Nitric Oxide 73 (2018) 15–21

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox

Is hydrogen sulfide a potential novel therapy to prevent renal damage during ureteral obstruction?

Shouzhe Lin[a,c], Smriti Juriasingani[a,c], Alp Sener[a,b,c,*]

[a] Department of Microbiology & Immunology, Schulich School of Medicine & Dentistry, University of Western Ontario, Dental Sciences Building, Rm 3014, London, N6A 5C1, Ontario, Canada
[b] Department of Surgery, Schulich School of Medicine & Dentistry, St. Joseph's Health Care London, PO BOX 5777, STN B, London, N6A 4V2, Ontario, Canada
[c] Matthew Mailing Centre for Translational Transplant Studies, University Hospital, London Health Sciences Centre, 339 Windemere Road, London, N6A 5A5, Ontario, Canada

ARTICLE INFO

Keywords:
Hydrogen sulphide
GYY4137
Urinary obstruction
Renal damage
Renal fibrosis
Epithelial-mesenchymal transition

ABSTRACT

In prolonged complete unilateral ureteral obstruction, reduced renal blood flow places the kidney in a state of ischemia, which can cause tubular injury and inflammation. Infiltrating inflammatory cells release transforming growth factor beta 1, which is a cytokine that initiates fibrosis through the epithelial-mesenchymal-transition pathway. Persistent fibrosis can lead to irreversible renal injury and loss of function. While surgical intervention can remove the obstruction, relief of obstruction may not fully reverse renal injury. Additionally, patients often encounter long wait-times between initial consultation and medical intervention, resulting in the accumulation of renal injury that may cause permanent dysfunction. Currently, accepted pharmacological therapies to mitigate the symptoms of ureteral obstruction include acetaminophen, cyclooxygenase-inhibitors, non-steroidal anti-inflammatory medications, opioids and alpha-receptor blockers. However, there is no evidence that they mitigate renal injury. Therefore, identifying potential therapies that could be administered during obstruction may help to improve renal function following decompression.

Evidence suggests that endogenously produced gasotransmitters can exhibit anti-inflammatory and anti-oxidant effects. Nitric oxide, carbon monoxide, and hydrogen sulfide have been identified as gasotransmitters and have been shown to have cytoprotective effects in various models of tissue injury. Studies have shown that treatment with sodium hydrogen sulfide (a hydrogen sulfide donor salt) mitigated transforming growth factor beta 1 expression, oxidative stress, fibrosis, and inflammation associated with urinary obstruction. More recently, the use of more directed hydrogen sulfide donor molecules, such as GYY4137, has led to significant decreases in inflammation, fibrosis, and expression of epithelial mesenchymal transition markers following urinary obstruction. Taken together, these findings suggest that hydrogen sulfide may be a novel potential therapy against renal injury caused by urinary obstruction.

This review will highlight the existing literature about the pathogenesis and treatment of renal damage caused by chronic urinary obstruction and propose novel upcoming strategies that could improve patient outcomes.

1. Obstructive uropathy: background and etiology

Obstructive uropathy is characterized by abnormalities in the urinary tract that result in the blockage of urine flow. The prevalence and etiology of obstructive uropathy vary with age. The highest rate of obstructive uropathy occurs in children; these incidences are typically congenital defects that arise during embryonic development, resulting in anatomical abnormalities that obstruct the urinary tract. Congenital obstructive uropathy is one of the leading causes of end stage renal disease (ESRD) in children and accounts for 16.5% of all pediatric renal transplantations in North America [1]. In the young and middle-aged adult, urinary obstructions are typically caused due to obstructive calculi (kidney stones). Studies estimate that approximately 10–15% of Americans will develop obstructive stones in their lifetime, with 40% risk of recurrence at 5 years that increases to 75% at 20 years [2]. In elderly patients, urinary tract obstructions are more common in males and are typically caused by benign prostatic hyperplasia or prostate cancer [3]. Ureteral obstructions can be unilateral or bilateral, and can

* Corresponding author. University Hospital, C4-208, London Health Sciences Centre, 339 Windemere Road, London, N6A 5A5, Ontario, Canada. Tel.: 1 519 663 3352; fax: 1 519 663 3858.
E-mail address: alp.sener@lhsc.on.ca (A. Sener).

https://doi.org/10.1016/j.niox.2017.12.004
Received 28 September 2017; Received in revised form 12 November 2017; Accepted 17 December 2017
Available online 19 December 2017
1089-8603/

be classified based on degree (complete or partial obstruction) and duration (acute and chronic). In this review, we will focus on the outcomes, pathophysiology, and potential therapies for mitigating renal damage caused by chronic complete unilateral ureteral obstruction (UUO).

2. Pathogenesis of obstructive uropathy

Urinary tract obstruction is one of the many causes of acute kidney injury (AKI) and chronic kidney disease (CKD). A possible treatment for AKI is dialysis, a process that can take days to weeks. While the mortality rate attributed to AKI is approximately 50%, death from CKD-related injury or the need for dialysis and renal transplantation is generally the ultimate outcome of chronic ureteral obstruction [4]. AKI and CKD share similar pathogenesis, including cellular injury, cell death and inflammation. Additionally, tubulointerstitial fibrosis is often observed in CKD and can also be detected in severe cases of AKI. All of these processes can contribute to the irreversible renal injury and dysfunction caused by UUO [4].

2.1. Hemodynamics and functional changes

Upon complete UUO, an initial increase in renal blood flow into the obstructed kidney is observed. This is a result of prostaglandin and prostacyclin production due to medullary compression. After a few hours with persisting obstruction, renal blood flow decreases due to increased vascular resistance and production of vasoconstrictors such as angiotensin II (Ang II) and thromboxane A2. Together, these events lead to the decrease in glomerular filtration rate (GFR). Correspondingly, an initial increase in intratubular pressure is observed. While this rise is observed in the first few hours, intratubular pressure decreases to pre-obstructive values within the first 24 h. This decline in pressure is caused by decreased GFR, increased sodium reabsorption, and increased removal of tubular fluid through lymphatic drainage. Collectively, these actions decrease renal fluid volume [3].

