Received: 23 May 2018 | Revised: 19 July 2018 | Accepted: 20 July 2018

DOI: 10.1111/1440-1681.13018

REVIEW ARTICLE

WILEY CEPP Clinical and Experimental Pharmacology and Physiology

Physiological and pathophysiological role of reactive oxygen species and reactive nitrogen species in the kidney

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Funding information
Japanese Society for the Promotion of Science, Grant/Award Number: 15KT0088, 16K09604, 16K15465, 18H02727 and 25461207

Summary

End-stage renal disease is a leading cause of morbidity and mortality worldwide. The prevalence of the disease and the number of patients who receive renal replacement therapy are expected to increase in the next decade. Accumulating evidence suggests that chronic hypoxia in the tubulointerstitium represents the final common pathway to end-stage renal failure, and that reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the key players in kidney injury. However, ROS and RNS that exceed the physiological levels associated with the pathophysiology of most kidney diseases. The molecules that comprise ROS and RNS play an important role in regulating solute and water reabsorption in the kidney, which is vital for maintaining electrolyte homeostasis and the volume of extracellular fluid. This article reviews the physiological and pathophysiological role of ROS and RNS in normal kidney function and in various kidney diseases.

KEYWORDS

acute kidney injury, chronic kidney disease, oxidative and nitrosative stress, reactive nitrogen species, reactive oxygen species

1 | INTRODUCTION

Although ROS and RNS play an essential role in the maintenance of human health, an excess of ROS or RNS has been implicated in the pathogenesis of various diseases.[1] The kidneys are remarkable organs, performing many of the functions that are essential to regulating body fluids and blood pressure, waste product excretion, and red blood cell production. Kidney diseases pose a worldwide health problem, and cause significant morbidity and mortality among adults, particularly among older people. Although blood supply to the kidney accounts for 20% of cardiac output, the presence of oxygen shunt diffusion between the arterial and venous vessels, which run parallel to and in close contact with each other, means that renal tissue oxygen tension is relatively low[2,3] (Figure 1). The O_2 consumption rates of kidney mitochondria are higher than those of other organs,[4] and hydrogen peroxide (H_2O_2) release accounts for 0.1%–0.2% of total consumed oxygen.[5] Lower oxygen tension reduces oxidative phosphorylation and participates in generation of $O_2^{\cdot-}$ and $^{\cdot}NO$, which in turn initiates the formation of a range of other ROS and RNS (Figure 2). Here, we review the physiological and pathophysiological role of superoxide ($O_2^{\cdot-}$), hydroxyl radical ($HO^{\cdot}$), H_2O_2, nitric oxide ($^{\cdot}NO$) and peroxynitrite ($O{=}NOO^-$) in the kidney.

2 | PHYSIOLOGICAL ROLE OF ROS AND RNS IN THE KIDNEY

The number of mitochondria in kidney cells varies from cell to cell. The renal phenotypes of most mitochondrial diseases associated with increased ROS are tubulopathies and focal segmental sclerosis,[6] suggesting that the main source of ROS differs among kidney cells (Figure 3). Most research to date has focused on the adverse effects of ROS in kidney diseases. However, Dugan et al [7] showed that $O_2^{\cdot-}$ generation was significantly lower in diabetic kidneys than

