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Tubular transport in acute kidney injury: Relevance for diagnosis, prognosis and intervention

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Abstract

The clinical diagnosis and recovery of acute kidney injury (AKI) are mainly based on the rapid decline of GFR and its subsequent recovery. The factors that determine recovery and reduce the risk of subsequent progression to chronic kidney disease (CKD), however, are poorly understood. Thus, there is a need to better define the magnitude and time pattern of changes in kidney function during AKI and its recovery that go beyond GFR. Tubular transport regulates body homeostasis and the associated transport work is a primary determinant of the kidneys energy needs. The tubular system is at the center of the pathophysiology of AKI and its recovery. In particular, proximal tubules and thick ascending limbs have been proposed to act as sensors, effectors, and injury recipients of AKI stimuli. Surprisingly little attention has been given to aspects of tubular transport function in AKI and the relevance for kidney recovery. This review aims to outline changes in tubular transport function in AKI, discusses their potential consequences and relevance for the diagnosis and prognosis of AKI and its recovery, including changes in GFR, and poses the question whether tubular transport provides an opportunity for intervention to rest the tubular system, which may have consequences for the progression to CKD.

Keywords

sublethal injury; reabsorption; secretion; ischemia-reperfusion; recovery

Need to define kidney function during AKI beyond GFR

Acute kidney injury (AKI) is increasingly recognized as a major contributor to adverse outcomes including the development of chronic kidney disease (CKD). Non-recovery from AKI is associated with worse outcomes including higher mortality, reduced functional status and increased resource utilization [1;2]. In most cases renal recovery has been defined as a return of GFR or dialysis independence at hospital discharge [3] without consideration of other kidney functions. The factors that determine recovery and reduce the risk of

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subsequent progression to CKD, however, are poorly understood. Thus, there is a need to better define the magnitude and time pattern of changes in kidney function during AKI and its recovery that go beyond GFR. Tubular transport regulates body homeostasis and the associated transport work is a primary determinant of the kidneys energy needs. Evidence is accumulating that places the tubular system at the center of the pathophysiology of AKI and its recovery, where cells of both proximal tubules (PT) and thick ascending limbs (TAL) have been proposed to act as sensors, effectors, and injury recipients of AKI stimuli [4]. Early events and subsequent signaling from these cells initiate complex and multidimensional cascades that mediate AKI pathophysiology [4;5]. This brief review will discuss changes in tubular transport function in AKI, the relevance for AKI diagnosis and prognosis, and its potential as a therapeutic target. The focus of the discussion will be on ischemic AKI but similar considerations may apply to nephrotoxic forms of AKI.

The paradigm of human ischemic AKI

(e.g. due to post-surgery renal hypoperfusion) is characterized by dissociation of structural and functional changes in the kidney. Significant increases in serum creatinine are often associated with near-normal renal morphology, including only mild interstitial edema and mononuclear infiltration as well as brush border diminishment, changes which have been associated with sublethal tubular injuries [6–8]. Apoptosis, necrosis, and cell loss are often subtle, focal, and localized to segments in the outer medulla (OM) including proximal straight tubule (PST), mTAL, and medullary collecting duct (CD). While tubular energy supply may be sufficient to maintain tubular cell viability, it can be insufficient to maintain normal tubular transport activities. Moreover, the persisting transport activities may aggravate hypoxia, injury and inflammation, particularly in the vulnerable OM. Due to limited availability of data in humans, the following discussion will be mostly based on experimental data in rodents with renal ischemia reperfusion (IR).

Ischemic AKI induces tubular brush border loss associated with impaired fluid/Na^+ reabsorption

Early sublethal injuries in IR-induced AKI in rodents are associated with a loss of the luminal brush border in proximal tubules that appear to have otherwise normal ultrastructure, thus resembling the above described human paradigm. Alterations in the brush border are associated with reduced proximal tubular Na^+ reabsorption and involve coalescence of the microvilli [9;10], fragmentation into the lumen, or invagination [9–11], followed by reappearance of microvilli on the apical surface during recovery [9;10]. Johnston et al. described in *in vivo* microperfusion studies in rats that at 25 min of reperfusion after total renal artery occlusion for 35 min the reabsorption of fluid/Na^+ in proximal convoluted tubules (PCT) was reduced to 30%, which was associated with a nearly complete loss of the brush border in these segments. Despite restoration of cell morphology including apical brush border to normal after 4 hours, transport of fluid/Na^+ in PCT recovered only partially to 50%. In contrast, proximal tubular reabsorption of angiotensin II and insulin were not affected, indicating a lower sensitivity of these transport mechanisms to IR [12]. While this IR protocol did not affect the recovery of inulin in PCT [18], it lead to

measurable inulin leakage in PS) and beyond [13], consistent with the greater vulnerability of these downstream segments. Temporal correlations between brush border loss and the increase in fractional renal Na^+ excretion following IR have been well established [9;14].

