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Renal ischemia/reperfusion injury; from pathophysiology to treatment

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ABSTRACT

Ischemia/reperfusion injury (IRI) is caused by a sudden temporary impairment of the blood flow to the particular organ. IRI usually is associated with a robust inflammatory and oxidative stress response to hypoxia and reperfusion which disturbs the organ function. Renal IR induced acute kidney injury (AKI) contributes to high morbidity and mortality rate in a wide range of injuries. Although the pathophysiology of IRI is not completely understood, several important mechanisms resulting in kidney failure have been mentioned. In ischemic kidney and subsequent of re-oxygenation, generation of reactive oxygen species (ROS) at reperfusion phase initiates a cascade of deleterious cellular responses leading to inflammation, cell death, and acute kidney failure. Better understanding of the cellular pathophysiological mechanisms underlying kidney injury will hopefully result in the design of more targeted therapies to prevent and treatment the injury. In this review, we summarize some important potential mechanisms and therapeutic approaches in renal IRI.

Review

Implication for health policy/practice/research/medical education:
Renal injury associated with ischemia/reperfusion results from a dynamic process involving inflammation and some mediators in a complex interaction. Formation of oxidative stress and lipid peroxidation seems to be major factors which promotes the inflammation process during ischemia/reperfusion injury. A better understanding of the pathophysiology and therapeutic approach underlying the functional defects found in ischemic acute renal failure will also require that we take into account the complexity of illness.

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Introduction

Ischemia/reperfusion injury (IRI) is characterized by restriction of blood supply to an organ followed by restoration of blood flow and re-oxygenation. The inevitable injuries may occur after infarction, sepsis and organ transplantation and this phenomena exacerbate tissue damage by initiating an inflammatory cascade including reactive oxygen species (ROS), cytokines, chemokines, and leukocytes activation (1,2). In the kidney, IRI contributes to pathological conditions called acute kidney injury (AKI) that is a clinical syndrome with rapid kidney dysfunction and high mortality rates (3,4). The pathophysiology of IRI in kidney is very complex but some pathological pathways such as activation of neutrophils, release of reactive oxygen species and other inflammatory mediators including adhesion molecules and a variety of cytokines are involved. Studies have demonstrated the beneficial effects of different agents in combat with IRI, for example, doxycycline through reducing the level of pro-inflammatory cytokines (5,6), leptin by decreasing tumor necrosis factor alpha (TNF-α) level and increasing nitrite level (7), levosimendan through antioxidant and NO-related mechanisms (8), iloprost by suppression of lipid peroxidation and (9) ascorbic acid via free radical scavenging and antioxidant activities (10).

Materials and Methods

For this review, we used a variety of sources by searching through PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was performed by us-

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ing combinations of the following key words and or their equivalents; renal injury, ischemia/reperfusion, AKI, reactive oxygen species. Manuscripts published in English as full-text articles and or as abstracts were included in the study.

Inflammation, leukocytes and adhesion molecules

Inflammation as a common abnormality in kidney IRI seems to link the various cell types and playing an important role in its pathophysiology. Renal IRI triggers an inflammatory cascade that involved in more renal damages, so inhibition of inflammatory responses is a therapeutic approach to protect renal tissue (11,12). Chemokines are major mediators of the inflammation that regulate pro-inflammatory cytokine, adhesion molecule expression, leukocyte infiltration and activation (13). Pro-inflammatory cytokines and cytokines such as interleukin 6 (IL6) and TNFα play a major role in renal dysfunction of IRI (14-16). Activation of Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway mediated many pro-inflammatory cytokines that involved in progression of renal IRI (17). Dexmedetomidine (a highly selective α2-adrenoreceptor agonist) has a cytoprotective effect against renal IRI by inhibiting the phosphorylation of JAK/STAT proteins, reducing IL6 and TNFα that indicating its anti-inflammatory effects (18-22).