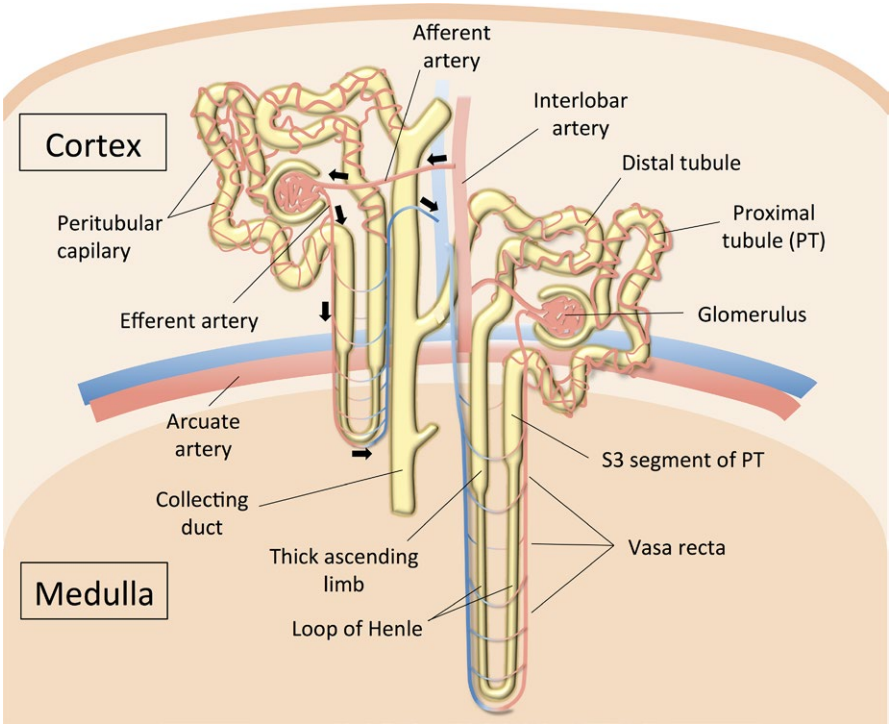

FIGURE 1 Microvasculature of the nephron. The renal artery first divides into segmental arteries, which then further branch to form the arcuate arteries. The arcuate arteries then branch to form interlobar arteries, from which arise the afferent arteries. Each afferent artery carries blood to a glomerulus, while efferent arteries usually lead to peritubular capillaries. Sometimes the efferent artery lead to vasa recta, which are the vessels which surround the loop of Henle and collecting ducts within the renal medulla. Blood from the peritubular capillaries and vasa recta enters venules, which merge to form interlobar veins. S3 segments of the proximal tubule (PT) can be found in the proximal straight tubules of the juxtamedullary nephron. As shown in the figure, the network of blood vessels is more developed in the cortex, and oxygen tension in the medulla is lower than in the cortex. Accordingly, the regions of the kidney which are most prone to ischaemia injury are the S3 segment of the PT and the medullary thick ascending limb of the loop of Henle, as these tubular areas physiologically exist under relatively lower oxygen conditions

in the non-diabetic controls; high plasma glucose levels reduced mitochondrial $O_2^{\cdot-}$ production in cortical homogenates of diabetic mice; and that high levels of mitochondrial $O_2^{\cdot-}$ were protective and restored renal function in an AMPK-dependent manner. In addition, Haque et al [8] showed that the endogenous production of $O_2^{\cdot-}$ induced by vascular nicotinamide adenine dinucleotide phosphate oxidase (Nox) plays an important regulatory role in maintaining normal renal vascular tone using $gp91^{PHOX}$, a subunit of Nox, knockout mice. In addition, myeloperoxidase (MPO), a peroxidase enzyme, knockout mice were reported to show exacerbated atherosclerosis,[9] while chronic antioxidant supplementation was reported to impair coronary endothelial function and myocardial perfusion in normal pigs. These findings suggest that ROS are more than simply "unwanted" second messengers, but rather play some physiological role in the kidney.

In the case of RNS, three isoforms of $^{\cdot}$NO synthase (NOS) are expressed at various locations in the kidney,[10] with higher $^{\cdot}$NO levels observed in the medulla.[11] In general, NO acts as a vasodilator and contributes to lowering vascular tone in the kidney.[12] On the other hand, $^{\cdot}$NO produced by the macula densa is involved in renin secretion and tubuloglomerular feedback via vasoconstriction of the afferent artery.[13,14] These findings suggest that the vascular response to RNS might depend on the amount of RNS and the vascular bed, as is also observed with ROS. The proximal tubules (PTs) play the major role in solute and fluid reabsorption in the kidney and regulate the pH of the filtrate by exchanging hydrogen ions (H^+) in the cytoplasm and bicarbonate ions in the filtrate. They also secrete organic acids, including creatinine, into the filtrate. Fluid is also reabsorbed into the peritubular capillaries from the lumen of the PTs via Na+/K+-ATPase and the Na+/H+ exchanger 3. In rats, intratubular administration of N^{ω}-nitro-L-arginine methyl ester, an NOS inhibitor, increased fluid reabsorption,[15] and nNOS knockout mice showed higher fluid reabsorption rates than wild-type mice.[16] In contrast, another report showed that high concentrations of $^{\cdot}$NO also stimulate reabsorption in the PT.[17] In addition, nNOS and iNOS knockout mice have lower PT reabsorption rates than wild-type mice.[18,19] These results suggest that $^{\cdot}$NO intricately regulates reabsorption in the PTs.

