Oxidative Stress to Renal Tubular Epithelial Cells – A Common Pathway in Renal Pathologies

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Abstract

Cellular damage to renal tubular epithelial cells (TECs) is commonly seen in the pathogenesis of renal pathologies, including various forms of acute kidney injury (AKI) and kidney diseases; however, the mechanisms of TEC injury are not fully understood. This chapter summarizes recent advances in understanding

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the impact of oxidative stress on these renal pathologies with a major focus on renal TECs in the cortex, the site in the kidney of high oxidative metabolic activity, and we also discuss the outcomes of antioxidant therapy in renal pathologies. Recent literature indicates that oxidative stress, induced by the excess levels of reactive oxygen species (ROS) from mitochondrial injury and/or nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mediates cellular oxidative damage in AKI, nephrolithiasis, and diabetic nephropathy, and that antioxidant therapy has varying degrees of success depending on the bioavailability and activity specificity of the antioxidant agent. The hypothesis is that the oxidative stress is a common feature for these renal pathologies, and ROS-activated molecular pathways in TECs are potential targets for antioxidant therapeutic approaches that can slow the progression of AKI and kidney diseases.

Keywords

Acute kidney injury • Kidney disease • Mitochondria • NADPH oxidase • Oxidative stress • Renal tubular epithelium

Introduction

The nephron is a functional unit of the kidney and is composed of a renal corpuscle and a tubule; therefore, the homeostasis of renal tubular epithelial cells (TECs) is essential for kidney function. Indeed, tubular atrophy is a fundamental part of kidney transplant rejection (Ganji and Harririan 2012; Pascual et al. 2012), chronic kidney diseases (Farris and Colvin 2012) including diabetic nephropathy (Najafian et al. 2011), and nephrolithiasis (Evan et al. 2005), but the pathways for TEC death in these pathophysiological conditions are not fully understood. It has been well documented that under oxidative stress, reactive oxygen species (ROS) cause cellular damage by reacting with and denaturing cellular macromolecules including lipid, protein, and nucleic acids and/or even mediating or activating intracellular death signaling pathways (Rhee 1999). Our hypothesis is that oxidative stress is a common pathway mediating cell death of TECs that have a high oxidative metabolic activity in the kidney. Hence, identification or dissection of this pathway may be critical for understanding the susceptibility of the kidney to nephrotoxic drugs/chemicals, infection/immune response, trauma, mineral crystal aggregation (kidney stone), and hyperglycemia and for developing therapeutic solutions to these renal disorders.

Cellular ROS Generation in TECs

During the course of normal metabolism in cells, superoxide ($O_2^{\bullet -}$), the precursor of ROS, can be produced as inevitable by-products from energy production within the mitochondria. Such ROS production can be normally neutralized by natural

antioxidant enzymes but causes oxidative stress under the condition of mitochondrial injury (Rocha et al. 2010). In addition to mitochondria, there are many cytosolic enzyme systems (e.g., cytochrome p450s, xanthine oxidase, 5-lipoxygenase) that produce $O_2^{\bullet -}$, but the major sources of this molecule production in response to stimuli including inflammation (e.g., hypoxia, immunologic stimuli) are nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in both professional phagocytes and non-phagocytic cells (Babior 1999; Forman and Torres 2001; Novo and Parola 2008).

NADPH oxidase transfers electrons from NADPH to molecular oxygen, which results in generation of ROS. The classic phagocytic NADPH oxidase is a complex of membrane-bound cytochrome b_{558}, cytosolic factors $p47^{phox}$, $p67^{phox}$, and $p40^{phox}$, and a small GTPase Rac2. The heme-binding component of cytochrome b_{558} is a complex of $gp91^{phox}$ (91 kDa subunit of the phagocyte oxidase or NOX2) and glycosylated flavoprotein associated with $p22^{phox}$ (Babior 1999). NOX proteins are the catalytic subunit of NADPH oxidase. In non-phagocytic NADPH oxidase, several members of the NOX family (i.e., NOX1, NOX3, NOX4, NOX5, or DUOX1/2) have been identified (Krause 2004; Novo and Parola 2008). Different NOX proteins vary in tissue distribution in light of their varying functions (Bedard and Krause 2007). The kidney, particularly its cortical substance, expresses a high level of NOX4 (Chabrashvili et al. 2002; Geiszt et al. 2000; Shiose et al. 2001), which has been confirmed in cultured proximal TECs (Geiszt et al. 2000; Reeves et al. 2002). These studies suggest that NOX4-containing NADPH oxidase in TECs plays a pivotal role in the generation of oxidative stress or ROS in the kidney in response to inflammation and cellular stress.