Inflammatory mediators, ROS and cell adhesion molecules – intracellular adhesion molecule-1 (ICM-1) and P-selectin – recruit leukocytes and neutrophil infiltration into post ischemic tissue, then leads to enhanced leukocyte – endothelial interactions, which can promote injury, swelling of the endothelial cell and physically impede blood flow (23-26). Administration of ICM-1 antibody and the kidneys of ICM-1 knockout were protected from IRI in mice (27,28). Takada et al. showed that soluble P-selectin ligand attenuates post-ischemic neutrophil infiltration and injury by inhibiting the binding between P-selectin and leukotriene aggregation (26). In addition Patel et al. showed that endogenous 5-lipoxygenase metabolites enhanced the degree of renal injury, dysfunction, and inflammation caused by kidney IRI via expression of adhesion molecules while in 5-lipoxygenase knockout mice the renal IRI were ameliorated (29). Involvement of the inflammatory leukotriene pathway in IRI has been demonstrated in acute and chronic renal failure (29-32). Activation of leukocytes, especially neutrophils have an important role in the development of renal IRI (33,34). Neutrophils releases ROS, cytokines, proteases and other mediators that exceed IRI (35). Montelukast, zafirlukast and cysteinyl leukotriene receptor blockers, demonstrated protective effects on renal IRI through inhibition of neutrophil infiltration, suppression of adhesion molecules and lipid peroxidation (30,36).

Many agents also have protecting effects on IRI through anti-inflammatory properties that mention in below. Nicotin is an anti-inflammatory cholinergic agonist, protect renal function after IRI by suppressing neutrophil infiltration, chemokines release and inflammation through an α7 nicotine acetylcholine receptor (α7nAchR) (37,38). These renoprotective effects also reported in vagotomized animals and suggest that cholinergic agonists act directly within the kidney (38).

Celastrol is a bioactive ingredient of chines herb "*Tripterygium wilfordii*" with anti-inflammatory and antioxidant activities that used in treating auto-immune diseases and chronic nephritis. Celastrol protect IRI by inhibiting neutrophil infiltration, lipid peroxidation and suppressing the induction of pro-inflammatory mediators synthesizes such as cyclooxygenase-2 (COX2) presumably by suppressing nuclear factor κB (NF-κB) signaling pathway (39). Besides controversial studies reported that celastrol promoted the kidney injury in renal IRI by upregulation of COX2 and prostaglandin E2 (PGE2) synthesis (40). As a conclusion it seems that inflammation, leukocytes and adhesion molecules are seriously involved in IRI process, and any agents that suppress inflammation process, or inhibit leukocytes and neutrophil infiltration may be suitable to attenuate the side effect of IRI in the kidney.

Oxidative stress and lipid peroxidation

During IRI, the damaged tissue produce excessive amount of ROS cause oxidative stress which changes mitochondrial oxidative phosphorylation, ATP depletion, increase intracellular calcium and activation of membrane phospholipids proteases (41-43). The blood flow during reperfusion phase of IRI can produce oxygen free radicals which leads to lipid peroxidation as main pathway of free radical tissue injuries (44). Formation of free radicals develops renal tissue injury via peroxidation of membrane lipids and oxidative damage of proteins and DNA contribute to apoptosis and cell death (45). Also the down regulation of the antioxidant enzyme system such as catalase, superoxide dismutase, and glutathione peroxidase could be responsible for the pathophysiology of ischemia-reperfusion injury (46). Therefore inhibiting this pathway or prevention of free radical production is the strategy to protect the tissue during IRI.