Ischemic AKI impairs expression of tubular Na^+ transporters

The basolateral Na^+-K^+- ATPase activity provides the concentration gradient for apical Na^+ uptake in kidney tubules. Dysregulation of basolateral Na^+-K^+-ATPase expression has been implicated in the early impairment of proximal tubular Na^+ reabsorption in IR, including reduced mRNA and protein expression [15–17] as well as a rapid, injury duration-dependent redistribution of Na^+-K^+-ATPase to the apical membrane as described by Molitoris and colleagues [18–20]. This loss of surface membrane polarity was associated with disruption of the cortical actin microfilament network and the opening of cellular tight junctions; the latter allows the lateral intramembranous diffusion of membrane components into the alternate surface membrane domain [18–20].

Kwon et al. performed bilateral renal artery occlusion for 30 or 60 min in rats followed by analyses at 1 or 5 days. They reported that the IR-associated increase in fractional renal Na^+ excretion on day 1 was associated with reductions in creatinine clearance as well as lower renal expression of Na^+-K^+-ATPase, as well as the apical transport proteins, Na^+-H^+ exchanger NHE3 in PT and TAL and the Na^+-inorganic phosphate cotransporter NaPi-II in PT [16]. Five days after low level ischemia (30 min), the creatinine clearance and fractional Na^+ excretion were normalized; however, the recovery of renal expression of the Na^+ transport proteins was incomplete. Sixty minutes of ischemia induced stronger changes in all these parameters on day 1 without any recovery at 5 day [16]. Notably, no statistically significant changes in expression were induced by ischemia in other proximal transport associated proteins like megalin and folate-binding protein, supporting the concept that the vulnerability to ischemia varies among proximal tubule transporters [16]. The study also indicated that the more distal transporters NKCC2 and NCC, expressed in TAL and DCT, respectively, were less strongly affected than NHE3 and NaPI-II, in particular in response to mild ischemia (30 min) whereas longer ischemia also strongly suppressed these distal transporters [16]. Downregulation of renal Na^+ transport protein expression in response to IR is often associated with reduced mRNA expression indicating lower gene transcription [17]. Renal Na^+ reabsorption is followed by osmotic water reabsorption through water channels including aquaporins 1–3, which all have been shown to be downregulated by IR [21;22].

A higher sensitivity of key Na^+ transporters in PCT versus TAL in experimental IR models [16;21] may be due to the applied complete ischemia which ceases GFR: while the ischemia-induced hypoxia impairs the obligatory oxidative metabolism in PCT, the ability of the TAL to perform glycolysis may sustain cell viability, particularly in the absence of transport work. Insults that induce kidney injury while maintaining substantial glomerular filtration, as expected in many human forms of AKI, show transport work-dependent injury in TAL [23].

Inhibition of tubular reabsorption in response to ischemic AKI activates tubuloglomerular feedback (TGF) and contributes to GFR reduction thereby conserving Na^+

Reduced tubular sodium and water reabsorption upstream of the macula densa is expected to lower GFR through tubuloglomerular feedback (TGF). In 1966, studies by Schnermann et al. showed that early distal Na^+ concentration inversely correlated with GFR after renal ischemia of 30–60 minutes or hemorrhage in rats [24]. The authors proposed that lowering GFR via TGF conserves Na^+ when tubular reabsorption is impaired. Subsequent studies supported this concept [25;26], and Thurau and Boylan coined the term “acute renal success” with regard to the reduction in GFR and urine flow rate in AKI [27]. Consistent with the concept that the reduction in GFR also serves to protect the vulnerable tubules, the antioxidant probucol was associated with higher SNGFR and tubular reabsorption at 2 hours of IR in rats but induced more tubular necrosis after 24 hours [28]. Peterson et al. showed that early distal NaCl concentrations inversely related with SNGFR in a single nephron model of uranyl nitrate injury in rats and concluded that activation of TGF best explains the reduction in GFR also in nephrotoxic tubular injury [29]. In addition to the TGF mechanism, a reduction in tubular Na^+ and fluid reabsorption is expected to lower GFR also by increasing the hydrostatic pressure in Bowman space; the latter can be further increased by tubular cast formation and obstruction [30].