Association of Oxidative Stress with Renal Pathologies

Drug/Chemical-Induced Acute Kidney Injury

Drugs are one of common factors causing damage to the kidney, which contributes to approximately 20 % of acute kidney injury (AKI) episodes (Bellomo 2006; Kaufman et al. 1991; Nash et al. 2002). Many of these drugs, such as aminoglycoside, pentamidine, cisplatin, and antiretrovirals, directly induce renal TEC necrosis, or others, such as penicillin vancomycin, lansoprazole, and thiazides, cause renal interstitial inflammation or immune-mediated tubular injury (Naughton 2008). Renal proximal TECs are a primary target of these nephrotoxic drugs because of their role in concentrating and absorbing glomerular filtrates including these nephrotoxic drugs (Perazella 2005). Oxidative stress is a common result of nephrotoxicant exposure in TECs (Baliga et al. 1997) and is induced by either mitochondrial injury or activation of NADPH oxidase. For example, the nephrotoxicity of gentamicin, cephalosporin, and aristolochic acid is associated with tubular cell death and oxidative stress (Kiyomiya et al. 2002; Pozdzik et al. 2008; Randjelovic et al. 2012), which is due to the mitochondrial injury (Pozdzik et al. 2008; Zorov 2010) or, in particular, depletion of cytochrome *c* in the respiratory

chain of the mitochondria (Kiyomiya et al. 2002; Morales et al. 2010), whereas cisplatin-induced TEC injury is associated with oxidative stress via activation of NADPH oxidase (Kawai et al. 2006) or upregulation of NOX4 expression (Pan et al. 2009), suggesting that potential antioxidative approaches to preventing drug/chemical-induced AKI should be designed differently depending on the sources of oxidative stress, mitochondrial injury, or NADPH oxidase.

Ischemic AKI or Renal Ischemia-Reperfusion Injury

Ischemia is the leading cause of AKI, as see in many clinical settings including renal transplantation, shock, and vascular surgery (Gueler et al. 2004). Clinical and experimental studies show that renal tissue damage that occurs following ischemia-reperfusion, especially during reperfusion, is due in part to excessive production of ROS (Kaminski et al. 2002; Kim et al. 2006; McCord 1985), evidenced by the increased formation of lipid hydroperoxides and other toxic products after such an injury (Beckman et al. 1991) and by the beneficial effects of antioxidant treatment on reducing ischemia-reperfusion injury (IRI) in both in vitro and in vivo systems (Nitescu et al. 2006). The molecular pathways of inducing oxidative stress in the kidney following ischemia-reperfusion are complicated as many enzymes, including oxidases and antioxidant enzymes, are involved; early studies have shown that during ischemia the content of the antioxidants glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) are decreased (Dobashi et al. 2000; Gonzalez-Flecha et al. 1993; Scaduto et al. 1988), while there is increased activation of xanthine oxidase (Sanhueza et al. 1992). The contribution of loss of antioxidant enzyme SOD to oxidative stress is further supported by the fact of worsening renal IRI in CuZnSOD (SOD1)- or extracellular SOD (SOD3)-deficient mice (Schneider et al. 2010; Yamanobe et al. 2007). The contribution of mitochondrial injury to the increase in renal oxidative stress during renal IRI has been reported in many studies (Cruthirds et al. 2003; Plotnikov et al. 2007; Sun et al. 2008) and also seen in a model of cold IRI (Saba et al. 2008), which is further supported by the beneficial effect of mitochondria-targeted antioxidants on the reduction of oxidative stress and renal IRI (Plotnikov et al. 2011; Szeto et al. 2011). On the other hand, there are not many studies in the literature showing the contribution of NADPH oxidase to oxidative stress in renal IRI. A recent study reports that NADPH oxidase (NOX4) interacts with Toll-like receptor (TLR) 4 and is required for hypoxia-induced production of ROS and cell death in renal IRI (Ben Mkaddem et al. 2010).