Studies have shown beneficial effects of free radical scavengers and antioxidants on IRI (47-49). Supplementations with antioxidants agents have protective effects in IRI induced oxidative stress (50-52). Oxygen free radical-mediated renal damage during the reperfusion period following ischemia was prevented by free radical scavengers and antioxidants activity of melatonin (53,54). In addition, inhibition of sympathetic nerve and decrease of catecholamine release (55) may be other mechanisms that melatonin protects renal against IRI. Ulinastatin a potent protease inhibitor with antioxidant activity attenuate renal injury after ischemia by inhibiting apoptosis and neutrophils infiltration (56). Propofol with antioxidant activity reduce IRI (57-59) through reduced lipid peroxidation, cytokines production, increased superoxide dismutase levels and up-regulation of bone morphogenetic protein-2 (BMP2) family that play important roles in diverse cell types (60-62). BMP2 down-regulation in IRI may contribute to an imbalance between cell proliferation and apop-

tosis thereby causing renal injury (63).
Recent attentions to herbal products encourage scientists to investigate natural agents on IRI. Most of these products exert renoprotective effects on IRI by the radical scavenging and antioxidant activities such as picroliv, an antioxidant extract of *Picrorhiza kurroa* (49), naringin, a bioflavonoid (64) and aqueous garlic extract (65). As conclusion, it is obvious that antioxidants agents could easily act against oxidative stress to protect the tissue against ischemia during IRI phase. However special attention is needed to use the dose of antioxidants, because some antioxidants showed toxic effects in particular dose (66,67).

Mitochondrial dysfunction

During ischemia, mitochondrial oxidative phosphorylation is suppressed by lack of oxygen. This phenomena impaired ATP synthesis and diminished activity of cellular energy-dependent processes which could contribute to cell death. Mitochondria are the major source of intracellular ROS, and are also the primary target for ROS. ATP depletion stops pumping calcium out of the cell by Na/Ca^{2+} antiporter channel therefore calcium accumulate in the cell and sodium accumulated within the cell cannot be removed by Na/K/ATPase (68). In addition intracellular calcium overload occurs from calcium redistribution of endoplasmic reticulum stores (69). Increased cytosolic calcium can activate calcium-dependent phospholipase A2, endonuclease and proteases within the cell that begin cell apoptosis (69,70). In the postischemic cell, mitochondria will be exposed to large amounts of Ca^{2+} and oxygen free radicals. These factors likely contribute to the progressive functional deterioration of mitochondria during the reperfusion phase (71). Therefore the ideal drug therapy needs to be targeted to mitochondria. A number of approaches have been used for targeted delivery of therapeutic agents to mitochondria and should demonstrate very powerful antioxidative properties inside the mitochondria under conditions of oxidative stress such as IRI (72-74). Gentamicin an antibacterial drug induce defect on mitochondrial oxidative phosphorylation and ATP/ADP ratio in reperfusion and therefore it causes renal damage in reperfusion phase more than ischemic phase (75-77).

Nitrite and nitric oxide

Nitric oxide (NO) the endothelial cell product plays an important role in blood circulation. The half-life of NO in circulation is very short which limited its direct measurement, therefore its metabolites; nitrite and nitrate usually are measured. NO in low concentrations considered as renoprotective against renal ischemia due to its vasodilatory, antioxidant and anti-inflammatory properties, as well as its beneficial effects on cell signaling and inhibition of nuclear proteins (78-80).
Renal IRI activate nitric oxide synthase (NOS) and increase the expression of NOS proteins (81). There are three different isoforms of NOS; endothelial NOS (eNOS) and neuronal NOS (nNOS) produce NO in short bursts in low concentrations for physiological purposes and inducible form of NOS (iNOS) which produces NO in high concentrations. It has been suggested that NO produced by iNOS is a toxic agent whereas eNOS is seen as a protective enzyme (82-84). NO produced in the renal proximal tubules in response to ischemic injury is mediated by iNOS (85).
Studies have suggested that increased NO via iNOS activity during renal ischemia is deleterious to the kidney and inhibition of iNOS before IRI has a dramatic functional protection of kidneys against ischemic renal injury (86). Treatment with sildenafil citrate and tadalafil (phosphodiesterase type 5 inhibitors) decreased lipid peroxidation and myeloperoxidase (indicator of polymorphonuclear infiltration) in renal tissues via inhibition of iNOS expression (87). In addition, ischemia itself can provide endothelial dysfunction, and disturb formation of NO endothelial form of eNOS (88).
The anion nitrite is an end product of NO metabolism (89). In hypoxia and ischemia conditions nitrite convert to NO by NOS and xanthine oxidase enzymes (90). Thus nitrite stored during normoxia and convert to NO in hypoxia conditions can be considered a NO buffer. Several recent reports have demonstrated NO and nitrite-mediated cytoprotection in IRI models (91-94). In addition of NO-dependent cytoprotection, nitrite may act via independent pathway (94,95).

