

ISCHEMIA SURVIVAL SIGNALING VIA PI3-K/AKT PATHWAY MEDIATES OVERACTIVE BLADDER PROGRESSION TO UNDERACTIVE BLADDER

Hypothesis / aims of study

Underactive bladder is an under-researched area that imposes major clinical challenges both in terms of accurate diagnosis and effective treatment. Underactive bladder is a common cause of lower urinary tract symptoms (LUTS) in both men and women. The specific features of aging bladder contributing to underactivity remain unknown. It is thought that aging-related comorbidities influence bladder neurotransmission, reduce sensation, impairs smooth muscle contractions and lead to an underactive bladder, characterized by prolonged emptying and/or a failure to achieve complete emptying within a normal time span. Clinical studies suggest that, in most cases, bladder underactivity in elderly patients is preceded by bladder overactivity, suggesting potential mechanisms that initiate overactivity then exhaust the bladder contractile apparatus and lead to underactivity [1]. However, aging-associated comorbidities contributing to overactive bladder progression to underactive bladder remain essentially unknown. We hypothesized that aging-associated peripheral arterial insufficiency and prolonged bladder exposure to ischemia may play a role in overactive bladder transition to underactive bladder. Our concept is supported by a close correlation between severity of LUTS and degrees of bladder ischemia documented in both men and women [2]. It was shown that bladder blood flow decreases with aging in both sexes [2]. Maximum urine flow rate in patients with bladder ischemia is significantly lower than controls [2]. Animal studies have shown that early-stage ischemia induces bladder overactivity, while prolonged ischemia impairs spontaneous bladder contractions and smooth muscle contractile reactivity [3]. Our goal was to investigate voiding behavior, cystometrograms (CMG), and molecular responses to ischemia after short-term (8 weeks) and long-term (16 weeks) bladder arterial insufficiency in a rat model.

Study design, materials and methods

Male Sprague-Dawley rats were randomly divided into treatment, sham, and age-matched control groups. The treatment group was placed on a 2% cholesterol diet for two weeks then, under general anesthesia, iliac artery ballooning was performed using a 2F Fogarty catheter. After the ballooning procedure, the treated animals were placed on a 2% cholesterol diet to create aorto-iliac atherosclerosis and bladder ischemia. The sham group underwent similar procedures without arterial ballooning and received a regular diet. The age-matched control group did not undergo any procedure and received a regular diet. Subgroups of animals underwent metabolic cage studies, hemodynamic measurements, and CMG at 8 weeks and 16 weeks after the induction of bladder ischemia. Bladder tissues were processed biochemical assays, molecular analysis and transmission electron microscopy (TEM).

Results

Aorto-iliac atherosclerosis decreased iliac artery and bladder blood flow resulting in varying degrees of bladder ischemia. At 8 weeks, 60% of treated group developed moderate bladder ischemia (MBI) and 40% had severe bladder ischemia (SBI). At 16 weeks, 30% of treated group had MBI and 70% had SBI. Voiding behaviour changes in metabolic cage and CMGs in early-stage ischemia (8 weeks) indicated bladder overactivity, while changes in long-term ischemia (16 weeks) were consistent with bladder underactivity. Metabolic cage studies showed increased micturition frequency (MF) and decreased voided volume (VV) in short-term MBI and SBI and long-term MBI. Long-term SBI decreased MF but did not alter VV. CMG showed marked fluctuations in intravesical pressure in MBI and decreased contractile activity in SBI. With filling, pre-micturition pressure increased and bladder compliance decreased in short-term MBI and SBI and in long-term MBI. In long-term SBI, pre-micturition pressure and bladder compliance decreased and residual volume increased. These changes in early-stage and long-term bladder ischemia were associated with markers of free radical incursion and progressive accumulation of oxidative products. Bladder overactivity in MBI was associated with activation of cell survival signaling via phosphoinositide 3-kinase (PI3-K)/protein kinase B (Akt) pathway, characterized by significant increases in PI3-K and phosphorylated Akt expression. Underactivity in long-term SBI was associated with loss of survival signaling characterized by significant decreases in PI3K and phosphorylated Akt expression. Activation of PI3-K/Akt pathway in MBI increased muscarinic M2 receptor expression and smooth muscle contractile reactivity. Impairment of PI3-K/Akt pathway in long-term SBI upregulated M1 expression, downregulated M3 expression and led to lack of smooth muscle contractile reactivity. TEM showed mitochondrial structural damage in MBI and decreased mitochondrial density in SBI.

Interpretation of results

Cell survival signaling via PI3-K/Akt pathway appears to regulate bladder responses to varying degrees and durations of ischemia. In moderate ischemia, the bladder coordinates a series of molecular responses mediated by PI3-K/Akt pathway to promote cell survival and preserve functional integrity of the nerves, smooth muscle cells, and microvascular. These defensive reactions appear to result in differential muscarinic receptor expression, smooth muscle hypersensitivity, and increased contractile activity. In long-term severe ischemia, the PI3-K/Akt pathway fails and the bladder undergoes numerous adaptations to cope with lack of nutrients and extreme levels of hypoxia. These adaptations disrupt muscarinic receptor expression, exhaust the bladder energy transduction system due to increased metabolic capacity, and lead to mitochondrial damage, impaired contractile dysfunction and underactivity.

Concluding message

Our data supports the concept of overactive bladder progression to underactive bladder. Functional consequences of bladder ischemia appear to depend on the severity and duration of pelvic arterial insufficiency. Prolonged ischemia may play a key role in mediating overactive bladder transition to underactive bladder. The mechanism appears to involve ischemia-mediated survival pathway, disruption of muscarinic M1, M2 and M3 receptors, and impairment of mitochondrial energy transduction system.

References

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Disclosures

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