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Review

Reducing Oxygen Demand to Alleviate Acute Kidney Injury

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Abstract

Maintaining a balance between the supply and demand of oxygen is vital for proper organ function. Most types of acute kidney injury (AKI) are characterized by hypoxia, a state where the supply of oxygen cannot match the demand for normal cellular activities. Hypoxia results from hypo perfusion and impaired microcirculation in the kidney. It inhibits mitochondrial oxidative phosphorylation, resulting in a decrease in production of adenosine triphosphate (ATP), which is essential to power tubular transport activities, especially reabsorption of Na^+, and other vital cellular activities. To ameliorate AKI, the majority of studies have focused on increasing renal oxygen delivery by restoring renal blood flow and altering intra-renal hemodynamics. However, to date these approaches remain inadequate. In addition to augmenting oxygen supply, increasing renal blood flow also increases glomerular filtration rate, leading to increased solute deliver and workload for the renal tubules, causing an increase in oxygen consumption. The relationship between Na^+ reabsorption and oxygen expenditure in the kidney is linear. Experimental models have demonstrated that inhibition of Na^+ reabsorption can alleviate AKI. Since the proximal tubules reabsorb approximately 65% of filtered Na^+, consuming the largest portion of oxygen, many studies focus on examining the effects of inhibiting Na^+ reabsorption in this segment. Potential therapeutics that have been examined include acetazolamide, dopamine and its analog, inhibitors of the renin-angiotensin II system, atrial natriuretic peptide, and empagliflozin. The effectiveness of inhibition of Na^+ reabsorption in the thick ascending limb of the Loop of Henle by furosemide has been also examined. While these approaches produced impressive results in animal models, their clinical benefits remain mixed. This review summarizes the progress in this area and argues that the combination of increasing oxygen supply with decreasing oxygen consumption or different approaches to reducing oxygen demand will be more efficacious.

Keywords: mitochondria; oxygenation; hypoxia; Na^+-H^+ exchanger 3; Na^+-dependent glucose transporter 2; Na^+ reabsorption

1. Introduction

Acute kidney injury (AKI) is defined by a sudden decrease in glomerular filtration rate (GFR), occurring within hours to weeks, along with the retention of nitrogenous waste products and renal parenchymal damage. Examples of AKI include acute tubular necrosis, acute interstitial nephritis, and glomerulonephritis. Based on the Kidney Disease: Improving Global Outcomes criteria, AKI is diagnosed by an absolute increase in serum creatinine levels of at least 0.3 mg/dL (26.5 μmol/L) within 48 hours, or a 50% increase in serum creatinine from baseline within 7 days, or a urine volume of less than 0.5 mL/kg/h for at least 6 hours [1]. Acute kidney injury occurs in a variety of settings, including major surgeries, transplantation, hemorrhage, burns, sepsis, lower limb ischemia/reperfusion, and the administration of nephrotoxic medications [2–6]. Conversely, chronic kidney disease (CKD) is the gradual loss of nephrons in both number and function. Chronic kidney disease is diagnosed by a persistent abnormality in kidney structure or function such as GFR $<$60 mL/min/1.73 m^2 or albuminuria $\geq$30 mg per 24 hours for more than 3 months. Arteriolosclerosis, glomerulosclerosis and tubulointerstitial fibrosis are the common pathologic themes of CKD. Important risk factors for developing CKD include hypertension, diabetes, polycystic kidney disease, and sickle cell disease [7–9]. Chronic kidney disease can eventually result in end-stage kidney disease. Traditionally, AKI and CKD were considered as separate entities. However, newer paradigms recognize continuity between these two diseases, with AKI resulting in CKD and CKD being a recognized risk factor for AKI [7,9].

Acute kidney injury is associated with poor outcomes. Acute kidney injury is independently associated with both short and long-term morbidity and mortality [6,10–13]. For example, a recent study of 1286 COVID-19 patients in Belgium demonstrated that all stages of AKI were associated with increased ICU mortality rates with 9.3% at stage 1, 40.1% at stage 2 and 47.0% at stage 3 compared to 3.6% with no AKI [14]. Furthermore, the incidence of AKI is steadily rising due to an aging population, increased prevalence of CKD, and improved recognition by physicians [15]. In addition to the high human cost, AKI imposes a heavy financial burden on society. In the United States, the in-hospital costs for AKI ranged from $5.4 to $24.0 billion annually [16]. In Queensland, Australia, a study found that the mean total hospital cost in patients with AKI was more than triple that of patients without AKI ($93,042 vs $30,778) [17].