Ischemic AKI impairs proximal tubular secretion of organic anions and cations

The secretion of organic anions and cations from peritubular capillary blood into the proximal tubule lumen involves specific transport proteins in the basolateral membrane (e.g., organic cation transporter OCT2, organic anion transporter OAT1 and OAT3) and luminal membrane (e.g., multidrug and toxin extrusion MATE, multidrug resistance proteins MRP2/4)[31]. These pathways are important for renal secretion and thus excretion of many endogenous and exogenous compounds, including: creatinine, a substrate of OCTs and OAT3 [32], whose secretion increases when GFR is reduced; many drugs, toxins (e.g., cisplatin, a OCT2 substrate) as well as para-amino hippurate (PAH; a OAT1 substrate [33]), which due to its efficient tubular secretion and renal elimination is used to determine renal plasma flow. OAT1 and OAT3 also contribute to the renal excretion of uremic toxins, in particular those with high protein binding like indoxyl sulfate [34].

Two days after 30 min bilateral renal pedicle clamp in rats, the renal protein expression was strongly reduced for OCT2 (to 20%), MATE1 (to 40%), OAT1 and OAT3 (both to <10%); this was associated with reduced renal clearance and plasma accumulation of the OCT2 substrates tetraethylammonium (TEA) and the histamine H_2-receptor antagonist famotidine [35]. Thus, organic cations can accumulate in plasma due to AKI-induced impaired uptake into proximal tubules by down-regulation of basolateral OCT2. This process may also limit the uptake and thereby the induced injury by nephrotoxins such as cisplatin [36]. On the other hand, IR also increased the kidney concentration of TEA, which may reflect renal accumulation due to impaired luminal exit via MATE1 [35].

A time-dependent rapid downregulation of OAT1 and OAT3 mRNA (to <30% at 24 hrs) was also shown after IR in rats (30 min bilateral pedicle clamp); this was associated with serum retention of creatinine but also of the uremic toxin IS [37], consistent with proposed roles of OAT1 and OAT3 in the renal secretion of IS [32;38]. Thus, AKI-induced downregulation of OAT1 and OAT3 is likely to contribute to the serum accumulation of uremic toxins and the potential detrimental consequences. The reported serum retention of creatinine in AKI may reflect the reduction in GFR and OCT/OAT-mediated tubular secretion. Downregulation of renal OAT1 expression after IR in rats (45 min bilateral renal artery clamp) was associated with reduced renal PAH secretion; furthermore, OAT1 expression, PAH secretion and GFR (by inulin clearance) normalized over 7 days after IR, indicating a coordinated recovery of tubular secretion and glomerular filtration [33]. Corrigan et al. determined PAH extraction in human post ischemic AKI, namely in allograft recipients, at 1–3 hrs after reperfusion and on postoperative day 7 [39]. Based on the results of inulin clearance measurements on day 7, the patients were divided into "recovering AKI" (> = 20 ml/min) or "sustained AKI" (<20 ml/min). They found that at 1–3 hrs after reperfusion, PAH extraction was greatly reduced (to ~5–30% vs ~90% in controls) with modestly lower levels among patients with subsequently "sustained AKI". Whereas PAH extraction increased to ~60% in patients with "recovering AKI" over the next 7 days, it was further reduced to <5% in patients with "sustained AKI" [39], indicating some coordination between the recovery of tubular secretion and glomerular filtration also in human. Finally, Corrigan et al. showed that the renal PAH clearance is not a good measure for renal plasma flow in human post ischemic AKI due to the impaired PAH extraction [39].

Implications of impaired tubular transport for diagnosis and prognosis of AKI

There is a need to better understand temporal changes in tubular transport functions and their role for GFR and kidney recovery after AKI, including their role in the transition to CKD. Which specific transport activity predicts outcome, what are the underlining mechanisms, and how can the transport activities be tested? The ability to concentrate the urine relative to plasma is a very sensitive and biologically important function that requires intact tubules including the OM and is impaired early on in AKI. Furthermore, the ability of the loop diuretic furosemide to induce diuresis and natriuresis has been used to predict the development and severity of AKI and its prognosis [40–42], demonstrating the potential relevance of assessing tubular function in early AKI. Do restoration of urine concentration and the responsiveness to furosemide after AKI also predict GFR recovery and/or protection from transition to CKD? Should other transport functions also be determined that have potential cardiovascular relevance: e.g. the ability to excrete a salt load with minimal blood pressure effects; or the renal sensitivity to key hormones implicated in renal transport regulation, body homeostasis, and cardiovascular health (e.g., the ratio of plasma levels of FGF23/PTH to fractional renal phosphate excretion)?

Is tubular transport a potential therapeutic target in AKI?