3 | ROS AND RNS IN ACUTE KIDNEY INJURY

Acute kidney injury (AKI), defined as abrupt renal dysfunction, is a common complication in critically ill patients. About 30% of patients

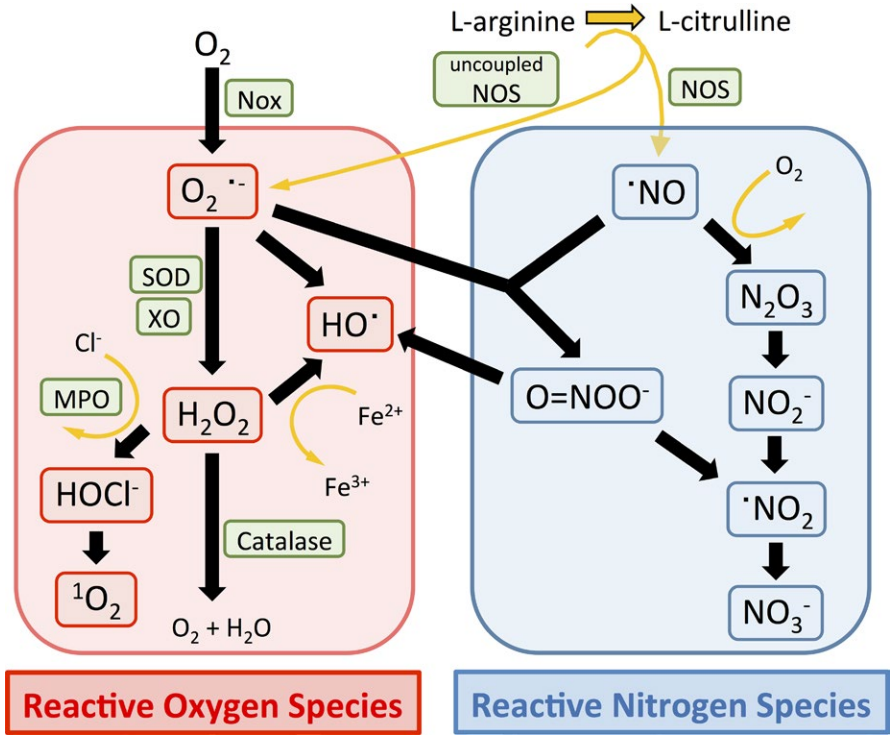

FIGURE 2 Close relationship between reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS and RNS are types of unstable molecules that contain oxygen or nitrogen, and include many reactive species. Major ROS are superoxide ($O_2^{\cdot-}$), hydroxyl radical (HO^-), hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$). Major RNS include nitric oxide ($^{\cdot}NO$), dinitrogen trioxide (N_2O_3), peroxynitrite ($O{=}NOO^-$), nitrogen dioxide ($^{\cdot}NO_2$) and other oxides of nitrogen. XO, xanthine oxidase; SOD, superoxide dismutase; NOS, nitric oxide synthase

admitted to intensive care units (ICUs) develop AKI, which is associated with high levels of morbidity and mortality.[20] AKI is not a transient pathology, and is a major risk factor for chronic kidney disease (CKD).[21,22] Numerous studies suggest that oxidative stress and its systemic effects play pivotal roles in the development of AKI. In this section we review the pathological role of ROS in AKI (Figure 4).