In order to achieve clearance, the human kidney filters approximately 180 liters of blood each day. This filtrate is composed of both harmful metabolites and essential elements for life, such as NaCl, amino acids, and glucose. Approximately 99% of water and ions, and 100% of amino acids and glucose are reabsorbed by the renal tubules through the transcellular and paracellular pathways. The Na^+,K^+-ATPase is fundamental for the absorptions. In the transcellular pathway, it keeps the intracellular Na^+ electrochemical potential lower than the extracellular one, which allows Na^+ and Na^+-coupled reabsorption [18–21]. In the paracellular pathway, the Na^+,K^+-ATPase-dependent ion transport generates the transepithelial voltage favoring certain ion absorption [21]. In aerobic states ATP is generated by mitochondria predominantly through oxidative phosphorylation. To meet the demand of mitochondria for oxygen, the kidney has the largest blood supply (approximately 25% of cardiac output) only next to the heart under a resting state [22]. There is an almost perfect linear relationship between Na^+ reabsorption and oxygen consumption by the kidney [23]. In addition to supporting aerobic metabolism, oxygen is also needed to generate reactive oxygen species which, at a low level, signal many fundamental cellular activities [24].

Despite diverse etiologies, the majority of AKI sub types share common pathophysiologic mechanisms, including microvascular dysfunction and inflammation [3]. Microvascular dysfunction leads to hypoxia. Hypoxia is a state where oxygen supply cannot meet oxygen demand, which has a profound impact on kidney function (Fig. 1). Artificially induced hypoxia by increasing oxygen consumption with triiodothyronine without other compounding factors induces kidney injury in rats [25]. Similarly, treating rats with normobaric hyperoxia per se helps renal recovery from warm ischemia-induced injury [26]. Hypoxia compromises mitochondrial aerobic metabolism by diminishing nicotinamide adenine dinucleotide hydrogen (NADH) supply and electron transport [27]. Hypoxia leads to the accumulation of non-esterified fatty acids, which contributes to activation of pro-inflammatory pathways and produces reactive oxygen species, resulting in apoptosis and necrosis [28,29]. Furthermore, inflammation directly inhibits mitochondrial respiration. As a result, the ability of mitochondria to generate ATP is compromised and the cellular ATP levels are reduced in AKI [30]. Therefore, AKI has been broadly characterized as a state of tubular ATP depletion [31].

To make matters worse, the efficiency of the kidney in using oxygen to reabsorb Na^+ is reduced in AKI. Redfors *et al*. [32] measured renal blood flow, oxygen extraction, Na^+ filtration and excretion in 12 patients with AKI and 37 patients without AKI in a cardiothoracic intensive care unit. They found that renal blood flow was reduced by 40% and renal Na^+ reabsorption was reduced by 59% in subjects with AKI. However, renal oxygen extraction was

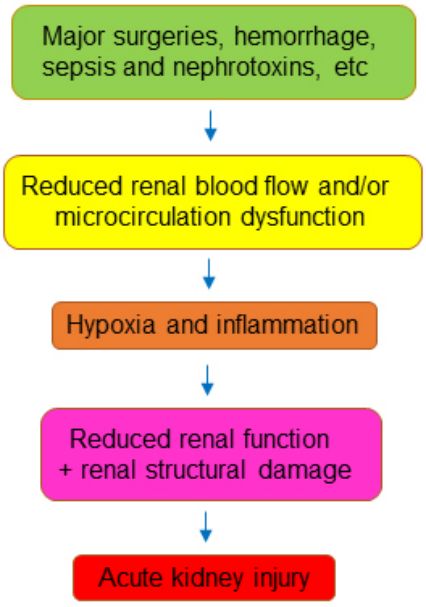

Fig. 1. A common mechanism for acute kidney injury.

increased by 68% in patients with AKI compared to those without AKI. This resulted in an approximately 2.4-fold increase in the amount of oxygen required to absorb the same amount of Na^+ [32]. Similar results were also found for sepsis-induced AKI in humans, rats, and mice [30,33,34]. A potential reason for this decrease in efficiency is the loss of epithelial polarization and tight junction integrity, which cause back leak and make Na^+ transport less efficient [32,34–36]. This has been observed in the mouse kidney after ischemia/reperfusion- and endotoxemia-induced injury [37,38]. Inhibition of nitric oxide synthase more than doubles renal oxygen extraction/Na^+ reabsorption in dogs and rats [39,40]. It is also possible that AKI damages endothelial cells and inhibits endothelial nitric oxide synthase, leading to inefficient use of oxygen for Na^+ reabsorption [32,34–36]. Regardless of the cause, if more ATP is consumed for reabsorption of Na^+, less ATP will be left for maintenance of cell integrity, resulting in cellular injury.

To restore the balance between oxygen supply and demand, many studies have examined increasing oxygen supply. Examples include fluid resuscitation, vasoconstrictors and removing the underlying cause of AKI (e.g., antibiotics and nephrotoxic medications). These approaches have been reviewed previously [41–43]. While these approaches unarguably improve patient outcomes, they are clearly insufficient. In most tissues, increasing blood flow will increase tissue oxygenation, however, the kidney is an exception to this rule. The variation in plasma Na^+ concentrations is minimal in both healthy and disease states. Therefore, the delivery of Na^+ into tubules is directly correlated to GFR. An increase of renal blood flow increases GFR, resulting in increased Na^+ delivery and subsequent Na^+ reabsorption and oxygen consumption [35,36]. For example, infusion of a vasodilator atrial natriuretic peptide (ANP) to

Table 1. List of the clinical results in treatments of AKI.