Obstruction can also cause functional changes in tubular cells. Initially, there is an increase in sodium reabsorption in the tubules to maintain renal fluid volume. However, as the obstruction persists, sodium wasting occurs due to tubular injury and defects in the sodium/potassium ATPase enzymes. This disrupts the lumen potential, which is necessary for hydrogen and potassium excretion. The resulting retention of hydrogen results in renal tubular acidosis. Furthermore, this prevents the distal nephrons from concentrating urine, which contributes to diuresis and an inability to acidify urine upon relief of obstruction [3].

In chronic UUO, the reduction of renal blood flow is maintained, which places the kidney in a state of ischemia. Consequently, reactive oxygen species (ROS) that are harmful to renal tubular cells are generated, resulting in tubular injury and activation of the renin-angiotensin system (RAS), which increases the production of Ang II. Together, these factors cause the recruitment of inflammatory cells to the site of injury, ultimately leading to cell death and the release of transforming growth factor beta 1 (TGF-β1) [3].

2.2. Tubular injury and cell death

Tubular cell death occurs via apoptosis or necrosis and is a result of the mechanical and oxidative stress associated with ureteral obstruction. Apoptosis (cell suicide) is the main form of cell death observed in urinary obstruction and CKD [4]. Apoptosis is characterized by chromosome condensation and cellular blebbing and this form of cell death is regulated by increased expression of intracellular lethal molecules and downregulation of pro-survival mediators. A large variety of factors associated with obstruction, such as ischemia, hypoxia, Ang II, ROS, tumour necrosis factor α (TNF-α), and mechanical stretching, can lead to mitochondrial destabilization and the release of cytochrome C. This ultimately stimulates the caspase-mediated apoptotic pathway and contributes to tubular cell death [5]. These apoptotic cells are subsequently removed by infiltrating macrophages and neighbouring native cells [5].

Necrosis, on the other hand, is characterized by loss of cell membrane integrity and uncontrolled released of intracellular contents. Lethal stimuli, released due to tissue injury, and oxidative stress cause necrotic cell death, which results in the release of damage-associated molecular patterns (DAMPs) such as high-mobility group box 1. The release of DAMPs activates toll-like receptors, which recruits leukocytes to the site of injury and subsequently initiates tissue inflammation [6]. Though prominent in the early stages of pathogenesis and inflammation, necrosis is not frequently observed in chronic renal injury [4].

2.3. Tissue inflammation

Interstitial inflammation is an early response to UUO and it is characterized by infiltration of leukocytes that are attracted to the cytokines, chemokines, and membrane adhesion molecules released by injured renal parenchymal and endothelial cells. Interstitial leukocyte population increases from 12 h to up to 14 days post-obstruction and consists predominantly of macrophages [4]. Macrophages can be classically activated (M1) to produce cytokines and chemokines that induce inflammation, tubular apoptosis, and fibrosis, or alternatively activated (M2) to attenuate inflammation. M1 macrophages generate ROS and TNF-α, which ultimately exacerbate the death of renal epithelial cells [7]. Additionally, interleukin (IL)-1β production can be observed. Together with TNF-α, IL-1β targets nuclear factor-κB (NF-κB) to increase the production of pro-inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1) and IL-1β [8], resulting in an amplified inflammatory response. M2 macrophages, on the other hand, appear in the later stages of inflammation. They play a critical role in the uptake of apoptotic cells, suppression of immune responses and induction of tissue remodelling [7]. These macrophages release IL-4, IL-13, IL-10 and TGF-β1 to reduce tissue inflammation and induce tissue repair. Importantly, TGF-β1 plays a crucial role in the induction of fibrosis, which leads to tissue scarring and loss of function [6].

2.4. Tubulointerstitial fibrosis

As the chronic inflammation associated with UUO persists, the fibrotic characteristics of CKD are eventually observed. Fibrosis is characterized by activation of fibroblasts that deposit extracellular matrix (ECM) components, such as fibronectin, collagen type I and III into the interstitial space [9]. These fibroblasts can be a result of proliferating resident fibroblasts or they can be derived from tubular epithelial cells undergoing epithelial-mesenchymal transition (EMT) [10]. TGF-β1 is a pro-fibrotic cytokine released during inflammation that plays a critical role in initiating the EMT response. Upon stimulation with TGF-β1, Smad 2 and Smad 3 proteins are phosphorylated to induce fibrosis. Meanwhile, Smad 7, an inhibitor of the fibrotic pathway, is degraded via ubiquitination. Under these circumstances, renal epithelial cells lose their adhesions to neighbouring cells and the basement membrane. They also display increased expression of mesenchymal proteins (such as vimentin), decreased expression of epithelial proteins (such as E-cadherin), and migration into the interstitium [4,11]. Propagation of tubulointerstitial fibrosis is commonly observed in CKD and it can lead to irreversible renal injury and loss of renal function [12].

Due to its ability to stimulate TGF-β1 production, Ang II is also a key mediator in the initiation of renal fibrosis. Previous studies have demonstrated that administration of enalapril, an angiotensin-converting enzyme (ACE) inhibitor, decreases production of TGF-β1 mRNA [13], and treatment with lorsartan, an angiotensin AT1 receptor inhibitor, attenuates the progression of renal fibrosis [14]. Additionally, the synthesis of active TGF-β1 requires the conversion of latent pre-pro-TGF-β1 to TGF-β1, its biologically active form, and this process is