3.1 | Ischaemia–reperfusion injury

Ischaemia–reperfusion injury (IRI) is another important pathological condition that leads to AKI. IRI-induced AKI occurs in association with several clinical conditions, and is the main cause of delayed graft function or graft loss after kidney transplantation.[23] Ischaemic cells die if blood flow is not restored, but most IRI damage is in fact initiated during reperfusion. The first damaging event that occurs after reperfusion is a burst of $O_2^{\cdot-}$ production from the mitochondria. This triggers the pathology that develops over the minutes, days, and weeks that follow reperfusion.[24,25] This mechanism contributes to the initiation and maintenance of AKI.[26] Even under normal physiologic conditions, oxygen delivery to the outer renal medulla is poor, because of the distance between the outer renal medulla and the descending vasa recta. The S3 segments of the PTs in the outer renal medulla are particularly susceptible to both the ischaemic and reperfusion phases of IRI, which can lead to acute tubular necrosis.[27] IRI induces an early infiltration of inflammatory cells that consist mainly of neutrophils.[28] ROS from neutrophils are prominent in inflammatory mechanisms, but the ROS themselves are important for neutrophil recruitment. Recently, Tanaka et al[29] showed that vascular adhesion protein-1 in pericytes, namely stromal cells which support the vasculature, plays a critical role in the pathophysiology of renal IRI. It does this by enhancing neutrophil infiltration via generation of a local H_2O_2 gradient. Furthermore, the importance of ROS has been confirmed by the findings of a study that showed the importance of nuclear factor erythroid 2-related factor 2 (Nrf2), which is the master regulator of the oxidative stress response.[30] Following IRI, Nrf2-regulated cell defense genes have been found to be elevated in the kidney of wild-type but not Nrf2-knockout mice[31,32] and the severity of renal IRI is exacerbated by the loss of Nrf2.[32] In addition, hyperactivation of Nrf2 in tubules prevents the progression of tubular damage by suppressing IRI-mediated oxidative stress during the early progressive phase of renal IRI injury.[33]

3.2 | Septic acute kidney injury

Sepsis is the most common pathological condition that causes AKI in ICUs.[34] While a variety of bacterial products cause the inflammatory response that occurs in sepsis, one of the most important endotoxins is lipopolysaccharide (LPS), a major component of the outer membrane of Gram-negative bacteria. A family of transmembrane proteins, the Toll-like receptors (TLRs), recognize and bind to a variety of bacterial products, including LPS. This binding triggers innate immune responses and the development of antigen-specific acquired immunity.[35] The LPS ligand is specific to TLR4 and, once activated by ligand binding, TLR4 transduces its downstream signalling mainly through the inhibitor of IκB kinase (IKK)/ inhibitor of kappaB (IκB)/NF-κB signalling pathway. IKK phosphorylates IκB and induces its degradation, consequently leading to NF-κB nuclear translocation and the transcriptional induction of pro-inflammatory

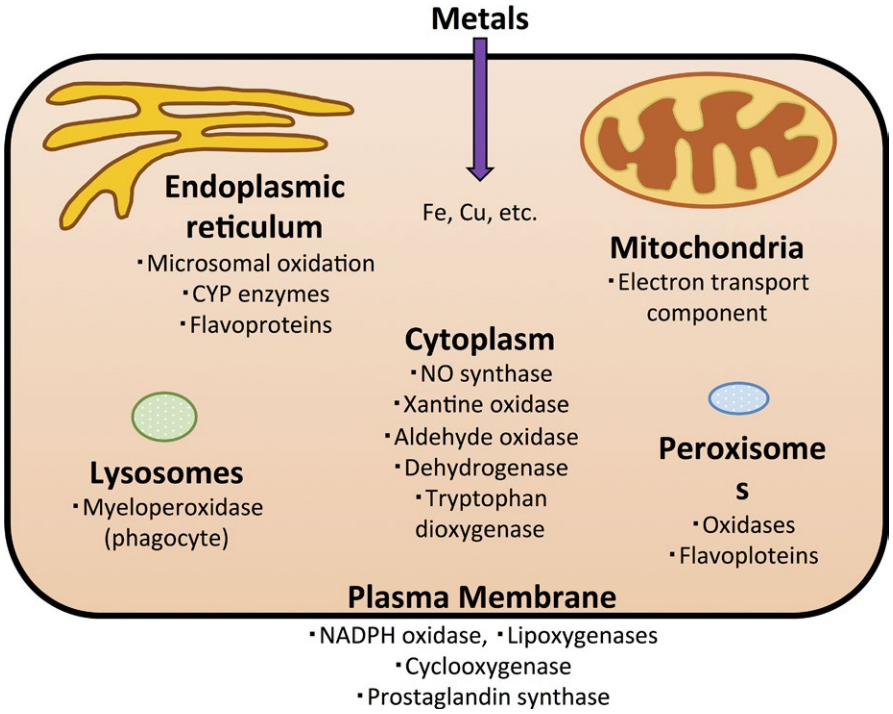

FIGURE 3 Intracellular sources of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Major intracellular sources of ROS and RNS are mitochondria, endoplasmic reticulum, lysosomes, peroxisomes, and enzymes in the cytoplasm or plasma membrane. In addition to these, extracellular metals are also a source of ROS and RNS. The main source of ROS and RNS differs from cell to cell and also will differ with the cause of renal diseases. CYP, cytochrome P450; NO, nitric oxide; NADPH, nicotinamide adenine dinucleotide phosphate

