JPP Journal of Pharmacy and Pharmacology

JPP 2007, 59: 837–842

Received October 26, 2006
Accepted February 19, 2007
DOI 10.1211/jpp.59.6.0009
ISSN 0022-3573

Montelukast reduces ischaemia/reperfusion-induced bladder dysfunction and oxidant damage in the rat

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Abstract

The present study aimed to investigate the possible beneficial effects of the cysteinyl leukotriene-1 receptor antagonist montelukast on contractility and oxidant damage after ischaemia/reperfusion (I/R) of rat urinary bladder. The abdominal aorta of Sprague-Dawley rats was occluded to induce I/R. Montelukast (10 mg kg^{-1}) or saline was administered intraperitoneally before I/R. In the sham-operated group, the abdominal aorta was left intact and the animals were treated with montelukast or saline. After decapitation, the bladder was removed and the tissue was either used for functional studies or stored for biochemical assays. In the I/R group, the isometric contractile responses of the bladder strips to carbachol (10^{-8}–10^{-4} M) were lower than those of the control group and were reversed by treatment with montelukast. Lipid peroxidation and myeloperoxidase activity of the bladder tissues in the I/R group were greater than in the sham-operated group. Montelukast treatment in the I/R group decreased these parameters compared with I/R alone. Similarly, the significant decrease in tissue glutathione level in the I/R group compared with controls was also prevented by montelukast. Treatment with montelukast almost completely reversed the low contractile responses of rat urinary bladder to carbachol and prevented oxidative tissue damage following I/R.

Introduction

Increasing evidence has suggested that bladder ischaemia as a result of a reduction of blood flow by surgical trauma could produce bladder dysfunction, such as a decrease in bladder contraction, compliance and capacity with increased post-voiding residual volume. Studies on preparations from whole bladder or bladder strips revealed significant bladder dysfunction following hypoxia or ischaemia (Lin et al 1995; Bratslavsky et al 1999). Reperfusion and re-oxygenation of ischaemic tissue generates reactive oxygen metabolites that cause lipid peroxidation of cellular membranes, and alters various cellular functions (Levin et al 1998; Ohnishi et al 1998). Thus, free radical reduction for the treatment of ischaemia/reperfusion (I/R) injury has found its first clinical application in the prevention of post-ischaemic organ dysfunction.

Leukotrienes (LT) are eicosanoids that are generated via biochemical pathways catalysed by lipoxygenase enzymes (Lewis & Austen 1984; Henderson 1994). They are components of the arachidonic acid cascade, which include prostaglandins, prostacyclins and thromboxanes, among other lipid mediators (Lewis & Austen 1984; Henderson 1994). Cysteinyl LTs (CysLTC4, D4 and E4) contract smooth muscles, particularly in the peripheral airways, and are regarded as pivotal mediators of bronchial asthma. In the microcirculation, they increase the permeability in post-capillary venules, which leads to extravasation of plasma. Thus, drugs that interfere with the biosynthesis and action of LTs have been marketed as novel medications against asthma and allergic rhinitis (Drazen et al 1999). LTs have also been detected in serum, urine and renal tissue during glomerular inflammation (Lianos 1988; Lianos & Noble 1989; Yared et al 1991; Petric & Ford-Hutchison 1994). In this setting, they have been implicated as triggers for neutrophil recruitment and activation, intrarenal vasoconstriction, mesangial cell contraction, and proliferation of resident glomerular cells (Badr et al 1984; Simonson & Dunn 1986; Badr et al 1987; Bresnahan et al 1992).

Montelukast has a high affinity for the CysLT1 receptor and has been demonstrated to reduce the inflammatory response during the development of eosinophilic airway inflammation, possibly by inhibiting the release of pro-inflammatory mediators such as

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endothelin-1 and interferon-γ (Finsnes et al 2002). Recent human studies revealed that montelukast resulted in significant improvement in urinary frequency and pain in both eosinophilic cystitis and interstitial cystitis (Bouchelouche et al 2001; Sterrett et al 2006). Thus, the data on animals and humans demonstrated that LTs dominate bladder tone and appear to have a leading role in decreased detrusor contraction and bladder overactivity under ischaemic conditions. The current study was designed to determine the effect of montelukast on contractile dysfunction and oxidant damage of rat bladder due to I/R.

Materials and Methods

Animals

Sprague-Dawley rats of either sex (200–250 g) were kept in a room at a constant temperature of 22 ± 1°C, with a 12-h light–dark cycle, and free access to standard pellet chow and water. The study was approved by the Marmara University, School of Medicine, Animal Care and Use Committee.