Renin-angiotensin system

Renin-angiotensin system (RAS) activation and angiotensin II (AgII) level elevation are the important risk factors in IRI (96,97). AgII make renal injury through constrict of renal vessels, enhance vascular sensitivity to sympathetic nerve stimulation (98), cause oxidative stress (99,100) and apoptosis induction (101).
RAS modulate inflammation in renal tissue with two opposite arms effects: angiotensin-converting enzyme (ACE)/AgII/AT1 receptor and angiotensin-converting enzyme 2 (ACE2)/(Ag-(1-7)/Mas receptor (deleterious and protective effect respectively) (102,103). Renal ischemia appears to change the balance of RAS axis (104). Administration of the Mas receptor agonist, AVE0991, attenuated renal tissue damage and infiltration of leukocytes in the kidney IRI (105). ACE2 is a modulator of AgII levels and it convert AgII to Ag-(1-7) in renal tissue and antagonize many deleterious effects of AgII (106,107). New therapeutic strategy is led to activation of ACE2/Ag-(1-7)/Mas axis in renal IRI. Studies have demonstrated that angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers have protective effects on IRI in the kidney (108,109). Aliskiren (rennin inhibitor) can directly decrease rennin plasma activity and AgII level (110), has a protective effect on renal IRI through inhibition of RAS, oxidative stress and enhance the anti-apoptosis activity (111).

Complement system

Many studies have shown the activation of complement system in various IR organs (112-116). Complement sys-

tem activation releases a number of biologically active products (C4a, C3a, and C5a, C5b-9 and the anaphylatoxins) with proinflammatory and upregulation of adhesion molecules activity (117,118). C5a and C5b-9 have been shown to stimulate endothelial cell expression of selectins and intercellular adhesion molecule-1 (119,120). The recognition of the involvement of complement has led to novel strategies to modulate IRI. Specific C5a receptor antagonist have shown protective effects against renal IRI (121). Also an interfering RNA (siRNA) that target complement 3 (C3) and caspase 3 genes reduced renal IRI (122). Zhou et al. in mice which deficient in C3, C4, C5, and C6 showed that C5b-9 mediated tubular cell damage was etiologic in IRI (123).

Ischemic preconditioning

Ischemic preconditioning (IP) is a tolerance or adaptability of organ or tissue after primary exposure to a brief ischemia stimulus (124). The kidney has the ability to be preconditioned by a non-lethal period of ischemia, which makes it tolerate to subsequent ischemia-induced injury (125). In studies, renal IP was reduced cell lysis, apoptosis and lipid peroxidation with improvement of renal function in ischemic kidney (126). Reduction of adhesion molecules and inflammatory responses may be the mechanism of IP preventing effects (127,128). But In other studies, ischemic preconditioning appears to be mediated via pre-ischemic activation of adenosine receptors, specifically A_1 adenosine receptors (129-131).

Conclusion

Renal injury associated with ischemia/reperfusion results from a dynamic process involving inflammation and some mediators in a complex interaction. Formation of oxidative stress and lipid peroxidation seems to be major factors which promotes the inflammation process during IRI. A better understanding of the pathophysiology and therapeutic approaches underlying the functional defects found in ischemic acute renal failure will also require that we bear in mind the complexity of illness.

