Partial Bladder Outlet Obstruction: Bladder Dysfunction and Related Issues in Animal Studies

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Bladder dysfunction following partial bladder outlet obstruction (PBOO) is a frequent consequence of benign prostate enlargement in aging males. Bladder dysfunction also occurs in both postmenopausal women and women with PBOO, and results from various etiologies such as anti-incontinence surgery or pelvic organ prolapse. These problems can be attributed to bladder outlet obstruction induced by secondary detrusor functional changes. In addition, PBOO often occurs in children with congenital abnormalities in the lower urinary tract, and leads to voiding dysfunction. Animal models of PBOO are useful for understanding many aspects of the pathophysiologic process. In this review, we describe the studies of bladder dysfunction and related issues based on animal models of PBOO.

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1. Introduction

Bladder dysfunction secondary to partial bladder outlet obstruction (PBOO) is a common problem in aging males with benign prostate hyperplasia. Bladder dysfunction also occurs in both postmenopausal women as well as women with PBOO, and results from various etiologies such as anti-incontinence surgery or pelvic organ prolapse. In addition, PBOO often occurs in children with congenital abnormality of the lower urinary tract, and leads to voiding dysfunction. Animal models of PBOO include in vivo models that show changes in structural, functional and molecular levels similar to those in humans, and have provided an understanding of many aspects of the pathophysiology.\textsuperscript{1,2}

2. PBOO and Oxidative Stress

2.1. Oxidative stress as a biomarker

Ischemia followed by reperfusion injury is one of the primary etiologies of progressive bladder dysfunction in a variety of animal models of PBOO.\textsuperscript{3,4} Lin et al.\textsuperscript{5} showed that urinary bladder blood flow is reduced by outlet obstruction, and the reduction in blood flow is associated with a decreased tissue content of high-energy phosphates. Greenland and Brading\textsuperscript{6} further demonstrated that bladder outflow obstruction is associated with repeated episodes of prolonged detrusor ischemia, which may account for the biochemical and neuronal alterations in such
bladders. Cyclic episodes of ischemia–reperfusion (IR) lead to both direct ischemic damage and the generation of free radicals. Both reactive nitrogen species and reactive oxygen species (ROS) can result in damage of membranes and subcellular organelles. Nitrotyrosine and protein carbonylation are markers of free radical damage due to reactive nitrogen species and ROS. Their expressions are significantly elevated with PBOO, but are then decreased after reversal of PBOO.4,7–9

PBOO reduces the tissue antioxidant capacity. Severely reduced activities of superoxide dismutase and catalase are associated with decompensated function of the bladder after 8 weeks of obstruction.10 In addition, glutathione and the glutathione reductase levels, which represent the total antioxidant capacity, are significantly decreased in obstructed bladders compared with controls.11

### 2.2. Application of antioxidants for intervention

Products (such as Kohki tea, grapes, edaravone, Pygeum africanum, coenzyme Q10, and α-lipoic acid) with strong antioxidant and cell membrane protective properties have protective effects against the damage mediated by both PBOO and IR as shown by *in vivo* and *in vitro* models.12–16 Coenzyme Q10, which is a lipid-soluble cofactor found in mitochondria, has been reported to have neuroprotective and antiapoptotic effects. In rabbits subjected to IR injury, Juan et al.17 demonstrated that pretreatment with coenzyme Q10 had a protective effect on the expression of vesicular acetylcholine transporter (a cholinergic nerve marker) by neurofilament immunostaining. The combination of two antioxidants could further enhance the contractile response and diminish contractile dysfunction induced by ischemia injury.16

### 2.3. Nitric oxide: a controversial role in oxidative stress

Nitric oxide (NO) is known to be a powerful and ubiquitous regulator of vascular tone, and has been shown to regulate blood flow in several systems. In cardiac studies, impaired release of NO may be an important factor in the development of IR injury. Administration of NO donors or L-arginine reduces infarct size and improves the post-ischemic recovery of cardiac performance and endothelial function in myocardial ischemia and reperfusion animal models.18–20 Other studies have shown that exogenously administered L-arginine may decrease oxidative stress in the liver and brain.21 In contrast, an increase in NO formation has a beneficial effect on progression of cellular and molecular parameters of tubulointerstitial fibrosis caused by obstruction of the ureter.22 With regard to bladder function, a previous study demonstrated that a high L-arginine diet fed to rabbits is beneficial in both control rabbits and those with 2 weeks of severe PBOO.23

In contrast to the above reported protective effects, NO can generate free radicals in IR injury, which has been shown in other studies to be one of the primary causes of progression of bladder dysfunction.24 It has been demonstrated that NO-related damage due to nitrotyrosine is elevated with PBOO.25 Pretreatment with N^6^-nitro-L-arginine methyl ester (L-NAME), which acts as a competitive inhibitor of NO synthase (NOS), significantly inhibits the generation of nitrotyrosine.26 Saito et al.27–29 showed that treatment with L-NAME can reduce apoptosis induced by IR in the bladder and significantly increases the contractile responses compared with IR without L-NAME.

