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ROLE OF MEDULLARY BLOOD FLOW IN THE PATHOGENESIS OF RENAL ISCHEMIA-REPERFUSION INJURY

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Abstract

Purpose of review—Renal ischemia-reperfusion injury (IRI) is a common cause of acute kidney injury (AKI). Alterations in renal medullary blood flow (MBF) contribute to the pathogenesis of renal IRI. Here we review recent insights into the mechanisms of altered MBF in the pathogenesis of IRI.

Recent findings—Although cortical blood flow fully recovers following 30–45 minutes of bilateral IRI, recent studies have indicated that there is a prolonged secondary fall in MBF that is associated with a long term decline in renal function. Recent findings indicate that angiopoeitin-1, atrial natriuretic peptide, heme oxygenase-1, and the gasotransmitters, carbon monoxide and hydrogen sulfide, may limit the severity of IRI by preserving MBF. Additional studies have also suggested a role for cytochrome P450 derived 20-HETE in the post-ischemic fall in MBF.

Summary—Impaired MBF contributes to the pathogenesis of renal IRI. Measurement of renal MBF provides valuable insight into the underlying mechanisms of many renoprotective pathways. Identification of molecules that preserve renal MBF in IRI may lead to new therapies for AKI.

Keywords

hemodynamics; kidney; renal medulla; acute kidney injury

INTRODUCTION

Acute kidney injury (AKI) is a common complication of acute illness and significantly increases morbidity, mortality, and resource utilization. (1, 2) Renal ischemia-reperfusion injury (IRI) is a common cause of AKI in many clinical settings. (3, 4) IRI results from multiple factors affecting both the renal tubular epithelium and renal microvasculature. (5–7) Ischemia markedly reduces intracellular ATP concentration and initiates cellular injury which is exacerbated upon reperfusion by an increase in oxidative stress and inflammation. (5, 6) Alterations in renal blood flow (RBF) following IRI can result from microvascular injury, impaired renal vascular reactivity, and as a consequence of impaired red blood cell trafficking in the peritubular capillaries due to the infiltration of inflammatory cells and increased parenchymal pressure. (5, 8–11) Indeed, sustained reductions in renal blood flow

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are seen following severe prolonged IRI (>45min) in numerous experimental studies and in patients with post-ischemic renal failure following kidney transplantation. (12–16). With shorter periods of ischemia and less severe IRI, whole kidney, cortical and inner medullary blood flow typically fully recovers following reperfusion, however, outer medullary blood flow remains compromised for prolonged periods.

The post-ischemic fall in outer medullary blood flow (MBF) may be a critical event in extending renal tissue injury following reperfusion. (10, 17–19) Several studies in rat models of IRI highlight the role of prolonged post-ischemic impairment in MBF in the pathogenesis of IRI. Vetterlein *et al.* demonstrated a marked reduction in medullary plasma flow one hour after of reperfusion utilizing fluorescent tracers. (10) Using laser-Doppler flowmetry (LDF), Olof *et al.* and Conesa *et al.* observed marked and sustained reductions in outer MBF following reperfusion. (17, 18) As illustrated in figure 1, we recently found that while cortical blood flow returns to baseline levels, there is a persistent impairment in outer MBF upon reperfusion in rats exposed to 30 minutes of renal ischemia. (19) The prolonged reductions in outer MBF can exacerbate tubular epithelial cell injury, particularly in the S3 segment of the proximal tubule which subsists in the hypoxic microenvironment of the renal outer medulla. (6, 7, 20) Given the importance of these hemodynamic changes in the pathogenesis of IRI, the identification of mediators that contribute to the reduction in renal outer MBF and identification of compounds that can prevent this deficit is a logical step in the development of new therapies for AKI. (21) In this review we will highlight findings of recent studies (summarized in Table 1) that shed new light on the mechanisms of altered MBF following IRI.

20-HETE

Arachidonic acid (AA) is released from membrane phospholipids in the renal outer medulla in response to ischemia and can be metabolized to 20-hydroxyeicosatetraenoic acid (20–HETE) by cytochrome p450 ω-hydroxylase. (22, 23) In the kidney, 20-HETE modulates vascular tone, renal blood flow, and tubular sodium transport. (23) 20-HETE increases vascular responsiveness to vasoconstrictors and would be expected to reduce tissue blood flow and exacerbate IRI. Indeed, 20-HETE has been shown to promote ischemic injury in the heart and brain. (24, 25) However, in the kidney 20-HETE was shown to increase MBF in a dose dependent manner in rats. (26) Two recent studies have addressed the effect of 20-HETE on renal IRI and the post-ischemic fall in MBF in rats.