Authors' contribution

MM conducted literature review and wrote the article. MN planned and conducted literature review, and finalized it. All authors read and signed the manuscript.

Conflicts of interest

The authors declared no competing interests.

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References

1. Jang HR, Rabb H. The innate immune response in ischemic acute kidney injury. Clin Immunol. 2009;130:41-50.
2. Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. Nat Rev Nephrol. 2011;7:189-200.
3. Kellum JA, Unruh ML, Murugan R. Acute kidney injury. Clin Evid. 2011;2011.
4. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006;10:R73.
5. Kucuk A, Kabadere S, Tosun M, Koken T, Kinaci M, Isikli B, et al. Protective effects of doxycycline in ischemia/reperfusion injury on kidney. J Physiol Biochem. 2009;65:183-91.
6. İhtiyar E, Yaşar NF, Erkasap N, Köken T, Tosun M, Öner S, et al. Effects of doxycycline on renal ischemia reperfusion injury induced by abdominal compartment syndrome. J Surg Res. 2011;167:113-20.
7. Erkasap S, Erkasap N, Koken T, Kahraman A, Uzuner K, Yazihan N, et al. Effect of leptin on renal ischemia-reperfusion damage in rats. J Physiol Biochem. 2004;60:79-84.
8. Grossini E, Molinari C, Pollesello P, Bellomo G, Valente G, Mary D, et al. Levosimendan protection against kidney ischemia/reperfusion injuries in anesthetized pigs. J Pharmacol Exp Ther. 2012;342:376-88.
9. Döslüoğlu HH, Aktan AÖ, Yeğen C, Okboy N, Yalçm AS, Yahn R, et al. The cytoprotective effects of verapamil and iloprost (ZK 36374) on ischemia/reperfusion injury of kidneys. Transpl Int. 1993;6:138-42.
10. Korkmaz A, Kolankaya D. The protective effects of ascorbic acid against renal ischemia-reperfusion injury in male rats. Ren Fail. 2009;31:36-43.
11. Jang HR, Ko GJ, Wasowska BA, Rabb H. The interaction between ischemia–reperfusion and immune responses in the kidney. J Mol Med (Berl). 2009;87:859-64.
12. Stroo I, Stokman G, Teske GJ, Raven A, Butter LM, Florquin S, et al. Chemokine expression in renal ischemia/reperfusion injury is most profound during the reparative phase. International immunology. 2010;22:433-42.
13. Furuichi K, Wada T, Yokoyama H, Kobayashi K. Role of cytokines and chemokines in renal ischemia-reperfusion injury. Drug News Perspect. 2002;15:477-82.
14. Voss A, Bode G, Kerkhoff C. Double-Stranded RNA Induces IL-8 and MCP-1 Gene Expression via TLR3 in HaCaT-Keratinocytes. Inflammation & Allergy-Drug Targets (Formerly Current Drug Targets-Inflammation & Allergy). 2012;11:397-405.
15. Patel NS, Chatterjee PK, Di Paola R, Mazzon E, Britti D, De Sarro A, et al. Endogenous interleukin-6 enhances the renal injury, dysfunction, and inflammation caused by ischemia/reperfusion. J Pharmacol Exp Ther. 2005;312:1170-8.
16. Donnahoo KK, SHAMES BD, HARKEN AH, MELDRUM DR. Review article: the role of tumor necrosis factor in renal ischemia-reperfusion injury.