Septic AKI

In the intensive care unit, sepsis often leads to AKI that occurs in about 19 % of patients with moderate sepsis, 23 % with severe sepsis, and 51 % with septic

shock (Rangel-Frausto et al. 1995) and is associated with oxidative stress, such as decreased total antioxidative capacity and/or increased lipid peroxidation (Roth et al. 2004; Ware et al. 2011). In animal models of sepsis-induced AKI, the tubular epithelium is the major injury target in the kidney that loses renal function as sepsis progresses (Guo et al. 2004; Wu et al. 2007; Yasuda et al. 2006). It has been proposed that ROS in combination with reactive nitrogen species (RNS) contribute to TEC injury during sepsis (Heyman et al. 2011; Wu et al. 2007; Wu and Mayeux 2007). This notion is supported by both clinical and experimental studies: the presence of nitrated plasma proteins is correlated with chronic renal failure in patients with septic shock (Fukuyama et al. 1997), nitrated proteins and oxidation products are seen in the kidney during lipopolysaccharide-induced renal injury in rats (Bian et al. 1999; Zhang et al. 2000), and, more importantly, septic AKI is prevented with antioxidant therapies, such as N-acetylcysteine (NAC) treatment (Campos et al. 2012). Fluorescence microscopic analysis analysis demonstrates that endotoxin is internalized by S1 proximal tubules through local TLR4 receptors and fluid-phase endocytosis but only induces oxidative stress in neighboring S2 tubules (Kalakeche et al. 2011). The molecular mechanisms by which sepsis induces oxidative stress in the kidney includes decreased antioxidant capacity, such as loss of SOD3 expression (Wang et al. 2003) or CAT (Perianayagam et al. 2007), mitochondrial dysfunction (Pathak et al. 2012), and/or activation of NADPH oxidase (Ben Mkaddem et al. 2010; Lanone et al. 2005; Perianayagam et al. 2007).

Nephrolithiasis

Nephrolithiasis, also known as kidney stones, is characterized by the formation of solid crystal aggregates in the kidney. Many clinical studies have reported that the incidence of nephrolithiasis is associated with many chronic inflammatory diseases (e.g., cardiovascular disease and type 2 diabetes) and systemic oxidative stress (Khan 2012; Lange et al. 2012; Tsao et al. 2007). Oxalate is a primary element most common in kidney stones. In a mouse model, the early stages of calcium oxalate crystal formation in the tubular lumen is associated with TEC injury, especially mitochondrial damage, and oxidative stress (Hirose et al. 2010). Similar data were reported in a rat model, where oxidative injury in the kidney correlated with hyperplasia of mitochondria in TECs as well as with decreased activities of SOD and GSH-Px in the mitochondria, but not with expression of NADPH oxidase subunits $p47^{phox}$ and NOX4 (Li et al. 2009). These studies suggest that mitochondrial injury may account for oxidative stress in the kidney with nephrolithiasis, which is further supported by an in vitro study in cultures of proximal (LLC-PK1) and distal (MDCK) tubular epithelial cells, where the intracellular $O_2^{\bullet -}$ from mitochondrial sources is significantly elevated

following treatment with calcium oxalate monohydrate (Khand et al. 2002). However, in cell cultures of NRK52E, a TEC line, calcium oxalate monohydrate upregulates $p47^{phox}$ expression and inhibition of NADPH oxidase activity reduces induction of ROS (Umekawa et al. 2009). The translocation of protein kinase C (PKC)-alpha and (PKC)-delta from the cytosol to the cell membrane, following Rac1 GTPase signaling, mediates oxalate-induced generation of ROS along with NADPH oxidase activity, lipid hydroperoxide formation, and cell death in LLC-PK1 cells (Thamilselvan et al. 2009, 2012). These studies suggest that both mitochondrial injury and NADPH oxidase may induce oxidative stress in the kidney in response to calcium oxalate crystal formation.