Experimental groups

After the rats were anaesthetized intraperitoneally with 100 mg kg^{-1} ketamine and 0.75 mg kg^{-1} chlorpromazine, a midline laparotomy was made and the abdominal aorta was isolated. The vessel was occluded for 60 min to induce ischaemia and then allowed 60 min of reperfusion. Montelukast (10 mg kg^{-1}) or saline was administered intraperitoneally 15 min before ischaemia and immediately before reperfusion. In the sham-operated control group, the abdominal aorta was excised but left intact. In this group, the rats were treated with either montelukast or saline. Each group comprised seven or eight rats.

When I/R was completed, the bladder dome was immediately removed and separated from the bladder base at the level of ureteral orifices. The bladder bodies were dissected free of fat tissue and blood vessels. Longitudinal strips of the posterior of the bladder dome (1.5×5 mm) were either immediately placed in organ baths, or stored at −70°C for the biochemical assays. Bladder samples were also taken for histological evaluation.

In-vitro organ bath experiments

Muscle strips were mounted in organ baths containing 20 mL of Tyrode's solution containing 124.9 mM NaCl, 2.6 mM KCl, 23.8 mM $NaHCO_3$, 0.5 mM $MgCl_2$, 0.4 mM NaH_2PO_4, 1.8 mM $CaCl_2$ and 5.5 mM glucose. The solution in the baths was aerated with a mixture of 95% O_2 and 5% CO_2, and maintained at 37°C. Isometric contractions were recorded using a force-displacement transducer (Model FT03; Grass Instruments, Quincy, MA, USA) coupled to a polygraph (Model 7; Grass Instruments). The strips were placed under a resting tension of 1 g and after a 60-min period of equilibration, the contractile responses to carbachol (10^{-8}–10^{-4} M) were obtained cumulatively.

Histological evaluation

For light microscopy, the bladder samples were fixed in 10% buffered formalin for 48 h and processed for routine paraffin embedding. Approximately 7-μm thick sections were stained with haematoxylin and eosin. Stained sections were investigated under the Olympus BX51 photomicroscope (Tokyo, Japan). For scanning electron microscopy, the samples were fixed in 4% phosphate buffered glutaraldehyde (0.13 M and pH 7.4) for 4 h and postfixed with 1% OsO_4 for 1 h, dehydrated in graded alcohol series, put into amyl acetate, dried with liquid CO_2 under pressure with a critical point dryer (Bio-Rad E 3000; Bio-Rad, Hertfordshire, UK) and covered with gold particles (Bio-Rad SC502). These samples were observed under a Jeol JSM (Tokyo, Japan) scanning electron microscope. The histological examination was performed by a histologist unaware of the treatment groups.

Lipid peroxidation and glutathione assays

The bladder samples were homogenized with ice-cold 150 mM KCl for the determination of malondialdehyde and glutathione levels, as described previously. Malondialdehyde levels were assayed for lipid peroxidation products and results are expressed as nmol malondialdehyde (g tissue)$^{-1}$ (Beuge & Aust 1978). Glutathione was determined by the spectrophotometric method, which is based on the use of Ellman's reagent (Beutler 1975). Results are expressed as μmol GSH (g tissue)$^{-1}$.

Measurement of myeloperoxidase (MPO) activity

MPO activity was measured in bladder samples as described previously (Hillegas et al 1990). Briefly, tissue samples were homogenized in 50 mM K_2HPO_4 buffer, pH 6.0, and centrifuged at 41 000 *g* for 10 min. Pellets were suspended in 50 mM K_2HPO_4 buffer containing 0.5% hexadecyltrimethylammonium bromide. After three freeze–thaw cycles, the samples were centrifuged at 41 000 *g* for 10 min. Aliquots (0.3 mL) were added to 2.3 mL of reaction mixture containing 50 mM K_2HPO_4 buffer, *o*-dianisidine and 20 mM H_2O_2 solution. One unit of enzyme activity was defined as the amount of the MPO present that caused a change in absorbance of 3 min^{-1} at 460 nm and 37°C.

Statistical analysis

Data are expressed as the mean ± s.e.m. The concentration causing 50% of the maximal response (EC50) of carbachol was derived from the concentration–response curves using a computer-assisted probit transformation. The unpaired *t*-test was used for the analysis of concentration–response curves. Other parameters were analysed using one-way analysis of variance followed by the Tukey-Kramer multiple comparisons test. Calculations were performed by using the Instat and Prism statistical analysis packages (GraphPad Software, San Diego, CA, USA). Values of $P < 0.05$ were considered statistically significant.