J Urol. 1999;162:196-203.
17. Yang N, Luo M, Li R, Huang Y, Zhang R, Wu Q, et al. Blockage of JAK/STAT signalling attenuates renal ischaemia-reperfusion injury in rats. Nephrol Dial Transplant. 2008;23:91-100.
18. Gu J, Sun P, Zhao H, Watts HR, Sanders RD, Terrando N, et al. Dexmedetomidine provides renoprotection against ischemia-reperfusion injury in mice. Crit Care. 2011;15:R153.
19. Billings IV FT, Chen SW, Kim M, Park SW, Song JH, Wang S, et al. α2-Adrenergic agonists protect against radiocontrast-induced nephropathy in mice. Am J Physiol Renal Physiol2008;295:F741-F8.
20. Kocoglu H, Ozturk H, Ozturk H, Yilmaz F, Gulcu N. Effect of dexmedetomidine on ischemia-reperfusion injury in rat kidney: a histopathologic study. Ren Fail. 2009;31:70-4.
21. Gonullu E, Ozkardesler S, Kume T, Duru LS, Akan M, Guneli ME, et al. Comparison of the effects of dexmedetomidine administered at two different times on renal ischemia/reperfusion injury in rats. Brazilian Journal of Anesthesiology (English Edition). 2013.
22. Si Y, Bao H, Han L, Shi H, Zhang Y, Xu L, et al. Dexmedetomidine protects against renal ischemia and reperfusion injury by inhibiting the JAK/STAT signaling activation. J Transl Med. 2013;11(1):141.
23. Linas SL, Whittenburg D, Parsons PE, Repine JE. Ischemia increases neutrophil retention and worsens acute renal failure: role of oxygen metabolites and ICAM 1. Kidney Int. 1995;48:1584-91.
24. Linas S, Whittenburg D, Repine JE. Nitric oxide prevents neutrophil-mediated acute renal failure. American Journal of Physiology-Renal Fluid and Electrolyte Physiology. 1997;41:F48.
25. Sheridan AM, Bonventre JV. Cell biology and molecular mechanisms of injury in ischemic acute renal failure. Curr Opin Nephrol Hypertens. 2000;9:427-34.
26. Takada M, Nadeau KC, Shaw GD, Marquette KA, Tilney NL. The cytokine-adhesion molecule cascade in ischemia/reperfusion injury of the rat kidney. Inhibition by a soluble P-selectin ligand. J Clin Invest. 1997;99:2682.
27. Kelly K, Williams WW, Colvin RB, Bonventre JV. Antibody to intercellular adhesion molecule 1 protects the kidney against ischemic injury. Proceedings of the National Academy of Sciences. 1994;91:812-6.
28. Kelly K, Williams Jr WW, Colvin RB, Meehan SM, Springer TA, Gutiérrez-Ramos JC, et al. Intercellular adhesion molecule-1-deficient mice are protected against ischemic renal injury. J Clin Invest. 1996;97:1056.
29. Patel NS, Cuzzocrea S, Chatterjee PK, Di Paola R, Sautebin L, Britti D, et al. Reduction of renal ischemia-reperfusion injury in 5-lipoxygenase knockout mice and by the 5-lipoxygenase inhibitor zileuton. Mol Pharmacol. 2004;66:220-7.