Diabetic Nephropathy

Diabetic nephropathy is the leading cause of end-stage renal disease in the developed world, but the mechanisms underlying hyperglycemia-induced renal injury are not fully understood. It has been suggested that the kidney normally filters ~180g of glucose daily, most of which is reabsorbed by means of sodium-glucose cotransporter 2 (SGLT2), expressed in proximal tubules (Mitrakou 2011). However, the capacity of the SGLT1 to reabsorb glucose from renal tubules is finite, and when plasma glucose concentrations exceed a threshold, glucose appears in the urine (Mitrakou 2011). Hyperglycemia induces oxidative stress by increasing ROS generation in diabetic kidneys (Baynes and Thorpe 1999; Matsuoka et al. 2005; Nishikawa et al. 2000). In streptozotocin (STZ)-induced or *db*/*db* diabetic mice, overexpression of SOD1 attenuates diabetic nephropathy (Craven et al. 2001; DeRubertis et al. 2004), and moderate exercise suppresses the progression of early diabetic nephropathy via upregulation of SOD expression independent of hyperglycemia (Ghosh et al. 2009). In vitro high-glucose levels significantly enhance generation of ROS, reduce levels of GSH and SOD, and increase production of malondialdehyde in TECs, glomerular mesangial cells, and glomerular epithelial cells (Jiao et al. 2011; Ogawa et al. 2011), which are in line with high glucose-induced apoptosis (Allen et al. 2003; Kitamura et al. 2009; Yoo et al. 2011). These studies suggest that hyperglycemia induces oxidative stress in the kidney, which may be a key mediator of renal tubular hypertrophy in diabetic nephropathy, and protection from ROS represents a valuable therapeutic strategy to treat diabetic nephropathy. The published data also suggest that both mitochondrial injury and NADPH oxidase activity contribute to hyperglycemia-induced ROS generation in the diabetic nephropathy; normalizing mitochondrial $O_2^{\bullet -}$ production prevents hyperglycemic damage (Nishikawa et al. 2000), while in both distal tubular cells and glomeruli of the kidney in STZ-induced diabetic rats, or cultured TECs treated with high glucose, the expression of NOX4 and $p22^{phox}$ is significantly increased (Etoh et al. 2003; Takao et al. 2011), indicating that NADPH-dependent overproduction of ROS could cause renal tissue damage in diabetes.

Pathways Activated by Oxidative Stress in the Kidney

The mitogen-activated protein kinase (MAPK) pathway is a signaling cascade of a group of serine/threonine kinases, including Ras, Raf-1, MAPK kinase (MEK)1/2, extracellular signal-regulated kinase (ERK)1/2, p38 MAPK, and c-Jun N-terminal kinase (JNK) (Kim and Choi 2010; Seger and Krebs 1995), and has been reported to be activated by oxidative stress in the kidney; direct exposure to H_2O_2, *Tert*-butyl hydroperoxide, or $O_2^{\bullet -}$ production from the catabolism of hypoxanthine by xanthine oxidase induces apoptosis in cultured TECs, which is regulated by either JNK (Wang et al. 2002) or MEK1-ERK1/2 signaling pathway (di Mari et al. 1999; Lee et al. 2006; Nowak et al. 2006). Similar results were reported in TEC cultures treated with the nephrotoxic chemical arachidonic acid that stimulates ROS generation by activation of NADPH oxidase, which subsequently activates JNK (Cui and Douglas 1997), or with high glucose that induces Raf-1 and ERK1/2 (Huang et al. 2007). In renal ischemia-reperfusion, oxidative stress-induced cell death may also be mediated by the activation of this pathway because inhibition of Ras-ERK1/2 or apoptosis signal-regulated kinase (ASK)1-MAPK kinase (MKK)3-p38 MAPK signal pathway reduces renal ischemia-reperfusion injury (Sabbatini et al. 2006; Wang et al. 2009). However, the activation of ERK1/2 signaling is not sustained under conditions of severe oxidative stress (Arany et al. 2006), suggesting that the role of MAPK pathway in ROS-mediated renal injury may depend on the severity of local oxidative stress.