Regner *et al.* demonstrated that inhibition of 20-HETE synthesis with HET0016 exacerbated renal IRI and that systemic administration of a stable 20-HETE analog, 5,14–20-HEDGE, mitigated renal IRI and prevented the post-ischemic decrease in renal outer MBF in rats. (19) 5,14–20-HEDGE also inhibited sodium transport and enhanced natriuresis in normal rats. These authors concluded that the 20-HETE analog mitigated IRI by preventing post-ischemic medullary hypoxia through a concurrent increase in renal MBF and a decrease in tubular transport and oxygen demand. (19) In a subsequent study, Hoff *et al.* demonstrated a ten-fold increase in 20-HETE levels in rat kidneys exposed to 45 minutes of ischemia. (27) They reported that bolus administration of the 20-HETE synthesis inhibitor, HET0016 or a 20-HETE antagonist, 6,15–20-HEDE, directly into the renal artery of a uninephrectomized rat attenuated the severity of renal IRI. 6,15–20-HEDE significantly improved medullary oxygenation and hastened the recovery of renal outer MBF. (27) However, 6,15–20-HEDE treatment did not fully return outer MBF to baseline levels, suggesting that the salutary effect of this compound on medullary oxygenation occurred via changes in oxygen utilization.

The reason for the divergent results remain to be determined but could be due to differences in the experimental design of these studies. (28) Regner *et al.* administered 5,14–20-HEDGE

subcutaneously at a high dose that produced elevated blood levels for several hours whereas Hoff *et al.* administered a much smaller dose of 6,15–20-HEDE by bolus injection directly into the renal artery that likely produced high first-pass blood levels but much lower systemic levels following redistribution. (19, 27, 28) In addition, Regner *et al.* used a model of 30 minutes bilateral ischemia, whereas Hoff *et al.* performed 45 minutes warm ischemia on the remaining kidney following uninephrectomy. (19, 27, 28) This experimental difference appears to be critical in interpreting the divergent hemodynamic findings in these two studies since uninephrectomy has been shown to rapidly alter renal hemodynamics by increasing both cortical and medullary blood flow in the remaining kidney. (29) These studies clearly indicate a role for 20-HETE in the regulation of medullary blood flow and oxygenation following IRI, but further studies are needed to clarify the therapeutic potential of 20-HETE agonists and/or antagonists in renal IRI and to determine their mechanism of action.

HEME OXYGENASE-1

Heme oxygenase-1 (HO-1) converts heme into biliverdin and carbon monoxide while simultaneously releasing iron. (30) HO-1 is induced in the kidney following a number cellular stressors and plays a protective role in animal models of AKI, including IRI. (30) HO-1 is highly expressed in the renal medulla and inhibitors of HO-1 significantly decrease renal MBF. (31) In a porcine model of warm renal ischemia, HO-1 mRNA expression was positively correlated with total RBF during reperfusion. (32) In contrast, in HO-1 knockout mice exposed to 15 minutes of renal ischemia and 4 hour reperfusion there was a significant reduction in GFR but no change in total RBF compared to control mice. (33) Salom *et al.* reported that induction of HO-1 with $CoCl_2$ decreased the severity of renal dysfunction in rats exposed to 45 minutes of renal ischemia. (34) Induction of HO-1 significantly decreased the post-ischemic fall in MBF as measured by LDF. This beneficial effect associated with a decrease in peroxynitrite formation during the ischemic period suggesting a role for reduced NO scavenging by reactive oxygen species rather than increased formation of carbon monoxide. (34) However, $CoCl_2$ is also a potent inducer of hypoxia inducible factor-1 alpha which alters the expression of many genes that may contribute to the renoprotective effect of $CoCl_2$. (35) Thus, further investigation is needed to identify the mediator of protective effect of HO-1 or $CoCl_2$ in renal IRI and whether the mechanism is due in part, to preservation of renal MBF upon reperfusion.