30. Şener G, Şehirli Ö, Velioğlu-Öğünç A, Çetinel Ş, Gedik N, Caner M, et al. Montelukast protects against renal ischemia/reperfusion injury in rats. Pharmacol Res. 2006;54:65-71.
31. Collin M, Rossi A, Cuzzocrea S, Patel NS, Di Paola R, Hadley J, et al. Reduction of the multiple organ injury and dysfunction caused by endotoxemia in 5-lipoxygenase knockout mice and by the 5-lipoxygenase inhibitor zileuton. J Leukoc Biol. 2004;76:961-70.
32. Şener G, Sakarcan A, Şehirli Ö, Ekşioğlu-Demiralp E, Şener E, Ercan F, et al. Chronic renal failure-induced multiple-organ injury in rats is alleviated by the selective CysLT1 receptor antagonist montelukast. Prostaglandins Other Lipid Mediat. 2007;83:257-67.
33. Lauriat S, Linas SL, editors. The role of neutrophils in acute renal failure. Seminars in nephrology; 1998.
34. Kaminski KA, Bonda TA, Korecki J, Musial WJ. Oxidative stress and neutrophil activation—the two keystones of ischemia/reperfusion injury. Int J Cardiol. 2002;86:41-59.
35. Rabb H, Postler G. Leucocyte adhesion molecules in ischaemic renal injury: kidney specific paradigms? Clin Exp Pharmacol Physiol. 1998;25:286-91.
36. Hagar HH, Tawab E, Abd R. Cysteinyl leukotriene receptor antagonism alleviates renal injury induced by ischemia-reperfusion in rats. J Surg Res. 2012;178:e25-e34.
37. Sadis C, Teske G, Stokman G, Kubjak C, Claessen N, Moore F, et al. Nicotine protects kidney from renal ischemia/reperfusion injury through the cholinergic anti-inflammatory pathway. PloS One. 2007;2:e469.
38. Yeboah M, Xue X, Duan B, Ochani M, Tracey K, Susin M, et al. Cholinergic agonists attenuate renal ischemia–reperfusion injury in rats. Kidney Int. 2008;74:62-9.
39. Chu C, He W, Kuang Y, Ren K, Gou X. Celastrol protects kidney against ischemia–reperfusion-induced injury in rats. J Surg Res. 2014;186:398-407.
40. Hwang HS, Yang KJ, Park KC, Choi HS, Kim SH, Hong SY, et al. Pretreatment with paricalcitol attenuates inflammation in ischemia–reperfusion injury via the up-regulation of cyclooxygenase-2 and prostaglandin E2. Nephrol Dial Transplant. 2013;28:1156-66.
41. Johnson KJ, Weinberg JM. Postischemic renal injury due to oxygen radicals. Curr Opin Nephrol Hypertens. 1993;2:625-35.
42. Paller MS. The cell biology of reperfusion injury in the kidney. J Investig Med 1994;42:632.
43. Bonventre JV. Mechanisms of ischemic acute renal failure. Kidney Int. 1993;43:1160-78.
44. Paller MS, Hoidal J, Ferris TF. Oxygen free radicals in ischemic acute renal failure in the rat. J Clin Invest. 1984;74:1156.
45. Kehrer JP. Free radicals as mediators of tissue injury and disease. Crit Rev Toxicol. 1993;23:21-48.
46. Singh I, Gulati S, Orak JK, Singh AK. Expression of antioxidant enzymes in rat kidney during ischemia-reperfusion injury. Mol Cell Biochem.