Medications	Mechanisms	Inducers of AKI	Timing therapy		Patient #		Results	References
			Prevention	Treatment	Control	Medications		
A. Proximal tubules								
1. Inhibition of NHE3								
Acetazolamide	Reducing production of H^+	Contrast	X		46 received HCO_3^-	50 received acetazolamide	Scr decreased	[62]
		Contrast	X		96 received HCO_3^-	96 received acetazolamide	Scr decreased	[64]
							eGFR increased	
		Cisplatin	X		20 received mannitol	15 received acetazolamide	AKI risk decreased from 30% to 8.9%	[63]
		Coronary artery bypass surgery	X		65 received placebo	65 received acetazolamide	ineffective	[65]
		ICU setting		X		868	AKI 26.8% vs vancomycin 16% and gentamicin 20%	[66]
Dopamine	Inhibiting NHE3 translation and surface expression and promoting NHE3 degradation	Operation for cardiac diseases		X	40 received furosemide, bumetanide or ethacrynic acid	60 received furosemide, mannitol and dopamine	Dialysis decreased from 90% to 6.7%	[82]
		Cardiac surgery	X		40 received saline	42 received dopamine	ineffective	[84]
Fenoldopam	Dopamine receptor agonist	Post operation		X	87 received furosemide	39 received furosemide and fenoldopam	Tend to increase urine output (p = 0.06)	[68]
Fenoldopam	Dopamine receptor agonist		X		Total patient #			[67]
		Post operation			958		Reduced onset and incidence of AKI	
					917		ineffective	
		Contrast-induced			501		Reduced onset and incidence of AKI	
					714		ineffective	
		ICU setting			417		Reduced onset and incidence of AKI	
					155		ineffective	
Human atrial natriuretic peptide (hANP)	Possibly modulating dopamine system	ICU setting		X	30 received placebo	29 received hANP	Improved creatinine clearance	[83]
hANP		ischemic or nephrotoxic insults		X	114 received placebo	108 received hANP	Increased morbidity and mortality	[85]
ARBs and ACEIs	Inhibiting the stimulatory effect of angiotensin II on NHE3	Major operation	X		18,871 received no ARBs or ACEIs	268 received ARBs and 1137 received ACEIs	Reduced incidence of AKI	[72]

Table 1. Continued.

Medications	Mechanisms	Inducers of AKI	Timing therapy		Patient #		Results	References
			Prevention	Treatment	Control	Medications		
ARBs and ACEIs		ICU setting		X	3179 received no ARBs or ACEIs	3179 received ARBs or ACEIs	Reduced all-cause mortality	[73]
ARBs and ACEIs		Multiple inducers		X	40,000 received no ARBs or ACEIs	30,801 received ARBs or ACEIs	Reduced all-cause mortality and recurrent AKI	[74]
ARBs and ACEIs		COVID-19	X	X	279 received no ARBs or ACEIs	164 received ARBs or ACEIs	Reduced all-cause mortality	[69]
ARBs and ACEIs		COVID-19	X		220 received no ARBs or ACEIs	80 received ARBs or ACEIs	Ineffective	[70]
ARBs and ACEIs		COVID-19	X		100 received no ARBs or ACEIs	30 received ARBs or ACEIs	Increased mortality and risk of AKI	[71]
Spironolactone	Inhibiting aldosterone-dependent Na^+ reabsorption	Cardiac surgery	X		118 received placebo	115 received spironolactone	Ineffective	[75]
Clonidine	Inhibiting sympathetic nerve-mediated activation of NHE3	Non-cardiac surgery	X		3452 received placebo	3453 received clonidine	Ineffective	[76]
Dexmedetomidine	Inhibiting sympathetic nerve-mediated activation of NHE3	Aortic surgery	X		54 received placebo	54 received dexmedetomidine	Reduced incidence of AKI	[78]
Dexmedetomidine		Laparoscopic prostatic surgery	X		44 received placebo	45 received dexmedetomidine	Ineffective	[77]
Dexmedetomidine		Sepsis		X	719 received placebo	719 received dexmedetomidine	Improved renal recovery rate and decreased in-hospital mortality	[79]
2. Sglt2 inhibitors								
Empagliflozin	Inhibiting Sglt2	Decompensated heart failure with and without diabetes		X	9 received placebo	10 received empagliflozin	Reduced tubular injury	[80]
Empagliflozin		Decompensated heart failure with and without diabetes		X	30 received standard medical care	10 received standard medical care plus empagliflozin	Increased urine output	[86]
Dapagliflozin	Inhibiting Sglt2	COVID-19	X		606 received placebo	613 received dapagliflozin	Ineffective	[81]
B. Thick ascending limb of the Loop of Henle								
Furosemide	Inhibiting NKCC2	Cardiac surgery		X	283 received placebo	283 received furosemide	Ineffective	[87]

Scr, serum creatinine concentrations; NHE3, Na^+-H^+ exchanger 3; ARBs, angiotensin receptor blockers; ACEIs, angiotensin converting enzyme inhibitors; AKI, acute kidney injury; Sglt2, Na^+-dependent glucose transporter 2; NKCC2, Na^+- K^+-2Cl^- cotransporter.

postoperative patients with normal renal function increases GFR by 15%, Na^+ reabsorption by 9%, and oxygen consumption by 25% [44]. Although direct evidence is lacking, since approaches that increase renal blood flow inherently raise oxygen demand, it is unlikely that these treatments alone will be able to restore the supply-demand balance [35,36].