cytokines/mediators, including tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). TNF-α and IL-1β promote H_2O_2 generation and exacerbate the inflammatory response.[36] Cunningham et al[37] showed that mice that lacked TLR4 were resistant to LPS-induced mortality and LPS-induced AKI. In addition, TLR4 knockout mice were resistant to cecal ligation and puncture, which is a well-established animal model of septic AKI.[38] These data indicate that the increase in the level of ROS induced by LPS-TLR4 signalling is the main pathological manifestation that underlies septic AKI.

3.3 | Contrast-induced nephropathy

Contrast-induced nephropathy (CIN) is defined as an impairment of renal function. This condition occurs when the serum creatinine (sCr) level increases by 25% from baseline or when the absolute sCr value increases to 0.5 mg/dL (44 μmol/L) within 72 hours of an intravascular injection of iodinated radiographic contrast media,[39] which is used to improve the visibility of organs and structures in X-ray-based imaging techniques, including computed tomography. The iodine-containing non-ionic radiocontrast iodixanol directly constricts the outer medullary descending vasa recta by reducing the bioavailability of $^{\cdot}NO$ and significantly increases the vasoconstriction induced by angiotensin II, thereby causing severe local hypoxia.[40] Animal experiments have demonstrated that the reductions in cortical and medullary microvascular blood flows induced by contrast medium are partly accounted for by the downregulation of endogenous renal cortical and medullary $^{\cdot}NO$ synthesis.[41] The protective effect of superoxide dismutase (SOD) against CIN has been demonstrated in animal models. The SOD mimetic Tempol lessens the iodixanol-induced vasoconstriction by reducing the levels of $^{\cdot}NO$ generated in the medullary descending vasa recta during the administration of contrast media.[40] Recombinant SOD2 reduced renal oxidative stress when administered to rats that had received diatrizoate, thereby preventing reductions in glomerular filtration rate (GFR) and the renal histologic damage that follows the administration of contrast media.[42] Although clinical trials have investigated the protective effects of antioxidants against CIN, findings have not clearly demonstrated a protective effect of N-acetyl-L-cysteine[43] or ascorbic acid[44] against CIN.

4 | ROS AND RNS IN CHRONIC KIDNEY DISEASE

Chronic kidney disease is the progressive loss of kidney function over months or years. Chronic hypoxia in the tubulointerstitium is thought to be the final common pathway to end-stage renal failure,[45] and, as described above, a major manifestation that induces oxidative stress. Many antioxidant systems protect the kidney against ROS-induced oxidative stress, and the major cellular defense against $O_2^{\cdot-}$ is SOD. All three SOD isoforms are present in the kidney.[46-48] The SOD1 isoform accounts for up to 80% of the total SOD activity in the mammalian kidney.[49] SOD1 activity declined in a chronic hypoxic kidney model induced by unilateral renal artery stenosis.[50] Furthermore, expression of SOD1 is lower in the kidneys of patients who have glomerular nephritis compared with that in healthy control individuals.[51] Usually, SOD levels in the mitochondrial matrix are low. Moreover, expression of the SOD2 gene in neutrophils from CKD patients is downregulated after LPS stimulation.[52] Besides, interstitial fibrosis is the common process in CKD, and ROS and oxidative stress appear to be important in renal fibrosis in a manner that is independent of the primary cause, leading to kidney damage.[53,54] In