Results

Organ bath experiments

In sham-operated rats, 10^{-8} to 10^{-4} M carbachol added cumulatively caused a concentration-dependent contraction in bladder strips, with an EC50 of 2.36×10^{-6}M. In the saline-treated I/R group, contraction responses of the strips to carbachol were significantly decreased compared with the saline-treated control group ($P<0.001$) (EC50 1.32×10^{-5}M). In the montelukast-treated I/R group, contractile responses to all doses of carbachol were greater than in the I/R group ($P<0.01$–0.001), with an EC50 of 4.77×10^{-6}M. Contractile responses in the montelukast-treated control group were not different compared with those of the untreated control group (Figure 1).

Histological evaluation

In the saline- or montelukast-treated sham-operated control groups, normal mucosa and overlying mucus layer (Figure 2A) and regular mucosal topography (Figure 2B) were observed in the bladder wall. In the saline-treated I/R group, loss of urothelial cells, detachment and loss of urothelial cells, and local ulcerated areas and severe inflammatory cell infiltration were observed (Figure 2C and 2D). In the montelukast-treated I/R group, the urothelium retained its integrity and a decrease in the density of inflammatory cell population (Figure 2E) was evident when compared with the I/R group. Scanning electron microscopy observations showed regeneration of luminal mucosa (Figure 2F).

Lipid peroxidation and glutathione

The mean level of malondialdehyde, which is a major degradation product of lipid peroxidation, in bladder samples showed a marked increase following I/R compared with the saline-treated control group ($P<0.001$). Montelukast administration abolished the increase in bladder malondialdehyde level ($P<0.001$). I/R decreased the bladder glutathione level compared with the saline-treated control group ($P<0.001$) and montelukast treatment reversed this effect ($P<0.001$). Montelukast alone had no effect on malondialdehyde and glutathione levels (Table 1).

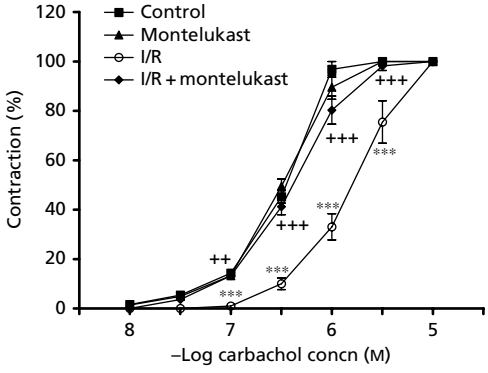

Figure 1 Concentration–response curves obtained by cumulative addition of carbachol (10^{-8}–10^{-4} M) to rat bladder strips obtained from experimental groups. Ischaemia/reperfusion (I/R) was performed by ischaemia of the abdominal aorta for 60 min followed by reperfusion for 60 min. Each group comprised seven or eight rats. ***$P<0.001$, versus sham-operated control group (C). $^{++}P<0.01$, $^{+++}P<0.001$, versus saline-treated I/R group.

Myeloperoxidase activity

The bladder MPO activity in the saline-treated I/R group showed a significant increase compared with the saline-treated control group ($P<0.001$). On the other hand, although montelukast treatment in the I/R group reduced this effect ($P<0.001$), MPO activity was still greater compared with controls ($P<0.001$). Montelukast treatment alone had no significant effect (Table 1).

Discussion

In this study, we observed that induction of I/R resulted in significant oxidative damage in the bladder, as evidenced by increased lipid peroxidation with a concomitant decrease in endogenous antioxidant glutathione level. Moreover, oxidative injury of the tissue was accompanied by neutrophil infiltration, as evidenced by high tissue MPO levels. The oxidative damage and tissue neutrophil accumulation due to I/R were totally abolished by montelukast. In accordance with these biochemical changes, morphological evaluation of the bladder samples revealed that montelukast was also effective in protecting the tissue from I/R-induced degenerative changes.