In addition to the MAPK pathway, renal oxidative stress also activates JAK-STAT signaling that mainly consists of a receptor, Janus kinase (JAK) and signal transducer and activator of transcription (STAT) (Aaronson and Horvath 2002). In vitro high glucose activation of the JAK2-STAT1/STAT3 pathway is associated with cell death and is blocked by cytoprotective NAC or taurine in cultured TECs (Huang et al. 2007), while inactivation of JAK2 protects TECs from H_2O_2 or nephrotoxic cyclosporin A (CsA)-induced cell death (Neria et al. 2009). In mouse models of renal IRI, severe oxidative stress increases tyrosine phosphorylation of STAT3 (Arany et al. 2006), and pharmacological interference of JAK2 signaling prevents renal IRI and CsA nephrotoxicity (Arany et al. 2006; Neria et al. 2009).

Several other signaling pathways have also recently been reported to mediate oxidative stress-induced TEC death. H_2O_2 increases prostate apoptosis response factor (Par)-4 expression in human TECs, and Par-4 silencing significantly protects TECs from apoptosis via activating the PI3K/Akt signaling pathway (Sun et al. 2011). Studies of nephrotoxic drug/chemical-induced nephrotoxic pathways using whole genome DNA microarray demonstrates that the nuclear factor erythroid 2-related factor (Nrf2) pathway is the most significant signaling response for oxidative stress in a proximal TEC cell line (HK-2) following challenges with nephrotoxins (cadmium, diquat dibromide) but not with cyclosporine A (Wilmes et al. 2011). The anticancer drug carboplatin-mediated ROS stimulation of calcineurin-NFAT3 (nuclear factor of activated T-cell 3) activation that is essential for carboplatin-mediated TEC apoptosis (Lin et al. 2010).

Table 114.1 Efficacy of antioxidants in preventing or treating oxidative stress in the kidney

Antioxidant therapy	Subjects	Outcome	References
NAC	CIN	Not effective	Aslanger et al. 2012; Hafiz et al. 2012; Jaffery et al. 2012; Kitzler et al. 2012; Thiele et al. 2010
	Postoperative AKI	Not effective	Adabag et al. 2009; Hilmi et al. 2010
	CKD	Not effective	Moist et al. 2010; Renke et al. 2008
NAC and losartan	DN	Not effective	Rasi Hashemi et al. 2012
Vitamin E	CIN	Not effective	Kitzler et al. 2012
Vitamin E and allopurinol	Postoperative AKI	Not effective	Nouri-Majalan et al. 2009
Vitamins E and α-lipoic acid	CKD	Not effective	Ramos et al. 2011
Ascorbic acid (vitamin C)	CIN	Not effective	Boscheri et al. 2007; Zhou and Chen 2012
Vitamin supplements	ESRD	Not effective	Kamgar et al. 2009
GSH	CIN	Effective in preventing the oxidative stress and CIN	Saitoh et al. 2011
BARD	DN	Improvement of eGFR up to 52 weeks	Pergola et al. 2011a, b
Allopurinol	Renal impairment, chronic gout	Reduction in serum urate concentration	Stamp et al. 2011
		Improvement of eGFR	Goicoechea et al. 2010
	DN	Reduction in proteinuria	Momeni et al. 2010

NAC N-acetylcysteine, *CKD* chronic kidney disease, *CIN* contrast-induced AKI/nephropathy, *DN* diabetic nephropathy, *ESRD* end-stage renal disease, *GSH* glutathione, *BARD* bardoxolone methyl