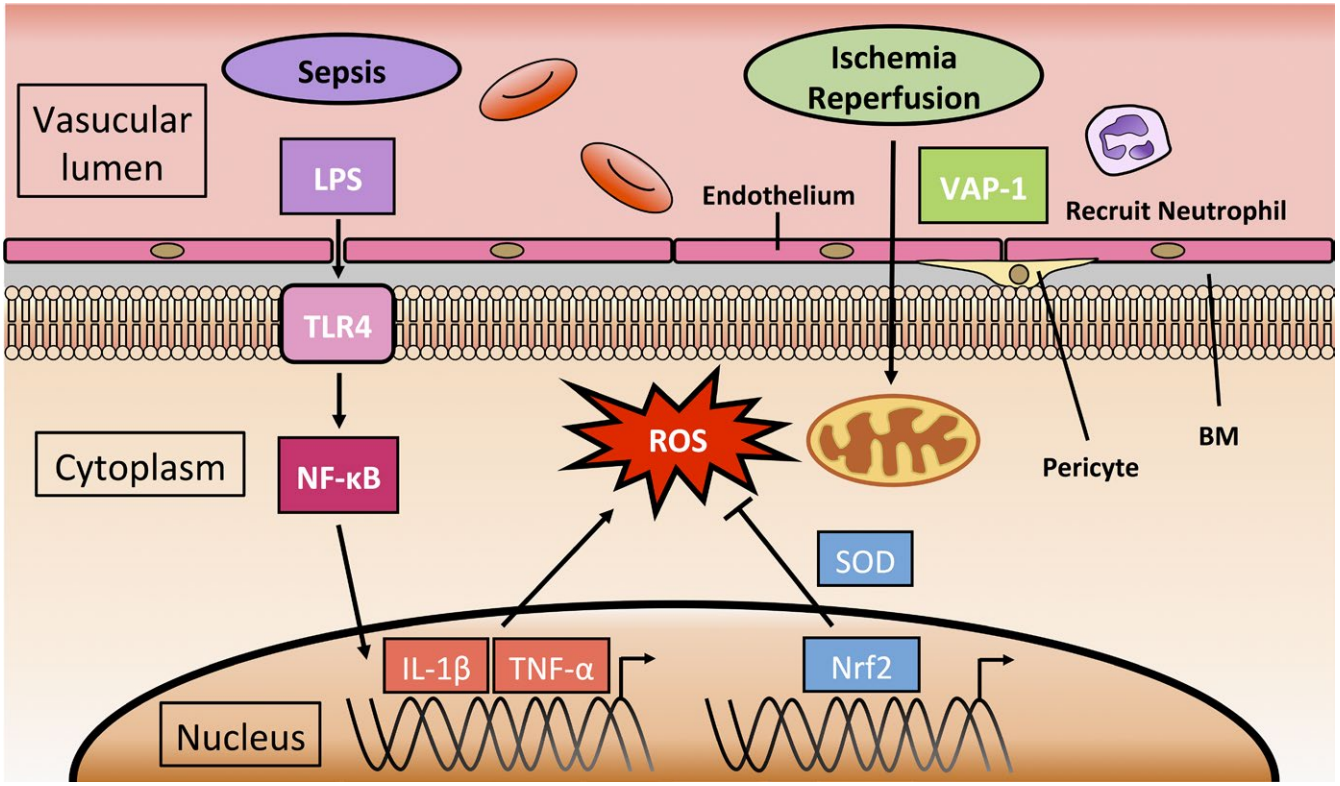

FIGURE 4 Scheme of ROS-related tubular damage in acute kidney injury (AKI). In sepsis, TLR4 recognizes LPS and transduces it by downstream signalling mainly through the NF-κB signalling pathway. This in turn increases the secretion of cytokines and mediators, including TNF-α and IL-1β, which promote H_2O_2 generation and exacerbate the inflammatory response. Mitochondria in tubular cells increase $O_2^{\cdot-}$ production in ischaemic reperfusion injury. Pericytes, which can be detached from endothelial cells in injured kidneys, express and release VAP-1, which catalyzes the oxidative deamination of primary amines, resulting in the production of H_2O_2 in the extracellular space. This generates a local H_2O_2 gradient, which in turn enhances the recruitment of neutrophils in ischaemia reperfusion kidney injury. Nrf2 translocates to the nucleus and binds to antioxidant-related elements in the promoter regions of antioxidants, including SOD. LPS, lipopolysaccharide, TLR4, Toll-like receptor 4; NF-κB, nuclear factor-κB; TNF-α, tumour necrosis factor-α; IL-1β, interleukin-1β; VAP-1, vascular adhesion protein-1; ROS, reactive oxygen species; BM, basement membrane

this section, we review the importance of ROS in the pathophysiology of the major causes of CKD.