The renal I/R animal model is well studied and has been valuable in examining the likely pathophysiological mechanisms underlying clinical settings, such as post-transplantation renal injury, acute renal failure after cardiopulmonary bypass, and renal involvement in multiple organ failure after hypovolaemia. Bladder ischaemia results in organ dysfunction characterized by bladder instability, and impairs detrusor contractility probably due to impairment of oxygen and nutrient supplies and the removal of waste products through the circulatory system. More recently, ischaemia-induced elevation of intracellular calcium has been reported to play an important role in these injuries (Zhao et al 1997). Thus, alterations of smooth muscle in ischaemia may be due to a lack of blood supplement, that is oxygen and nutrition, and to elevation of intracellular calcium in the tissue. Bouchelouche et al (2003) showed that LTD4 increases the force of contractions of human detrusor smooth muscle cells by stimulating calcium release from intracellular stores. These findings support the results of a study that has shown that clamping of the abdominal aorta reduced the contractile response of the bladder dome to carbachol in a time-dependent manner (Saito et al 1998). In accordance with these observations, the findings of the present study also demonstrated that 60 min of ischaemia followed by 60 min of reperfusion caused a marked decrease in bladder contractility upon stimulation with carbachol. Seccombe et al (1994) reported the possibility that oxygen-derived radicals during ischaemia impair the signal transduction system in

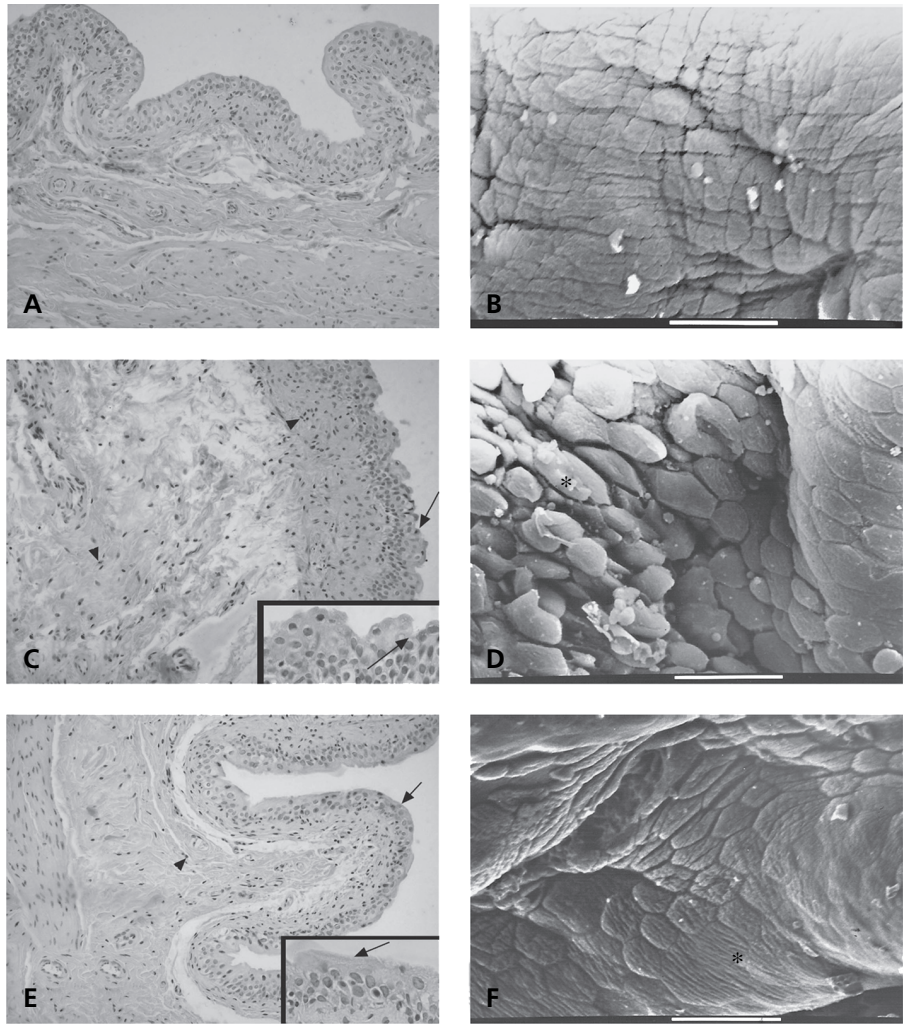

Figure 2 Histological evaluation of bladder tissues in the experimental groups. Saline-treated control group: A. urothelial mucosa with regular mucus layer and epithelial cells; B. luminal surface of the bladder with mucosal folding, mucus covered areas and polygonal shaped apical cells, scale bar: 10 μm. Saline-treated ischaemia/reperfusion group: C. degeneration of the urothelial layer and local ulceration areas (→) with accumulation of neutrophils (►); D. ulcerations in most of the urothelium with mucus and epithelial cell loss (*), scale bar: 10 μm. Montelukast treated ischaemia/reperfusion group: E. regeneration of urothelium (→) in most areas and decrease in the number of inflammatory cells (►) in mucosa; F. healing of the urothelial mucosa (*) and mucus layer. A, C, E: haematoxylin and eosin staining, ×200; inset: ×400; B, D, F: scanning electron micrograph, scale bars: 10 μm.