Lin et al.30 investigated the influence of NOS activity on the response of chronic PBOO in rabbits. They demonstrated that increasing blood flow by stimulating NOS in L-arginine-pretreated rabbits significantly protects the bladder from PBOO dysfunction, which can further be enhanced by L-NAME-inhibited blood flow.

### 3. PBOO and Age

In response to repeated electro-stimulations, aged rat bladders become fatigued faster than young bladders. A decreased capability to produce energy (phosphocreatine and adenosine triphosphate concentrations) might be one contributing factor for faster exhaustibility of aged urinary bladders.31 Yu et al.32 demonstrated that aged rabbits are unable to maintain a suitable bladder contraction to empty urine completely through an increased outlet resistance. Guven et al.33 compared the physiologic and structural changes after short-term PBOO in young and old rabbits. In young rabbits, the responses to field stimulation decreased progressively for the first, third and seventh day, and increased significantly on the 14th day. In old rabbits, there was a progressive decrease in response to field stimulation to a minimal response by the third day of PBOO, and the response remained at this level over 14 days. In the young rabbits, nerve density was decreased more than that in old rabbits with PBOO. In the older group, the smooth muscle to collagen ratio was increased throughout the duration of PBOO and was higher than that in young rabbits. The compartment of connective tissue was considerably greater than in the young rabbits. In addition, the basal mucosa of old rabbits had vacuoles that were not apparent in young bladders.

Guven et al.34 examined the expression of Rho-kinase (ROK) isoforms in the detrusor smooth muscles of young and old rabbits during the progression of short-term PBOO. ROK was correlated with the time course of bladder outlet obstruction. In young rabbits, the expression of ROK-α was increased in the 1- to 7-day obstructed groups and was decreased in the 14-day group. However, ROK-α increased progressively in old rabbits at both the messenger RNA and protein levels. Compared with ROK-α, there was a significant inverse decrease in the expression of ROK-β in young obstructed rabbits, which gradually decreased during the course of the 1- to 7-day obstruction.
period and increased after 14 days of obstruction. In the older group, there was a decrease in expression after 1 day of obstruction and this decreased level remained throughout the course of the study. These studies concluded that the adaptive changes to PBOO are faster in younger rabbit bladders than in older rabbits. Guven et al. compared mitochondrial and SR function after short term PBOO in young versus old rabbits by measuring thapsigargin-sensitive sarco/endoplasmic reticulum Ca\(^{2+}\) ATPase activity and citrate synthase. Their results indicated that the urinary bladders of young rabbits have a considerably greater ability to adapt to PBOO than those of old rabbits.

4. PBOO and Acute Urinary Retention

4.1. Effect of acute urinary retention on the bladder

The effect of acute urinary retention (AUR) on either the bladder or other organs is an interesting issue that needs to be clarified. A study designed by Tong et al. evaluated whether acute distention of the urinary bladder can induce an increase in DNA synthesis ([\(^{3}H\)]-thymidine incorporation). Their results showed that acute overdistention for 8 hours induced a slight decrease in the DNA concentration, which was mediated by edematous changes in the bladder wall. A fivefold increase in [\(^{3}H\)]-thymidine incorporation and a threefold increase were found in the bladder body and base, respectively. Radioautoradiography of the overdistended bladder showed significant and substantial labeling, which was confined within the urothelial basal cells. These results indicate that acute distention following partial outlet obstruction initiates the proliferative response of the bladder to outlet obstruction, and the urothelium is the initial target of the proliferative response.

Lin et al. investigated the existence and functional significance of enhanced lipid peroxidation in bladder injury due to overdistention and explored the effect of mannitol, a free radical scavenger. Results revealed that decompression of an overdistended bladder leads to enhanced lipid peroxidation, which is associated with an additionally decreased energetic metabolism and further impaired contractile function. Mannitol effectively prevents enhanced lipid peroxidation and facilitates functional recovery. These results show that ROS play a significant role in bladder injury resulting from overdistention.

Yu et al. investigated whether hypoxic preconditioning minimizes oxidative injury induced by overdistention/emptying in the rat bladder. Their results demonstrated that hypoxia preconditioning upregulates Bcl-2 expression in the bladder and significantly reduces the levels of ROS and apoptosis detected in overdistended/empty bladders, and preserves partial voiding function. Bcl-2 up-regulation by hypoxia preconditioning gives protection against overdistention and emptying-induced oxidative stress and injury in the bladder.