4.1 | Diabetic kidney disease

Hyperglycaemia can cause a rise in the concentration of both $O_2^{\cdot-}$ and $^{\cdot}NO$.[55-57] Indeed, an increase in the production of ROS/RNS, and the subsequent changes in the redox state and in cellular homeostasis, have been described in association with diabetes. While there are many sources of ROS/RNS, we will focus on the mitochondria, Nox and peroxynitrite ($ONOO^-$) in diabetic kidney disease (DKD). A master regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), is downregulated in patients with diabetes,[58] and a decrease in the mitochondrial DNA (mtDNA) content has been found in the peripheral blood of patients with non-insulin-dependent diabetes mellitus before diabetes developed.[59] MtDNA is essential for normal mitochondrial function, and a decrease in mtDNA is associated with an increase in the production of $O_2^{\cdot-}$ from the mitochondria. In addition to regulating mitochondrial biogenesis, PGC-1α is a broad and powerful regulator of ROS metabolism that induces ROS-detoxifying enzymes,[60] which are associated with increases in ROS levels in DKD. A renoprotective role of PGC-1α has been reported but is still elusive in diabetes.[61] Mitochondria are extremely dynamic organelles that shift between elongation (fusion) and fragmentation (fission).[62] Mitochondrial fragmentation is the key mechanism in high glucose-induced increases in mitochondrial ROS production.[63] Patients with type 2 diabetes have reduced expression of the mitochondrial fusion protein mitofusin-2,[64] and increased levels of activity of the fission protein dynamin-related protein 1 (Drp1).[65] Deletion of Drp1 from podocytes isolated from diabetic mice reduced $O_2^{\cdot-}$ production, and the pharmacologic Drp1 inhibitor, Mdivi-1, reduced the high glucose-induced mitochondrial $O_2^{\cdot-}$ levels in podocytes.[66] However, the question of whether mitochondria increase $O_2^{\cdot-}$ production in DKD is controversial. Some reports have shown decreased mitochondrial $O_2^{\cdot-}$ production in DKD.[67,68] This discrepancy among studies might be explained by the different animal models used and different stages of DKD. In any case, the relationships among mitochondria and oxidative stress in DKD require further investigation.

Nox is a key source of $O_2^{\cdot-}$ production in different organs, including the kidney, under hyperglycaemic conditions. Nox4 isoform is a major source of $O_2^{\cdot-}$ in the kidney, and plays a pivotal role in the initiation and development of DN.[69] Nox4 expression is elevated in the diabetic rat kidney,[70] and Nox4 inhibition or the genetic deletion of Nox4 protects against DN.[71,72] High glucose-induced increases in Nox4 expression also involved reductions in the activity of adenosine monophosphate-activated protein kinase (AMPK), while the activation of AMPK by 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside inhibited Nox4 and Nox4-dependent kidney hypertrophy, albuminuria, and matrix protein expression.[72,73]

$ONOO^-$ and its secondary metabolites can damage a variety of cellular components. Due to the extremely short lifetime (~10 ms) of $ONOO^-$ in physiological environments, it has proved difficult to measure, but recent progress in fluorescent image methods has shown an increase in $ONOO^-$ levels in the kidney of diabetic rats.[74] This finding is consistent with previous findings of increased $ONOO^-$ in renal homogenates.[75] In this manner, the importance of RNS in the pathophysiology of diabetic kidney might in future be revealed.

4.2 | Nephrosclerosis

Nephrosclerosis is a gradual and prolonged deterioration of the renal arteries. However, renal vascular lesions are seen in some patients in the absence of or preceding the onset of hypertension,[76] and aging kidneys display lesions that are similar to those associated with nephrosclerosis without the accompanying high blood pressure. The direct and indirect actions of ROS may cause vasoconstriction of the intrarenal vessels.[77] ROS can inactivate endothelial $^{\cdot}NO$, which results in impaired vasodilatation, and excessive oxidative stress is involved in impaired endothelium-dependent vasodilatation in patients with renovascular hypertension.[78] While ROS can induce vasoconstriction or vasodilation, depending on the amount produced and the vascular bed,[79] the more common response to $O_2^{\cdot-}$ is vasoconstriction.[77] $O_2^{\cdot-}$ induces an increase in intracellular calcium levels in smooth muscle and endothelial cells,[80] which mediate the actions of other vasoconstrictors, including angiotensin II. Oxidative stress also plays a central role in the pathophysiology of sodium and water retention, given that angiotensin II increases aldosterone secretion and antidiuretic hormone production, which accelerate hypertension.