GASOTRANSMITTERS

Gasotransmitters are gaseous molecules that modulate a variety of intracellular signaling pathways. (36) Nitric oxide (NO) is the best characterized of these paracrine factors and plays a key role in the regulation of renal medullary perfusion by promoting dilatation of vasa recta capillaries and antagonizing the effects of vasoconstrictors. (37–39) From this standpoint, NO would be expected to have a beneficial effect in renal IRI. However, NO produced in response to ischemia can combine with superoxide to produce peroxynitrite leading to an increase in oxidative stress and exacerbation of renal injury. (6, 40) Therefore, the impact of NO in renal IRI is dependent upon a number of factors including the temporal and spatial distribution of NO production and the type of nitric oxide synthase (NOS) activated following ischemia. The role of NO and NOS in the pathogenesis of renal IRI and AKI is very complex and has be extensively reviewed elsewhere. (41–44)}

In contrast to NO, much less is known about the role of the other gasotransmitters, hydrogen sulfide (H_2S) and carbon monoxide (CO), in the control of MBF and the pathogenesis of renal IRI. H_2S is enzymatically synthesized from L-cysteine or L-homocysteine and has been shown to activate ATP-sensitive potassium channels (K_{ATP}) in numerous cell types. (45) H_2S is produced in the kidney through substrate dependent metabolism of L-cysteine

and infusion of H_2S donors into the renal artery of rats increases total RBF, GFR, and urine sodium excretion. (46) Tripatara *et al.* demonstrated that IRI increases the production of H_2S in the kidney and that endogenous and exogenous H_2S decreased the severity of renal dysfunction following IRI in rats. (47). Hosgood *et al.* subsequently demonstrated that H_2S infusion improved total RBF and renal function in a porcine model of 25 minutes of warm ischemia and 18 hours of cold storage. (48) Whether the protective effect of H_2S in renal IRI is mediated by an improvement in MBF remains to be studied. However, one would expect to find that H_2S should produce a medullary vasodilation since K_{ATP}channels are expressed by pericytes in the vasa recta. (45)

CO is produced from the metabolism of heme by heme oxygenase. The protective effect of HO-1 in models of renal injury appears to be mediated, in part, through the vasodilator actions of CO. (30, 49) Furthermore, the effect of HO-1 on MBF may be a result of CO mediated activation of guanylate cyclase. (31) Notably, CO donor compounds protected against renal IRI in mice, even in the presence of a heme oxygenase inhibitor, indicating that CO-mediated protection from IRI may be independent of HO-1 activity. (50) The influence of CO on renal hemodyamics following IRI has been explored in various models of IRI. In a rat model of kidney transplantation, exposure of recipient rats to inhaled CO (250 ppm) significantly decreased tubular injury and inflammation. This was associated with a significant increase in renal cortical blood flow upon reperfusion. (51) Hosgood *et al.* demonstrated that administration of the carbon monoxide releasing molecule, CORM-3 preserved renal function and improved total RBF in a porcine model of 10 minutes of warm renal ischemia and 16 hours of cold storage. (52) However, it remains to be determined whether the protective effect of CO in renal IRI is mediated by preservation of post-ischemic MBF.

ATRIAL NATRIURETIC PEPTIDE

Atrial natriuretic peptide (ANP) is secreted by cardiomyocytes following volume expansion and elevations in end diastolic filling pressure. Infusion of ANP increases GFR and MBF in rats. (53) Chujo *et al.* recently reported that MBF was significantly higher following IRI in rats treated with ANP as compared to vehicle treated controls. (54) This improvement in outer MBF in the ANP treated rats was associated with improvements in renal function and reduced tubular injury 24 and 48 hours following ischemia. (54) ANP, like NO, is a potent activator of guanylyl cyclase and suggests that strategies to increase cGMP, like NO, ANP or phosphodiesterase 5 inhibitors, might be useful in the treatment of ischemic AKI. Recent clinical trials using ANP for treatment or prevention of AKI have had mixed results depending on the treatment strategy and patient population. In this regard, it appears that low dose ANP therapy may decrease the need for renal replacement therapy in patients with post-operative AKI. (55)