As discussed, AKI-induced impairment of tubular Na^+ and fluid reabsorption may lower GFR to limit Na^+ and fluid losses. Thus, restoration of tubular integrity and Na^+ and fluid reabsorption capacity may be a prerequisite for GFR recovery. Maintaining a polarized cell and normal Na^+-K^+-ATPase activity requires a constant energy supply, and impaired mitochondrial function and dynamics have emerged as an important aspect in AKI cellular injury and dysfunction [43]. AKI-induced mitochondrial alterations include fragmentation with reduction in ATP-generating capacity, enhanced production of reactive oxygen species (ROS), and mitochondrial permeability transition pore opening; minimizing these mitochondrial events has the potential to reduce injury and improve cellular energetic, integrity and function [44;45]. The latter may help to repair cell membranes, restore the microvilli, and thereby the function of renal epithelial cell transport mechanisms.

On the other hand, the persisting energy-consuming tubular transport activities or maneuvers that increase tubular transport may aggravate hypoxia, injury and inflammation. This may particularly apply to the most vulnerable tubular segments including the proximal tubule and the OM, the injury of which has been implicated also in distal tubule injury, fibrosis, and whole kidney outcome [46–48]. Molitoris proposed that controlling early tubular events in AKI may offer the best strategy to a successful therapy by limiting the number of downstream events [4]. Chawla, Kellum and Ronco proposed that resting the kidney (by allowing hypofiltration and providing early renal replacement therapy analogous) may improve survival and decrease permanent loss of kidney function in AKI [49]. This brings up the question: can the kidney also be rested by limiting transport activity in early AKI and does this facilitate recovery? Inhibition of transport in TAL was shown to limit tubular damage in an experimental model (isolated perfused kidney) [50], but systematic and long-term studies are missing. We hypothesize that particularly the inhibition of transport in the vulnerable OM improves the metabolic homeostasis of the tubular cells in this region which facilitates their recovery, but may also help to restore the integrity and function (reabsorption/secretion) in neighboring cortical/medullary segments, in part by limiting the spreading of inflammation from the OM (Figure 1).

Are there specific transport activities that should not be inhibited or even enhanced in AKI? Inhibiting reabsorption only in the PCT can enhance transport work in the downstream PST and mTAL, which may be deleterious. Energy consuming transport in the OM includes glucose reabsorption via apical Na-glucose cotransporter SGLT1 in PST, while most tubular glucose is normally reabsorbed by SGLT2 in the upstream PCT. At 25 minutes of IR in rats (35 minutes occlusion of renal artery) glucose reabsorption was strongly reduced in PCT, with partial recovery after 4 hours [12]. Molitoris and Kinne showed that 15 minutes of bilateral renal pedicle clamp in rats reduced Na^+-dependent-glucose transport rates in cortical brush border membrane vesicles (without affecting L-alanine uptake). This was associated with reduced high affinity Na-dependent phlorizin binding sites, indicating lower SGLT2 expression [51]. The latter may enhance glucose load to the S3 segment, however little is known about changes in SGLT1 expression in AKI and whether this glucose delivery is detrimental or may even have benefits if AKI induced a relevant glycolytic shift in outer medullary proximal tubules [52;53]. The latter is also relevant for effects of SGLT2

inhibitors, a new class of anti-hyperglycemic drugs that enhance urinary glucose excretion but also increase transport via SGLT1 and thereby may reduce oxygen tension in the OM [54].

How do potential benefits of “resting” tubular cells compare with consequences on fluid and electrolyte homeostasis, and GFR? Can the induced inhibition of fluid and electrolyte reabsorption be compensated by dietary changes? To which extent does specific inhibition of OATs and OCTs protect the OM and whole kidney? What are the systemic consequences or costs for the organism including a greater accumulation of uremic toxins like IS? Particular attention is required to the renal effects of drugs that are transported by renal tubules including their effect on tubular energetics and integrity as well as their potential systemic accumulation. Finally, there is a need to refine experimental models of AKI for clinical relevance, and this has to include the tubular transport phenotypes observed in humans. In this regard, consideration should also be given to comorbidities (e.g., diabetes and CKD) and age, which themselves affect tubular function and thus may modulate the tubular function response to AKI and/or its implications in kidney recovery and transition to CKD.

Conclusion

There is a need to better define the changes in kidney function during AKI and its recovery that go beyond GFR. Tubular transport is critical to regulate body homeostasis. However, the associated tubular transport work, which is a primary determinant of the kidneys oxygen consumption, may have deleterious effects in the setting of AKI, in particular in the semi-hypoxic and highly vulnerable outer medullary region. This concept may provide new opportunities for the diagnosis, prognosis and therapeutic intervention in AKI.