4.3 | Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic disorders.[81] ADPKD causes a gradual decline in renal function and the formation and enlargement of multiple renal cysts. This cyst growth is due to the proliferation of cyst epithelial cells. Clinical studies have shown that an increase in oxidative stress is present during the early stages of ADPKD, even when a patient's renal function is preserved.[82] We found that a decrease in intracellular calcium concentration caused by polycystin-1 dysfunction, which causes ADPKD, downregulates PGC-1α, thereby reducing mtDNA and increasing mitochondrial $O_2^{\cdot-}$ levels in the cyst epithelial cells. This in turn enhances proliferation via extracellular signal-related kinase 1 and 2 activation.[83] In addition, a recent study suggested a direct role of polycystin-1 in regulating mitochondrial function in renal epithelial cells.[84] These various findings indicate that mitochondria and $O_2^{\cdot-}$ play important roles in the pathogenesis of ADPKD.

5 | RECENT CLINICAL TRIALS TARGETING OXIDATIVE STRESS

Chronic kidney disease-associated oxidative stress is caused by the increased production of ROS and a diminished antioxidant capacity. The latter is largely caused by impaired Nrf2. Indeed, rats in which CKD was induced by 5/6 nephrectomy showed marked and time-dependent reductions in nuclear Nrf2 content in the remnant kidneys.[85] The renal protective effect of Nrf2 is supported by evidence that Nrf2 gene ablation intensifies diabetes-induced inflammation, oxidative stress, and renal injury in an animal model of CKD,[86] and that Nrf2 knockout mice exhibit autoimmune nephritis.[87] The most potent known activators of the Nrf2 pathway are the synthetic triterpenoid bardoxolone methyl and its analogues. Clinical trials have investigated the renoprotective effect of bardoxolone methyl in patients with type 2 diabetes and CKD. The first trial targeted patients with type 2 diabetes and stages 3b and 4 CKD, and showed that bardoxolone methyl increased kidney function after treatment for 56 days.[88] The second study investigated the longer term effects of bardoxolone methyl in patients with CKD and type 2 diabetes, and showed improvements in estimated GFR at 24 weeks which persisted at 52 weeks.[89] While a third clinical trial also demonstrated that patients treated with bardoxolone methyl showed significant improvements in their estimated GFRs compared with placebo, the patients administered bardoxolone methyl also showed a significantly higher incidence of cardiovascular events, and the trial was terminated early because of safety concerns.[90] However, all of these findings showed improvements in kidney function. Based on these results, a new clinical study (the TSUBAKI Study, https://clinicaltrials.gov/ct2/show/NCT02316821) is ongoing in Japan, because the incidence of cardiovascular diseases is lower among Japanese people than in European and American people. The individuals participating in the TSUBAKI study are patients with stages 3-4 CKD and type 2 diabetes who do not have cardiovascular risks, and the results show improvements in the GFR that are calculated based on insulin clearance (unpublished).

6 | CONCLUSIONS

In summary, ROS and RNS are important intracellular messengers in both the kidneys as well as other organs. ROS itself is not harmful; rather, problems arise in relation to the strength and duration of exposure to ROS. Rather than inhibit ROS totally, it is important to control ROS moderately at the right time. As explained in this review,

the kidney has strong associations with ROS, and progress in this area of research will improve the prognosis of patients who are diagnosed with kidney disease.

ACKNOWLEDGEMENTS

This work was supported by Japan Society for the Promotion of Science (25461207, 15KT0088, 16K15465, 16K09604 and 18H02727).

COMPETING FINANCIAL INTERESTS

The authors declare that they have no competing financial interests.

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How to cite this article: Ishimoto Y, Tanaka T, Yoshida Y, Inagi R. Physiological and pathophysiological role of reactive oxygen species and reactive nitrogen species in the kidney. *Clin Exp Pharmacol Physiol*. 2018;45:1097–1105. https://doi.org/10.1111/1440-1681.13018