ANGIOPOIETIN-1

Angiopoietin-1 (Ang1) is a key regulator of vascular development during embryogenesis and contributes to the vascular adaptation to injury and stress. (56) Cartilage oligomeric matrix protein-Ang1 (COMP-Ang1) is an engineered form of Ang1 with improved solubility and potency compared to native Ang1. (57) Jung *et al.* recently reported on the effects of adenovirus overexpression of COMP-Ang1 on renal injury and renal hemodynamics in mice exposed to 22 minutes of bilateral renal ischemia. (58) In comparison to vehicle treated controls, renal function in the COMP-Ang1 overexpressing mice was significantly improved 1, 2, and 3 days following reperfusion. Renal MBF was significantly higher in the COMP-Ang1 overexpressing mice at 2 hours and 2 days following ischemia. Most notably, COMP-Ang1 had long term benefits and was associated with a decrease in renal tubulointerstitial fibrosis 30 days after IRI. (58)

LONG-TERM EFFECTS OF IRI ON RENAL MBF

Recovery of renal function following AKI in humans is often incomplete and many patients develop long term complications. (59, 60) Several experimental studies have highlighted the importance of renal microvascular injury in the pathogenesis of chronic kidney disease and hypertension following IRI. Basile *et al.* evaluated the long-term effects of bilateral renal ischemia in rats. (61) They reported that renal function and tubular morphology fully recovered to control levels within 2 weeks. However, the rats developed proteinuria and tubulointerstitial fibrosis several months after the initial injury. (61) Notably, these abnormalities were preceded by a 30 to 50% reduction in the density of vasa recta capillaries in the outer medulla of the kidney as early as 4 weeks after ischemia. (61) In a subsequent study, this group demonstrated that IRI in rats leads to decreased GFR and RBF, impaired autoregulation of MBF, relative renal medullary hypoxia and sodium sensitive hypertension 5 weeks after ischemia. (62) These findings highlight the importance of injury to the vasa recta capillaries and the fall in MBF during recovery from ischemic injury and may explain the increased risk for the development of microalbuminuria, hypertension, and chronic kidney disease in patients with AKI. (59, 60, 63)

CONCLUSION

Sustained alterations in RBF are well described following renal IRI. This perturbation in RBF is primarily due to regional hypoperfusion in the renal outer medulla. Identification and characterization of mediators that can mitigate microvascular injury and preserve MBF following IRI may lead to therapies for AKI. Assessment of MBF is essential in determining the mechanism of action of putative renoprotective agents in IRI.

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SUMMARY

- Renal ischemia-reperfusion injury is a common cause of acute kidney injury.
- Ischemic renal injury is associated with prolonged reductions in renal medullary blood flow following reperfusion.
- Reduced medullary blood flow promotes tubular necrosis and fibrosis in the outer medulla.
- Nitric oxide, carbon monoxide, atrial natriuretic peptide and eicosanoids help preserve medullary blood flow and reduce ischemic renal injury.