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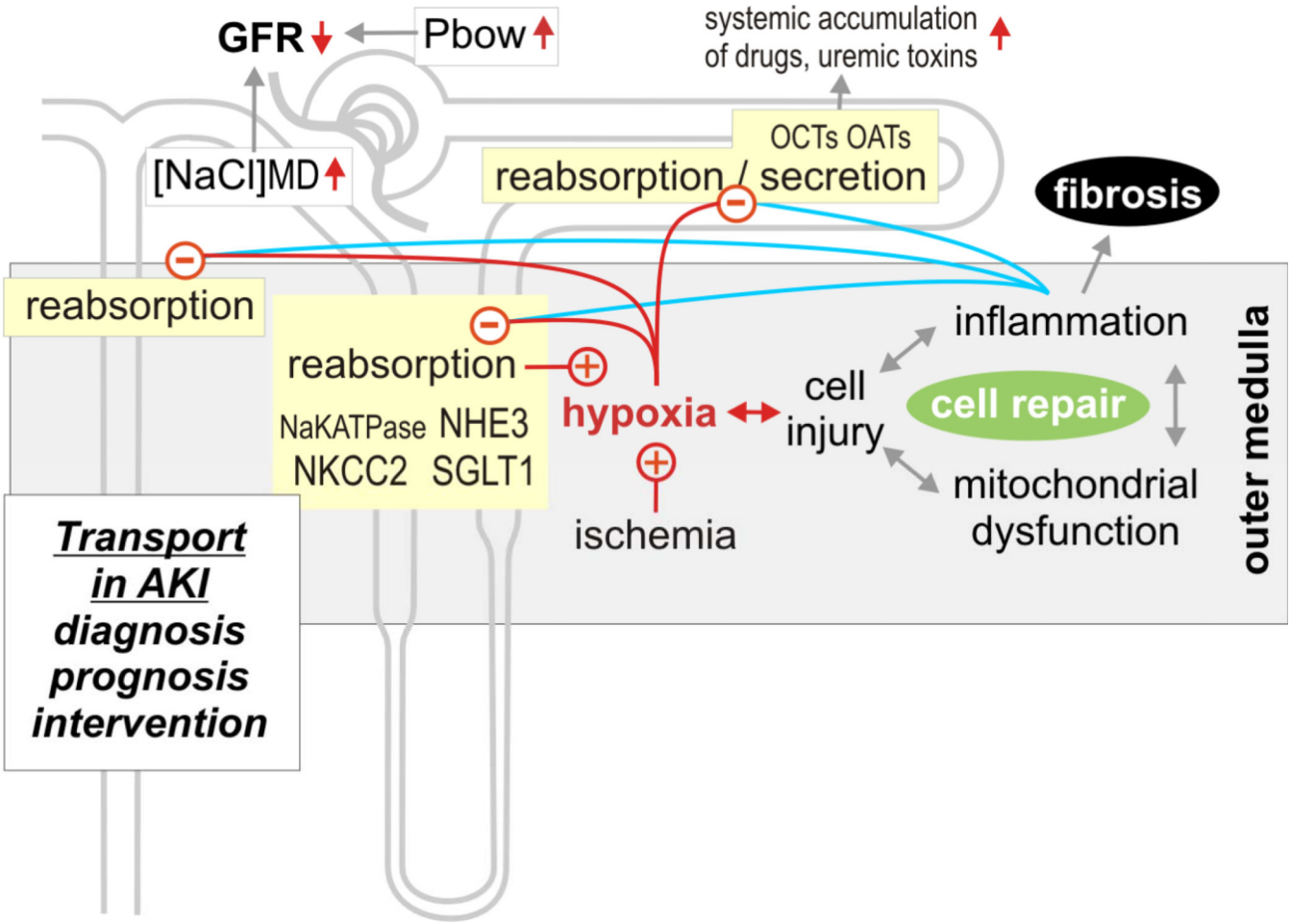

Figure 1. Tubular transport in ischemia-induced acute kidney injury

Renal ischemia is associated with hypoxia-induced inhibition of tubular Na^+ and fluid reabsorption, which enhances NaCl concentrations at the macula densa ([NaCl]MD) and hydrostatic pressure in Bowman space (Pbow); these changes lower GFR to conserve Na^+ and fluid and also limit tubular transport work ("acute renal success"). Illustrated is also the hypothesis that the persisting outer medullary reabsorption enhances the hypoxia-induced pro-inflammatory effects, which impair cell repair and recovery in this region; this has consequences for transport function and recovery of whole kidney and GFR, in part via spreading of inflammatory cytokines.