Reducing oxygen demand is another way to maintain the supply-demand balance of oxygen when supply is low. Western painted turtles (*Chrysemys picta*) can survive under water with little oxygen for as long as 30 hours. They tolerate anoxia in part by reducing Na^+ channels and metabolism in the hepatocytes and brain (channel arrest), therefore, reducing oxygen consumption [45,46]. A similar defensive mechanism may occur in AKI. In one study, mitochondrial oxygen consumption in the proximal tubules is reduced 4 hours after septic AKI despite increased mitochondrial content and biogenesis [30]. This reduction in oxygen consumption is most likely due to reduced demand for ATP synthesis [30]. The Na^+-H^+ exchanger 3 (NHE3) reabsorbs approximate 65% of Na^+ in the proximal tubules [47]. The NHE3-dependent pathway is one of the large oxygen consumers in the renal cortex, if not the largest. Acute kidney injury induced by ischemia/reperfusion, injection of lipopolysaccharides or mercury chloride decreases mRNA and protein levels of NHE3 in murine models [48–51]. In human AKI, there is a loss of the brush border in the proximal tubules where NHE3 is localized [52]. This down-regulation of NHE3 has been interpreted as a defense mechanism against AKI [53]. The hypoxia-inducible factor (HIF) pathway, a key mediator of cellular adaptation in low oxygen tension states, may be another defense mechanism. Epithelial Na^+ channels (ENaC) in the distal nephron participates in Na^+ reabsorption. HIF-1α activation by hypoxia reduces expression of the γ-subunit of ENaC in mice and activity of ENaC in cultured principal cells [54]. Despite marked reduction in renal reabsorption and function, structural injury such as necrosis appears to be relatively mild in AKI [30,55–57]. These observations have led to the hypothesis that early organ dysfunction is a defense mechanism that preserves energy to reduce cell injury and death [53].

How can reducing tubular cell injury and death help preserve and/or delay deterioration of GFR? The renal tubular cells are the primary site of injury in AKI. When the tubular cells undergo necrosis or apoptosis, they detach from the supporting basement membrane and obstruct the tubular lumen, causing back leakage of fluid with resultant decreased clearance. Even a sub-lethal injury can disrupt tight junctions, causing a loss of epithelial integrity and back leakage of fluid. The fluid back leakage further diminishes already impaired glomerular filtration induced by hypoperfusion of the kidney, eventually contributing to the filtration failure [58–61]. Therefore, reducing oxygen demand through inhibition of Na^+ transport in the renal epithelial cells may prevent injury and maintain clearance.

The present review summarizes progress in balancing supply and demand to prevent or treat AKI in patients (Table 1, Ref. [62–87]) and animal models. Acute kidney injury is also associated with oxidative stress, which in turn increases oxygen consumption resulting in kidney tissue hypoxia [88,89]. While various antioxidants have been shown to improve renal oxygenation and ameliorate AKI, reviewing the effect of antioxidants is beyond the scope of this article [90–93].

2. Approaches to Reduce Oxygen Demand in the Proximal Tubules

2.1 NHE3 Inhibition

2.1.1 Chemical Inhibitors

Inhibition of NHE3 with the NHE3 inhibitor #4167 protects against acute rejection of renal grafts in a rat model, an effect associated with preservation of the renal ATP levels [94]. Inhibitors of NHE3, 5-(N-ethyl-N-isopropyl) amiloride and S3226 protect against ischemia/reperfusion-induced AKI in rodents [95,96]. Hypoxia induces intracellular acidosis. Activation of Na^+-H^+ exchanger 3 in the proximal tubules is critical to restore physiologic pH by extruding H^+, but also increases intracellular Na^+ levels, which lead to increased intracellular Ca^{2+} concentrations through the reverse mode of the Na^+/Ca^{2+} exchanger. This increase in intracellular Ca^{2+} above the normal physiological levels (Ca^{2+} overload) contributes to AKI [97,98]. Inhibition of NHE3 by S3226 induces acidosis [95]. Whether inhibition of NHE3 reduces the intracellular Ca^{2+} concentrations in the proximal tubules remains unknown, however multiple studies have demonstrated that inhibition of NHE1 reduces Na^+-dependent Ca^{2+} overload in the heart [99]. Therefore, prevention of Ca^{2+} overload could be another mechanism by which NHE3 inhibitors in alleviate AKI.