Table 1 Effects of ischaemia/reperfusion (I/R) and montelukast treatment on malondialdehyde (MDA) and glutathione (GSH) levels and myeloperoxidase activity (MPO) of the urinary bladder tissues of treatment groups

	Sham-operated control groups		**I/R groups**	
	Saline-treated	Montelukast-treated	Saline-treated	Montelukast-treated
MDA (nmol g^{-1})	31.5 ± 1.14	31.8 ± 1.59	53.0 ± 3.9***	38.2 ± 3.1^{+++}
GSH (μmol g^{-1})	1.5 ± 0.1	1.4 ± 0.1	0.6 ± 0.06***	1.2 ± 0.1^{+++}
MPO (U g^{-1})	10.7 ± 1.4	10.3 ± 1.2	28.1 ± 2.9***	13.5 ± 1.4^{+++}

I/R was performed by ischaemia of the abdominal aorta for 60 min followed by reperfusion for 60 min. Each group comprised seven or eight rats. Data are mean ± s.e.m. ***$P < 0.001$ compared with the saline-treated control group. $^{+++}P < 0.001$ compared with the saline-treated I/R group.

coronary endothelium. Therefore, the reduction in contractility of bladder muscles may be attributed to the impairment in signal transduction originating from the stimulation of muscarinic receptors by carbachol. Another possibility is that I/R may directly damage the contractile apparatus in smooth muscles of the bladder dome. Moreover, it has been suggested that LTs predominate over prostaglandins to maintain bladder tone under ischaemic conditions (Azadzoi et al 2003)

The CysLTs (LTC4, LTD4 and LTE4) are potent proinflammatory lipid mediators that play a central role in inflammation, contraction and remodelling of airways observed in asthmatics. Montelukast, a competitive inhibitor of the CysLT-1 receptor, attenuates asthmatic airway inflammation by inhibiting the release of pro-inflammatory mediators such as endothelin-1 and interferon-γ (Finsnes et al 2002) and also diminishes the pulmonary response to antigen, tissue eosinophilia, and the number of cells expressing interleukin-5 mRNA (Ihaku et al 1999). These results suggest that LTs may also regulate the allergic response through the modulation of inflammation and cytokine synthesis. In a recent study which aimed to examine the efficacy of montelukast for treating patients with interstitial cystitis and detrusor mastocytosis, the investigators found that CysLT-1 receptor antagonism resulted in significant improvement in urinary frequency and pain (Bouchelouche et al 2001). Sterrett et al (2006) have also demonstrated that eosinophilic cystitis in children who presented with peripheral eosinophilia would often require long-term treatment with montelukast sodium. These findings implied a role of LT receptor antagonists for managing interstitial cystitis. Moreover, in previous studies we have shown that montelukast showed significant protection against alendronate-induced gastric lesions (Şener et al 2005a), burn-induced oxidative injury of the skin and remote organs (Şener et al 2005b), and pyelonephritis-induced kidney damage (Tugtepe et al 2007) via its anti-inflammatory actions.

In the present study, I/R-induced an increase in bladder MDA levels along with a depletion of tissue GSH level, indicating an enhancement of lipid peroxidation as a result of an impaired antioxidant defence mechanism. Since montelukast treatment was associated with preservation of GSH content and normal lipid peroxide level, it appears that the agent attenuates toxicity through its antioxidant effects. Several reports indicate that tissue injury, induced by various stimuli, is coupled with GSH depletion. Our results showing the inhibition of tissue lipid peroxidation along with replenishment of GSH content by montelukast, imply that the compound is beneficial in maintaining oxidant–antioxidant balance.

Neutrophils are known to release MPO as a response to various stimulatory substances. In the present study, the elevated tissue MPO activity indicates the contribution of neutrophil infiltration in I/R-induced tissue injury. The reversal of elevated MPO activity by montelukast treatment suggests that the mechanism of the protective effect of montelukast involves the inhibition of inflammatory cell infiltration.

In conclusion, this study demonstrates that montelukast, a CysLT-1 receptor antagonist, reduces I/R-induced bladder injury by maintaining a balance in the oxidant–antioxidant status and by inhibiting neutrophil infiltration. Thus, montelukast is a highly promising agent for the protection of organs of the lower urinary tract from pathologic conditions in which oxidants are involved.

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