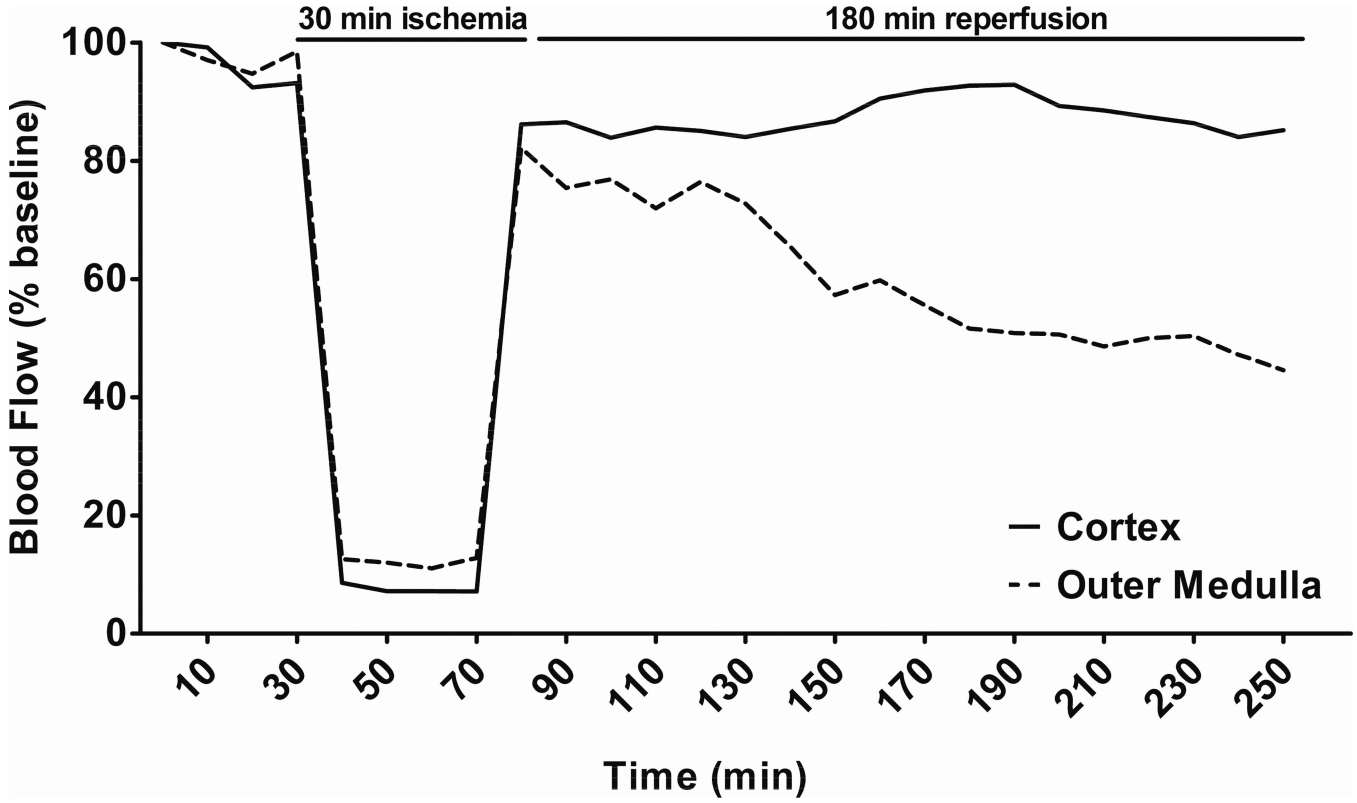

Figure 1. Effect of renal ischemia-reperfusion injury on regional blood flow in the kidney

Sprague-Dawley rats underwent 30 minutes renal ischemia and 180 minutes of reperfusion. Cortical blood flow (CBF) and outer medullary blood flow (MBF) were measured by laser-Doppler flowmetry. CBF and MBF decreased dramatically during the ischemic period and CBF rapidly recovered to baseline levels following reperfusion. In contrast, a transient improvement in MBF was seen immediately after reperfusion followed by a gradual decline to approximately 50% of baseline that was sustained for the 3 hour period of the experiment. Adapted from Regner *et al.* (19)

Table 1

Summary of recent studies examining the regulation of renal MBF following IRI.

Pathway	Renal IRI Model	Results	Reference
20-HETE	30 min bilateral warm ischemia in rats	20-HETE analogue preserved post-ischemic MBF and mitigated renal injury	19
	45 min warm ischemia after uninephrectomy in rats	20-HETE inhibitor improve post-ischemic MBF and mitigated renal injury	27
HO-1	45 min of warm ischemia in rats	Induction of HO-1 decreased the post-ischemic fall in MBF and severity of renal dysfunction	34
H_2S	45 min bilateral warm ischemia in rats	Endogenous and exogenous H_2S decreased renal injury and improved renal function	45
	Porcine model of 25 min of warm ischemia and 18 hrs cold storage	H_2S infusion improved total RBF and renal function	46
CO	Porcine model of 10 min renal ischemia and 16 hrs of cold storage	Administration of CO releasing molecule-3 (CORM-3) preserved renal function and improved total RBF	50
ANP	Porcine model of 10 min warm ischemia and 18 hrs cold storage	ANP treatment improved MBF and renal function and reduced tubular injury	52
Ang1	22 min of bilateral warm ischemia in mice	Adenovirus overexpression of COMP-Ang1 improved post-ischemic MBF and renal function	56

IRI, ischemia-reperfusion injury; MBF, medullary blood flow; min, minute; 20-HETE, 20-hydroxyeicostetraenoic acid; HO-1, heme oxygenase-1; H_2S, hydrogen sulfide; hrs, hours; RBF, renal blood flow; CO, carbon monoxide; ANP; atrial natriuretic peptide; Ang1, angiopoietin-1; COMP-Ang1, cartilage oligomeric matrix protein-Ang1.