2.1.2 Acetazolamide

Acetazolamide is an inhibitor of carbonic anhydrase. It is used clinically to treat glaucoma, epilepsy, high altitude sickness, and congestive heart failure [100]. It is also a diuretic, because inhibition of carbonic anhydrase indirectly leads to inhibition of NHE3 due to reduced production of H^+ [101]. In animal models under healthy conditions, acetazolamide reduces cellular demand for oxygen by inhibiting Na^+ reabsorption and increases oxygen delivery by stimulating blood flow (likely as a result of CO_2 retention) [102–105]. Acetazolamide has been shown to attenuate lower limb ischemia/reperfusion-induced AKI in mice [106]. However, the results for acetazolamide on renal artery-clamp-induced AKI are inconsistent. An *et al.* [107] pre-treated mice with 60 mg/kg/day in drinking water for 48 hours before they clamped the renal artery unilaterally for 30 minutes then released clamps for 48 hours. They found that acetazolamide reduced AKI by restoring renal blood flow, an effect that was associated with in-

creased endothelial nitric oxide synthase (eNOS) activity, nitric oxide (NO) production, hypoxia inducible factor 1 subunit alpha (HIF-1α) expression, and decreased vascular permeability [107]. Conversely, Nensen *et al.* [108] intravenously injected 50 mg/kg of acetazolamide into rats 45 minutes prior to clamping the renal pedicle for 45 minutes unilaterally and then allowed reperfusion for 2 hours. Rats were kept under general anesthesia throughout the experiment. Under this condition, they found that acetazolamide impaired renal oxygenation, increased oxygen consumption, and decreased GFR compared to vehicle-treated rats [108]. In small human trials, there is some evidence to suggest that acetazolamide ameliorates contrast-, cisplatin-, cardiopulmonary bypass- and rhabdomyolysis-induced AKI (Table 1) [62–64,109,110]. However, other clinical studies have demonstrated no beneficial effect or even induction of AKI with acetazolamide (Table 1) [65,66,111]. Acetazolamide-induced AKI was attributed to intra-tubular obstruction by acetazolamide-induced crystalluria in some of these populations [111].

2.1.3 Dopamine

Dopamine inhibits NHE3 activity by inhibiting NHE3 translation [112], promoting ubiquitin-dependent NHE3 degradation [113], decreasing NHE3 exocytosis and cell membrane recycling [114,115]. Dopamine has been shown to increase renal oxygenation in post-cardiac surgery patients. This effect was associated with profound pre- and post-glomerular vasodilation [116]. Fenoldopam is a dopamine receptor agonist, which has been used clinically to treat hypertension in part because of its inhibition of NHE3 [117]. Fenoldopam was effective in reducing the onset of postoperative AKI in adult patients, when used prophylactically (Table 1) [67,68,118]. However, other studies have failed to demonstrate a beneficial effect for fenoldopam (Table 1). Furthermore, its potential benefit to prevent AKI after cardiac surgery in pediatrics remains uncertain [119].

2.1.4 Natriuretic Peptides

Atrial natriuretic peptide is a peptide hormone that is produced by the walls of the heart in response to an increase in blood volume and pressure. It reduces blood volume and pressure in part through inhibition of NHE3 in the proximal tubules [120,121]. Its analogs brain-type and c-type natriuretic peptides have similar functions [122]. How ANP inhibits NHE3 remains incompletely understood, but evidence indicates that it may be mediated in part by modulating the renal dopaminergic system [123]. It appears that while infusion of ANP raises oxygen supply by increasing renal blood flow, it also increases GFR and the subsequent burden for tubular Na reabsorption [44]. However, one small study in high risk surgery patients demonstrated a potential protective effect for ANP on kidney function (Table 1) [122]. Atrial natriuretic peptide is degraded by the endopeptidase neprilysin. Strategies that inhibit neprilysin offer an alternative means by which to raise the ANP levels. The challenge of this approach is that neprilysin also degrades endothelin, bradykinin, vasopressin and angiotensin II, which are critical for many physiologic activities. To circumvent this potential complication, Novartis Pharmaceuticals manufactures a drug named LCZ696, a mixture of the neprilysin inhibitor sacubitril and the angiotensin II receptor 1 blocker valsartan and markets it as Entresto®. Entresto protected the kidney from ischemic AKI in a porcine model of partial nephrectomy [124]. Multiple clinical trials have shown that Entresto does not increase the risk of AKI in patients with heart failure [122,125]. However, whether Entresto has protective and/or therapeutic benefits against AKI in patients remains unknown.