4.2. Effect of AUR on the liver

Yu et al. further investigated the complicated effect of AUR on other organs. They investigated whether the vesico-vascular reflex evoked by bladder overdistention could affect hepatic function, specifically ROS-induced inflammation and apoptosis through the activation of hepatic sympathetic nerves. Their results showed that AUR increases the hepatic sympathetic-dependent vesico-vascular reflex, which causes hepatic vasoconstriction/hypoxia and increased superoxide anion production from the periportal Kupffer cells and hepatocytes, which are aggravated by the increase in volume and duration of urinary retention. The ROS-enhanced proinflammatory nuclear factor \( \kappa \)B, activator protein-1, and intercellular adhesion molecule-1 expression also promote proapoptotic mechanisms including increases in the Bax to Bcl-2 ratio, caspase-3 (CPP32) expression, poly(adenosine diphosphate-ribose) polymerase cleavages, DNA fragmentation, and apoptotic cells in the liver.

5. Bladder Dysfunction and Estrogen

Estrogen is essential for mediating physiologic functions in the female bladder. Deficiency of estrogen has been speculated to be an etiologic factor for bladder dysfunction in postmenopausal women. Lin et al. investigated the changes in the contractile and regulatory proteins in female rabbits with ovariectomy and estrogen supplements. The results of their study provided further understanding about the role of contractile and regulatory proteins in detrusor muscle, in both dysfunctional atrophy induced by ovariectomy and functional hypertrophy induced by estrogen supplementation. Reduced circulating estrogen concentrations during and after menopause have been linked to various bladder dysfunctions including incontinence and recurrent urinary tract infections. Lin et al. further evaluated the effects of ovariectomy and estrogen therapy on free fatty acid (FFA) content, endogenous lipase activity, and phospholipid (PL) content of the urinary bladder. Both FFA and PL concentrations of the mucosa are approximately three times greater than those of smooth muscle. Ovariectomy significantly reduced FFA and PL concentrations in both muscle and mucosa, while estrogen therapy restored them to normal levels. Reduced FFA and PL contents in smooth muscle membranes decrease their fluidity and contribute to a decreased compliance and contractility.

Juan et al. investigated whether low-dose estrogen supplementation is as effective as high-dose estrogen in increasing bladder contractile function, mediating bladder hypertrophy and angiogenesis. Their results demonstrated that low-dose estrogen produces similar physiologic, morphologic and biochemical effects on the bladder as those for high-dose estrogen. Lin et al. further investigated the effect of estrogen on vasculature
density and distribution. They found that ovariectomy resulted in significant vascular degeneration and decreased density, whereas estradiol administration mediated a significant angiogenic effect characterized by increased vascular density and distribution of new vasculature within the smooth muscle bundles of the detrusor.

6. PBOO and Corpus Cavernosum Smooth Muscle

Growing clinical evidence suggests that benign prostatic enlargement-induced PBOO is associated with an increased incidence of erectile dysfunction. Chang et al. determined whether corpus cavernosum smooth muscle (CCSM) from rabbits with PBOO showed any molecular or functional differences versus controls. CCSM from rabbits with PBOO generated 40–50% more force than that of sham operation rabbits in response to potassium chloride or phenylephrine and relaxation was more difficult. An increased basal CCSM tone associated with an elevated level of smooth muscle myosin phosphorylation in PBOO was compared with sham operation control rabbits. Morphologic examination of CCSM sections revealed a decreased innervation and an increased smooth muscle bundle size in rabbits with PBOO compared with the sham surgery group. Chang et al. further demonstrated that increased smooth muscle myosin basal phosphorylation (necessary for smooth muscle contraction) in the CCSM of PBOO rabbits, which is mediated via increased ROK expression and activity, results in CCSM relaxation being more difficult (necessary for erection).

Lin et al. investigated the effect of different severities of bladder dysfunction on CCSM physiology, morphology and expression of ROK in rabbits. Their results showed that severe bladder dysfunction secondary to chronic PBOO induces significant physiologic dysfunctions of CCSM as well as morphologic changes. Activities of both ROK isoenzymes show an increase at 2- and 8-week obstructions. An increase in ROK expression and activity is expected to make relaxation more difficult for CCSM and also contribute to a reduction of electric field stimulation-induced relaxation of CCSM after chronic PBOO. Lin et al. also investigated the changes in CCSM related to reversal of PBOO in rabbits. They found that the poor relaxation response at 4 weeks of reversal was associated with incomplete decreased expression of both isoforms of ROK, whereas the incomplete recovery of CCSM relaxation response at 8 weeks of reversal may be associated with structural alterations in the corpus cavernosum and irreversible damage from PBOO.

7. Conclusion

PBOO is the initiator of a pathophysiologic cascade leading to structural and functional changes in the bladder. In this review, we described the recent studies exploring the pathologic mechanisms of bladder dysfunction, either secondary to PBOO or hormones. In particular, from the view point of oxidative damage, oxidative stress could be a biomarker for assessment of bladder dysfunction and follow-up of treatment. Numerous reports on PBOO revealed that there is profound impact on liver and penile function. Further studies on the complicated consequences arising from PBOO are required.

References


