown that hemodynamic disturbances and rapid changes of bladder blood flow and oxygen tension induce hypoxia/reoxygenation and lead to free radicals in the overactive bladder. We hypothesize that overactivity-associated oxidative stress plays an important role in structural deterioration of the overactive bladder. Our goal was to examine the roles of oxidative stress-responsive genes and oxidatively modified products in structural changes of the overactive bladder.

Study design, materials and methods: The rabbit model of overactive bladder was developed by inducing atherosclerosis-induced ischemia and hypoxia. Bladder ischemia/reperfusion and hypoxia/reoxygenation were determined using laser Doppler blood flowmetry and oxygen sensing electrodes, respectively. Cystometrograms from 8 weeks (n=5) and 16 weeks (n=5) overactive bladders were compared with age-matched controls (n=5). Bladder tissues were processed for analysis of oxidative stress-responsive genes hypoxia inducible factor (HIF), superoxide dismutase (SOD), aldose reductase (ALDR), vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-beta) using quantitative real-time PCR. Oxidatively modified products were measured by enzyme immunoassay. Bladder vascular density, smooth muscle content and ultrastructure were examined by immunohistochemical staining, histomorphometry and transmission electron microscopy (TEM), respectively.

Results: Arterial atherosclerosis and subsequent reduction of blood flow and oxygen to the pelvis led to an overactive bladder. Significant overactivity was evident in the 8 and 16 weeks ischemic bladders. Oxidative stress-responsive genes SOD, ALDR and transcriptional HIF were significantly upregulated in the 8 and 16 weeks overactive bladders. Oxidatively modified products progressively accumulated in the 8 and 16 weeks overactive bladders. Gene expression of VEGF and TGF-beta at 8 and 16 weeks after the induction of bladder overactivity followed virtually the same pattern as HIF and ALDR with significant correlation. These molecular changes in the overactive bladder were associated with microvascular degeneration, loss of smooth muscle, increased connective tissue and new microvascular outgrowth. TEM revealed ultrastructural changes in the overactive bladder typical of oxidative damage characterized by swollen mitochondria with disrupted membrane, loss of mitochondrial granules, endoplasmic reticulum (ER) atrophy and fragmentation, along with diffuse epithelial vacuolization, disrupted fascicles with separated and twisted muscle cells and protrusion junctions.

Interpretation of results: Upregulation of HIF, SOD and ALDR gene expression implies overactive bladder reaction to oxidative stress. Alterations of VEGF and TGF-beta gene expression in a similar manner as HIF and ALDR may suggest oxidative regulation of vascular and fibrotic growth factors in the overactive bladder. Ultrastructural changes in association with mitochondrial and ER damage and accumulation of oxidative products imply oxidative injury in the overactive bladder.

Concluding message: The overactive bladder undergoes continuing oxidative stress as a result of recurring ischemia/reperfusion and hypoxia/reoxygenation. Oxidative stress triggers a cascade of molecular reactions in the overactive bladder involving oxidation sensitive genes. Ultrastructural alterations of the overactive bladder appear to involve free radical injury and oxidative modification of vascular (VEGF) and fibrotic (TGF-beta) growth factors. Oxidative structural damage characterized by microvascular degeneration, smooth muscle atrophy and fibrosis may contribute to non-compliance of the overactive bladder.

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