2.1.5 Angiotensin II inhibitors

It has been well described that angiotensin II stimulates NHE3, which contributes to angiotensin II-induced hypertension [126–128]. Angiotensin II increases the levels of NHE3 mRNA and protein [129], stimulates cellular trafficking and exocytotic membrane insertion [130,131], counteracts inhibitory phosphorylation by cAMP/PKA [132], and increases transport activity [133]. Not surprisingly, angiotensin II increases oxygen consumption by renal mitochondria [134]. While angiotensin receptor blockers (ARBs) have repeatedly shown benefits in animal models of AKI [135–138] and CKD in humans [139–141], the results from clinical trials of AKI with ARBs and angiotensin converting enzyme inhibitors (ACEIs) have had mixed results (Table 1). One potential adverse impact of ACEIs and ARBs in the setting of AKI is that they could worsen renal hypoperfusion. In the cases where ACEIs and ARBs have shown potential benefit, namely hypertensive COVID-19 and sepsis, it remains unclear whether the effect was mainly due to control of blood pressure or reducing oxygen consumption in the proximal tubules [69,142,143]. Conversely, other studies have shown either no difference or increased risk of AKI and mortality in the hospitalized COVID-19 patients treated with ACEIs or ARBs [70,71,144,145].

The results from trials examining patients undergoing major surgeries are also mixed. One study showed that ARBs and ACEIs were associated with a reduced risk of AKI after major surgery [72]. However, Zhou *et al.* [146] reported no significant association between perioperative use of renin-angiotensin system inhibitors and postoperative AKI in patients undergoing cardiac surgery. Other studies generally agree that ACEIs or ARBs increase survival, but also increase acute kidney disease, which is defined as persistent AKI from 7–90 days [73,74,147].

2.1.6 Aldosterone Inhibitors

Aldosterone binds to the mineralocorticoid receptors to increase sodium reabsorption and potassium secretion

in the distal nephron. The expression of mineralocorticoid receptors has been detected in other tissues as well, where its activation may be pathophysiologic. Angiotensin II stimulates the biosynthesis and release of aldosterone from the adrenal cortex zona glomerulosa [148,149]. Aldosterone stimulates NHE3 and Na^+,K^+-ATPase activities in cultured human renal proximal tubule cells [150,151]. Whether aldosterone has a similar effect on NHE3 and Na^+,K^+-ATPase in the native proximal tubules remains unknown, but aldosterone appears to inhibit NHE3 in the microperfused medullary thick ascending limb [152]. Inhibition of angiotensin II (as reviewed above) should inhibit the effect of aldosterone. Blockade of aldosterone from binding its mineralocorticoid receptors with receptor antagonists, for example spironolactone, have been shown to prophylactically and therapeutically attenuate AKI in rats and pigs [138,153–155]. However, the benefits of spironolactone seen in these animal models have not been reproduced clinically. A clinical trial with 115 patients on spironolactone and 118 patients on placebo demonstrated that spironolactone was not protective against AKI after cardiac surgery and there may be even a trend towards harm [75]. Indeed, a survey of the MEDLINE and EMBASE databases found that spironolactone had the highest odd ratio of inducing AKI among the reported medicine-induced AKI cases [156].

2.1.7 Angiotensin 1-7

Angiotensin 1-7 is generated mainly by angiotensin-converting enzyme 2 and exerts its actions via activation of its receptor Mas. Its functions frequently oppose angiotensin II [157]. Angiotensin 1-7 has been shown to inhibit NHE3 activity in the proximal tubules of normotensive and hypertensive rats [158,159]. Angiotensin 1-7 also inhibits NHE3 activity by modulating the renal dopamine system [160]. Angiotensin 1-7 decreases oxygen consumption in the thick ascending limb of the loop of Henle and presumably in the proximal tubules as well [161]. Angiotensin 1-7 alleviates AKI in a variety of animal models [162–165]. However, whether it has a similar effect in humans remains unknown.

2.1.8 Adenosine Receptors

Adenosine is present at low concentrations in the extracellular space, but its levels are greatly increased in conditions of metabolic stress, such as hypoxia as a result of enzymatic cleavage of the nucleotide adenosine 5′-monophosphate (AMP) by 5′-nucleotidase. Four types of adenosine receptors have been identified along the nephron. They are A_1, A_{2A}, A_{2B} and A_3. Although the exact molecular mechanisms are unclear, activation of A_1 and A_3 inhibits NHE3, whereas activation of A_{2A} inhibits the action of A_1 [166,167]. Inhibition of A_1 receptors by its knockout or its selective antagonist 1,3-dipropyl-8-cyclopentylxanthine worsens sepsis- and ischemia/reperfusion-induced AKI [168,169]. On the contrary, activation of A_1 receptor by its selective agonist 2-chlorocyclopentyladenosine, inhibits ischemia/reperfusion-induced AKI in mice [168].