Antioxidant Therapies for Oxidative Stress in the Kidney

Antioxidants consist of enzymes, such as SOD, CAT, and GSH-Px, and small molecular antioxidant scavengers, such as vitamin E, *N*-acetylcysteine (NAC), and α-lipoic acid. These antioxidants neutralize the activity of free radicals in the body by donating electrons, suggesting their therapeutic potential for mitigating oxidative stress-mediated kidney diseases. Several antioxidant therapies for reducing oxidative stress in the kidney have been recently reported (Table 114.1), but many antioxidant agents, such as NAC and vitamins, have not successfully passed the scrutiny of

clinical trials for prevention and treatment of renal pathologies, while others, such as allopurinol, have varying degrees of success (Table 114.1). We discuss possible reasons for the failure or the success of these antioxidant therapies.

NAC, the *N*-acetyl derivative of L-cysteine, is the best studied antioxidant for preventing contrast medium-induced nephropathy (CIN) and other renal pathologies in patients, but the outcomes are not satisfactory (Table 114.1). NAC is metabolized in the gut wall and liver and is converted to L-cysteine and, ultimately, from the cysteine to the antioxidant glutathione (GSH). The antioxidant activity of NAC requires prior conversion to GSH in a study using human platelets (Gibson et al. 2009). Thus, the efficacy of antioxidant therapy using NAC is dependent on the conversion or metabolism of NAC to GSH. Recently, Nolin et al. reported that the conversion of NAC to GSH is largely limited in patients with end-stage renal disease (ESRD) as compared with that in healthy control subjects (Nolin et al. 2010), which may explain the reason why NAC is not effective in patients with renal pathologies.

Vitamin E is the term for a group of tocopherols and tocotrienols, of which α-tocopherol has the highest biological activity. As an antioxidant, vitamin E is a peroxyl radical scavenger, preventing the propagation of free radicals by lipid peroxidation by reacting with them to form a tocopherol radical that will then be reduced by a hydrogen donor (such as ascorbic acid) and thus return to its reduced state (Traber and Stevens 2011). However, in addition to antioxidant/radical scavenging, vitamin E also has other biological functions, such as inhibition of protein kinase C activity, resulting in suppressing smooth muscle growth (Schneider 2005; Zingg and Azzi 2004), upregulation of connective tissue growth factor in tumor necrosis factor-treated smooth muscle cells (Villacorta et al. 2003), and inhibition of platelet aggregation (Zingg and Azzi 2004). Therefore, the outcome of antioxidant therapy using vitamin E not only is determined by its bioavailability and antioxidant activity that can be affected by the levels of ascorbic acid or other reducing agents but also is complicated by its non-antioxidant activities in the body. This concept is supported by the clinical observations of vitamin E against kidney injury as listed in Table 114.1 and many other studies demonstrating that vitamin E is not able, at physiological concentrations, to protect against oxidant-induced damage or prevent disease allegedly caused by oxidative damage (Azzi 2007).

Ascorbic acid (vitamin C) is another antioxidant that has no benefit in the prevention and treatment of kidney injury in patients (Table 114.1). This compound does not directly reduce oxidative stress. Instead, its antioxidant activity is via the interaction with vitamins E – the vitamin E redox cycle (Halliwell and Gutteridge 1999; Liebler et al. 1989). In addition to this antioxidant activity, ascorbic acid primarily acts as an essential cofactor for a number of enzymes – α-ketoglutarate-dependent dioxygenases, particularly prolyl hydroxylases that play a role in the biosynthesis of collagen and in downregulation of hypoxia-inducible factor (HIF)-1, a transcription factor that regulates many genes responsible for tumor growth, energy metabolism, and neutrophil function and apoptosis (Traber and Stevens 2011). Therefore, like vitamin E, ascorbic acid is a nonspecific antioxidant agent.