2.1.9 Sympatholytics

The kidney is densely innervated by sympathetic nerves. Activation of these nerves increases renal vascular resistance and reduces renal blood flow by releasing norepinephrine and renin [170,171]. Moreover, activation of these nerves increases NHE3 and Na^+,K^+-ATPase activity [172–174]. Acute kidney injury is frequently accompanied by activation of the sympathetic nerves. Inhibition of the sympathetic nervous system has been repeatedly demonstrated to alleviate AKI in various animal models [170,171]. However, the clinical benefit of this approach is inconsistent. The sympatholytic effect of clonidine and dexmedetomidine is mediated by stimulating the pre-synaptic α_2 adrenoceptors, thereby decreasing norepinephrine release from both central and peripheral sympathetic nerve terminals. A multi-center clinical trial of 6905 non-cardiac surgery patients with 3453 patients on clonidine and 3452 patients on placebo found that perioperative clonidine administered did not reduce the risk of AKI [76]. Similarly, dexmedetomidine has not shown a benefit for preventing AKI in patients undergoing laparoscopic prostatic surgery (Table 1) [77]. On the other hand, a single center trial with 54 patients on dexmedetomidine and 54 patients on placebo showed a beneficial effect for dexmedetomidine in patients undergoing aortic surgery [78]. A recent updated systematic review and meta-analysis of 16 studies involving 2148 patients revealed that dexmedetomidine administration may prevent AKI and postoperative delirium after cardiac surgery. This meta-analysis also suggests that dexmedetomidine may reduce the length of stay in the intensive care unit [175]. Likewise, dexmedetomidine administration was associated with improvements in renal function recovery and in-hospital survival in critically ill patients with septic AKI [79]. Whether the way of administration and types of AKI causes the different clinical outcomes of the sympatholytics on AKI remains unclear.

It is important to emphasize that the renoprotective effects of fenoldopam, ANP, activation of adenosine receptor A1, inhibition of angiotensin II system and sympatholytics are not entirely mediated by inhibition of NHE3. The well-known hemodynamic effects of these approaches also contribute significantly to their reno-protection [67,118,122,157,176,177].

2.2 Na^+-Dependent Glucose Transporter 2 (Sglt2) Inhibitors

Na^+-dependent glucose transporter 2 has a high capacity and is responsible for reabsorption of almost all filtered glucose. By reducing glucose re-absorption from the proximal tubules, Sglt2 inhibitors are a class of anti-diabetic medications, which include empagliflozin, canagliflozin

and dapagliflozin [178]. Hyperglycemia increases the burden of reabsorption of glucose and energy expenditure in the proximal tubules and induces hypoxia in the diabetic rat cortex. Inhibition of Sglt2 normalizes oxygen tension in the renal cortex of the diabetic rats [179,180]. However, a lack of effect of dapagliflozin on renal microvascular oxygen tension in diabetic rats was recently reported [181]. Multiple systemic reviews of clinical studies and trials have revealed that diabetic patients who took Sglt2 inhibitors had lower odds of AKI compared to those who did not [178,182–186]. However, this beneficial effect of Sglt2 inhibitors on AKI risk has not been universally observed [178, 187,188]. The potential nephro-protective mechanisms of Sglt2 inhibitors include lowering blood glucose and body weight, inhibiting inflammation, improving cardiovascular function, increasing tubuloglomerular feedback, and increasing tubular oxygenation [178,182–185,189]. The effects of Sglt2 inhibitors on AKI in non-diabetic patients have not been widely reported. Empagliflozin significantly reduced AKI parameters in patients with acute decompensated heart failure [80]. Dapagliflozin had no significant effect on the risk of AKI in the hospitalized COVID-19 patients (Table 1) [81]. In these two studies, both diabetic and non-diabetic patients were included. In contrast, the beneficial effects of Sglt2 inhibitors on AKI in non-diabetic animals has been repeatedly demonstrated. Na^+-dependent glucose transporter 2 inhibitors protect the kidney against sepsis-, ischemia/reperfusion-, contrast-, and myocardial infarction-induced AKI in rodents [179,190–193]. However, knockout of Sglt2 offers no protection against renal artery clamping-induced AKI, implying that the reno-protective effects of Sglt2 inhibitors may not be mediated through Sglt2 in rodents [194]. Na^+-dependent glucose transporter 2 is co-localized with NHE3 [195]. Studies have shown that empagliflozin inhibits NHE3 in the kidney and NHE1 in the heart [196,197]. The cardioprotective effect of empagliflozin against ischemia is thought to be due to its inhibition of NHE1 [197]. Therefore, it is possible that the reno-protective effect of Sglt2 inhibitors against AKI may also involve inhibition of NHE3.

3. Approaches to Reduce Oxygen Demand in the Thick Ascending Limb of the Loop of Henle

Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) is located in the apical membrane of the epithelial cells in the thick ascending limb of the loop of Henle. It facilitates approximately 20–25% of the reuptake of filtered NaCl. Therefore, oxygen consumption by this segment of nephron is second only to the proximal tubule. Furosemide, a diuretic that inhibits NKCC2, was shown to improve renal oxygenation in patients [44,198] and reduces ischemia/reperfusion-induced AKI in animal models [199,200]. However, furosemide has had disappointing results in clinical studies (Table 1). A meta- analysis of 2084 patients in 9 studies found that furosemide combined with intravenous fluids had no significant impact on the incidence of contrast-induced AKI in patients after coronary intervention, but could reduce major adverse cardiovascular events and mortality [201]. Combination of infusing furosemide with dopamine or ANP in patients with AKI after cardiac surgery decreased the need for dialysis and improved dialysis-free survival rates in two studies [82,83]. However, a systemic review and meta-analysis of randomized clinical trials found that the quantity and quality of evidence for using furosemide to treat AKI in adult post-operative patients were very low with no firm evidence for benefit or harm [202]. Abraham *et al*. [203] also found that furosemide infusion in early-onset AKI did not reduce the progression to a higher stage of AKI in critically ill children.

4. Na^+,K^+-ATPase

Na^+,K^+-ATPase is localized to the basolateral membrane of the entire renal tubules, from the proximal tubules to the inner medullary collecting ducts. The basolaterally located Na^+,K^+-ATPase is the only pathway to pump out intracellular Na^+ that enters the renal epithelial cells from the apical NHE3, Sglt2, NKCC2 and other Na^+-dependent transporters. Inhibition of the apical Na^+ entry will reduce the availability of Na^+ to Na^+,K^+-ATPase, thus reducing the activity of the enzyme and oxygen expenditure, whereas stimulation of apical Na^+ entry does the opposite. Dopamine inhibits Na^+,K^+-ATPase activity [204, 205]. Dopamine stimulates cAMP-dependent inhibitory phosphorylation α-subunit of the enzyme [206]. The renal dopaminergic system and ANP acted synergistically to produce a potent inhibition of Na^+,K^+-ATPase [123]. Dopamine and hypoxia induces endocytosis of Na^+,K^+-ATPase through protein kinase C-dependent phosphorylation of the α-subunit [207]. Angiotensin II stimulates Na^+,K^+-ATPase activity [208], whereas angiotensin 1-7 does the opposite [209]. However, it remains unknown whether these hormones directly regulate Na^+,K^+-ATPase or indirectly regulate the pump by affecting Na^+ entry from the apical membrane [210].

4.1 Improving the Na^+,K^+-ATPase Efficiency

Chen *et al*. [211] recently reported the development of the third generation of a synchronization modulation electric field device. This device consists of three phases: synchronization, modulation and maintenance. In the synchronization phase, the device uses electric field to synchronize the Na^+,K^+-ATPase molecules by using ATPs to actively transport Na^+ and K^+. At the same time, the device applies electric energy to the Na^+,K^+-ATPase molecules so that the pumps could synthesize one ATP at the end of each pumping cycle. Thus, ATP consumption is markedly reduced. In the modulation phase, the Na^+,K^+-ATPase transporting rates are gradually modulated (increased or decreased) to the desired values, and the transporting rates are sustained

at the target value throughout the maintenance phase. Application of this technique to a renal ischemia-reperfusion injury mouse model preserved Na^+,K^+-ATPase activity, thereby reducing kidney injury, as reflected by 40% lower plasma creatinine in the treated group as compared to the untreated control group. In a mouse kidney transplantation model, renal graft function was improved by more than 50% with the application of this technique based on GFR measurement compared with the untreated group.

4.2 Endothelin Inhibition

Endothelin-1 is an endogenous 21 amino acid peptide that has powerful vasoactive properties. In the kidney, endothelin-1 is produced by endothelial, epithelial and mesangial cells. Endothelin-1 acts through binding to its type A and type B endothelin receptors to modulate renal blood flow, GFR, reabsorption of sodium and water, and acid-base balance [212–214]. Ischemia/reperfusion of the kidney increases endothelin concentration in the renal cortex and decreases renal blood flow [215,216]. Endothelin receptor antagonists such as ambrisentan and bosentan attenuated ischemia/reperfusion-induced experimental AKI [217,218]. However, the reno-protective effect is due to an increase in oxygen supply from increased renal blood flow rather than a reduction of oxygen consumption [216–219], because endothelin-1 actually inhibits Na^+,K^+-ATPase [220,221] and NKCC2 [222]. The clinical benefits of endothelin receptor antagonists on AKI have not been reported.

5. Perspectives

The pathophysiology of AKI is complex, involving hypoperfusion, impaired microcirculation, hypoxia, oxidative stress, abnormal coagulation, and inflammation. There is no single approach that can address all aspects of this complicated pathophysiology. Further, addressing one aspect may exacerbate other aspects, even within the concept of reducing oxygen demand. For example, although furosemide reduces oxygen consumption by inhibiting NKCC2 in the thick ascending limb of the Loop of Henle, it also activates the renin-angiotensin-aldosterone system. Combining different treatments that increase oxygen supply and decrease oxygen consumption or different approaches to reduce oxygen consumption may be a better approach. A good example is the synergistic effect observed with using fenoldopam in combination with furosemide in treatment of AKI in critically ill surgical patients [68].

Abbreviations

ACEIs, angiotensin converting enzyme inhibitors; AKI, acute kidney injury; ANP, atrial natriuretic peptide; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease; NHE3, Na^+-H^+ exchanger 3; NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; Scr, serum creatinine concentration; Sglt2, Na^+-dependent glucose transporter 2.

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Author Contributions

XZ conceived ideas, searched for references, drafted, edited and approved the manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The author declares no conflict of interest.

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