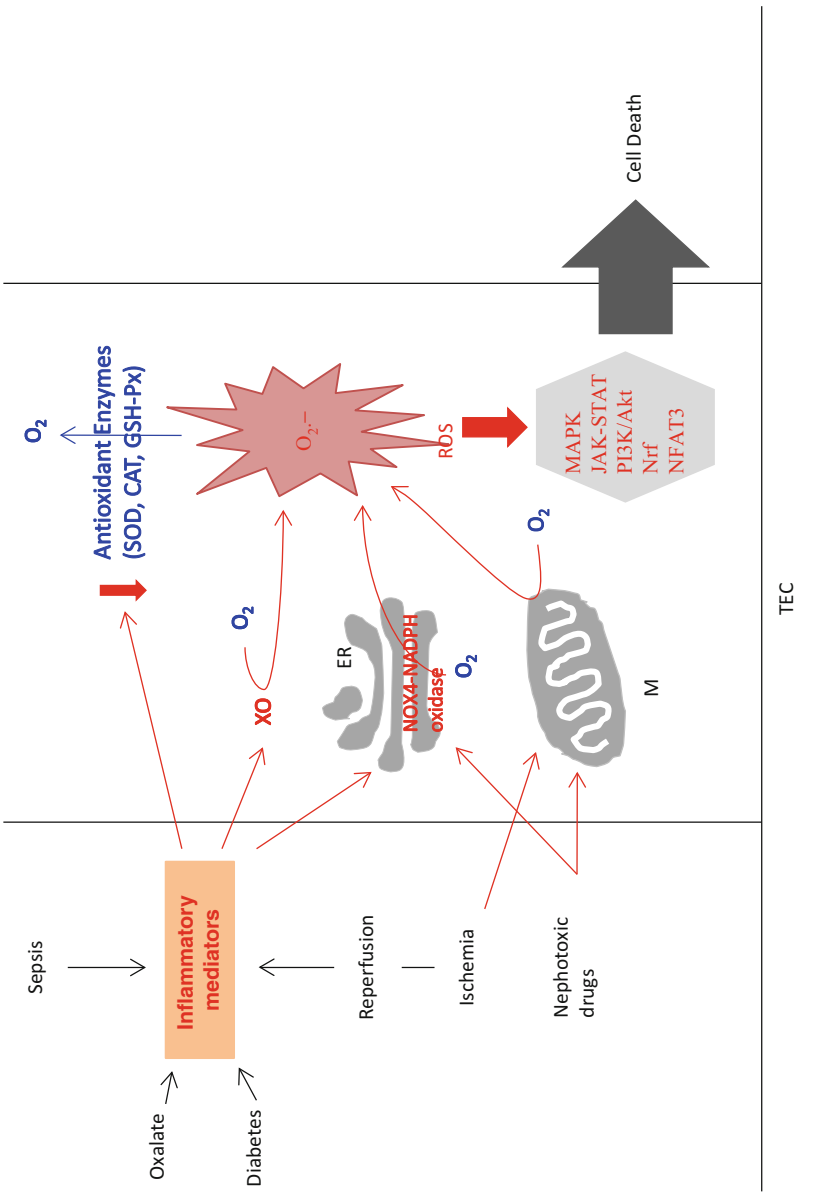

Fig. 114.1 (continued)

Allopurinol is a purine-like drug that reduces uric acid production from xanthine and hypoxanthine by inhibition of xanthine oxidase (XO) activity and has been used for the clinical management of gout and conditions associated with hyperuricemia for several decades (Pacher et al. 2006). Allopurinol is metabolized by XO to an active metabolite, oxypurinol, which inhibits the production of uric acid and ROS (i.e., H_2O_2) from XO. Because oxypurinol is eliminated in urine via the kidneys, patients with impaired renal function are prone to prolonged excretion and elevated levels of circulating oxypurinol (Elion et al. 1968), which has been reported to be closely involved with the occurrence of allopurinol hypersensitivity syndrome (Hande et al. 1984). Therefore, although allopurinol has a protective effect on renal function in patients but not in AKI (Table 114.1), as antioxidant therapy for renal pathologies, it can be limited by its high risk for allopurinol hypersensitivity syndrome and its XO target specificity – not attenuating other sources of oxidative stress. Recently, a new generation of XO inhibitor, a non-purine-selective febuxostat, has been tested in preclinical models for preventing ischemic AKI (Tsuda et al. 2012) and unilateral ureteral obstructive nephropathy (Omori et al. 2012). This new XO inhibitor may be safe for patients with mild to moderate renal impairment without dose adjustment (Tatsuo and Iwao 2011), but its antioxidant activity in patients with renal pathologies remains under investigation.

Similar to cyclopentenone prostaglandins – endogenous activators of Nrf2 pathway and inhibitors of NF-κB (Surh et al. 2011) – bardoxolone methyl (BARD) has been demonstrated to activate the Nrf2 pathway (Liby et al. 2005; Sporn et al. 2011; Yates et al. 2007) that plays a central role in the maintenance of redox balance and protection against oxidative stress. It has been recently documented that impaired Nrf2 activity is associated with renal oxidative stress and inflammation in animals with chronic kidney disease (Kim et al. 2011; Kim and Vaziri 2010; Kim et al. 2010; Yoh et al. 2001). BARD activates the Nrf2 pathway in the kidney (Reisman et al. 2012), so that treatment with BARD ameliorates ischemic AKI in experimental studies (Wu et al. 2011) and improves eGFR in patients with diabetic nephropathy (Table 114.1). However, a phase III clinical trial to evaluate safety and efficacy of BARD (20 mg/day) in patients with CKD and type 2 diabetes has been discontinued due to safety concerns related to the many adverse side effects and high mortality rates in patients receiving BARD (October 18, 2012, www.marketwatch.com). Although the mechanism of BARD toxicity in these patients is currently unknown, it is possible that BARD may not only reverse the impaired Nrf2 pathway in diseased kidneys but could also activate Nrf2 pathways in healthy organs,

Fig. 114.1 A simple scheme of oxidative stress in renal tubular epithelium in renal pathologies. Accumulation of superoxide ($O_2^{\bullet -}$), the precursor of ROS, results from mitochondrial dysfunction, upregulation of oxidases, and/or downregulation of antioxidant enzymes in renal tubular epithelium in the response to inflammatory stimuli, ischemia, and exposure to toxic chemicals. ROS activates or disrupts intracellular signaling pathways (e.g., MAPK), resulting in cell death. *TEC* tubular epithelial cells, *XO* xanthine oxidase, *ER* endoplasmic reticulum, *M* mitochondria

whereby the expression of antioxidant enzymes (e.g., NADPH quinone oxidoreductase, glutamate-cysteine ligase, heme oxygenase) could be upregulated to increase oxidative stress instead.

Taken together, evidence from these studies indicates that the efficacy of antioxidant therapy using different agents is dependent on their bioavailability and target/disease specificity. It is likely that new avenues that are have more specific targeting as antioxidants and which possess better pharmacokinetic profiles will lead the way for future treatment strategies of patients with renal diseases. This requires a great focus on designing procedures to reduce renal mitochondrial injury and the use of specific inhibitors of Nox-4-NADPH oxidase that have better improved bioavailabilities in patients with renal pathologies.

Conclusion

Over the past several years, both clinical and experimental studies have advanced our understanding of the pathological role of oxidative stress in the development of various renal pathologies. This review discusses the pathways that lead to the generation of ROS in the kidneys or cultured TECs following a variety of nephrotoxic insults and the pathways activated by ROS in their nephrotoxicity (Fig. 114.1). In these renal pathologies, both mitochondrial injury and NADPH oxidase are considered the main sources of ROS that activate MAPK, JAK-STAT, or other pathways. However it remains unclear whether each renal disorder has its own unique source of ROS generation. Despite the large number of studies testing antioxidant reagents in the prevention of oxidative stress-mediated renal injury, there is as yet no drug available that directly targets renal ROS activity; it is clear that this would be a valuable strategy for drug discovery to protect against drug nephrotoxicity, AKI, kidney stone or diabetes-associated kidney damage.

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