1993;125:97-104.
47. Giovannini L, Migliori M, Longoni B, Das DK, Bertelli A, Panichi V, et al. Resveratrol, a polyphenol found in wine, reduces ischemia reperfusion injury in rat kidneys. J Cardiovasc Pharmacol. 2001;37:262-70.
48. Rhoden EL, Pereira-Lima L, Telöken C, Lucas ML, Belló-Klein A, Rhoden CR. Beneficial Effect of. ALPHA.-Tocopherol in Renal Ischemia-Reperfusion in Rats. The Japanese Journal of Pharmacology. 2001;87:164-6.
49. Seth P, Kumari R, Madhavan S, Singh AK, Mani H, Banaudha KK, et al. Prevention of renal ischemia–reperfusion-induced injury in rats by picroliv. Biochem Pharmacol 2000;59:1315-22.
50. Bayati A, Källskog Ö, Wolgast M. The long-term outcome of post-ischaemic acute renal failure in the rat. I. A functional study after treatment with SOD and sucrose.Acta Physiol Scand. 1990;138:25-33.
51. Baker GL, Corry RJ, Autor A. Oxygen free radical induced damage in kidneys subjected to warm ischemia and reperfusion. Protective effect of superoxide dismutase. Ann Surg. 1985;202:628.
52. Greenwald RA. Superoxide dismutase and catalase as therapeutic agents for human diseases a critical review. Free Radic Biol Med. 1990;8:201-9.
53. Sener G, Sehirli AO, Keyer-Uysal M, Arbak S, Ersoy Y, Yegen BC. The protective effect of melatonin on renal ischemia-reperfusion injury in the rat. J Pineal Res. 2002 Mar;32:120-6.
54. Sahna E, Parlakpinar H, Ozturk F, Cigremis Y, Acet A. The protective effects of physiological and pharmacological concentrations of melatonin on renal ischemia-reperfusion injury in rats. Urol Res. 2003;31:188-93.
55. K-Laflamme A, Wu L, Foucart S, de Champlain J. Impaired Basal Sympathetic Tone and α1-Adrenergic Responsiveness in Association With the Hypotensive Effect of Melatonin in Spontaneously Hypertensive Rats. Am J Hypertens. 1998;11:219-29.
56. Chen CC, Liu ZM, Wang HH, He W, Wang Y, Wu WD. Effects of ulinastatin on renal ischemia-reperfusion injury in rats. Acta Pharmacol Sin. 2004;25:1334-40.
57. Yang S, Chou WP, Pei L. Effects of propofol on renal ischemia/reperfusion injury in rats. Exp Ther Med. 2013;6:1177-83.
58. Yuzbasioglu MF, Aykas A, Kurutas EB, Sahinkanat T. Protective effects of propofol against ischemia/reperfusion injury in rat kidneys. Ren Fail. 2010;32:578-83.
59. Yuzer H, Yuzbasioglu MF, Ciralik H, Kurutas EB, Ozkan OV, Bulbuloglu E, et al. Effects of intravenous anesthetics on renal ischemia/reperfusion injury. Ren Fail. 2009;31:290-6.
60. Sorescu GP, Song H, Tressel SL, Hwang J, Dikalov S, Smith DA, et al. Bone morphogenic protein 4 produced in endothelial cells by oscillatory shear stress induces monocyte adhesion by stimulating reactive oxygen species production from a nox1-based NADPH oxidase. Circ Res. 2004;95:773-9.
61. Shin V, Zebboudj AF, Boström K. Endothelial cells modulate osteogenesis in calcifying vascular cells. J Vasc Res. 2004;41:193-201.
62. Sorescu GP, Sykes M, Weiss D, Platt MO, Saha A, Hwang J, et al. Bone morphogenic protein 4 produced in endothelial cells by oscillatory shear stress stimulates an inflammatory response. J Biol Chem. 2003;278:31128-35.
63. Yang YL, Ju HZ, Liu SF, Lee TC, Shih YW, Chuang LY, et al. BMP-2 suppresses renal interstitial fibrosis by regulating epithelial–mesenchymal transition. J Cell Biochem. 2011;112:2558-65.
64. Singh D, Chopra K. The effect of naringin, a bioflavonoid on ischemia-reperfusion induced renal injury in rats. Pharmacol Res. 2004;50:187-93.
65. Kabasakal L, Sehirli Ö, Çetinel S, Cikler E, Gedik N, Sener G. Protective effect of aqueous garlic extract against renal ischemia/reperfusion injury in rats. J Med Food. 2005;8:319-26.
66. Singh D, Chander V, Chopra K. RETRACTED: The effect of quercetin, a bioflavonoid on ischemia/reperfusion induced renal injury in rats. Arch Med Res. 2004;35:484-94.
67. Allison SJ. Basic research: Kidney-specific antioxidant targeting for renal ischemic injury. Nat Rev Nephrol. 2012;8:194.
68. Devarajan P. Cellular and molecular derangements in acute tubular necrosis. Curr Opin Pediatr. 2005;17:193-9.
69. Kosieradzki M, Rowiński W, editors. Ischemia/reperfusion injury in kidney transplantation: mechanisms and prevention. Transplant Proc. 2008;40:3279-88.
70. Orrenius S, Zhivotovsky B, Nicotera P. Regulation of cell death: the calcium–apoptosis link. Nat Rev Mol Cell Biol. 2003;4:552-65.
71. Malis C, Bonventre J. Susceptibility of mitochondrial membranes to calcium and reactive oxygen species: implications for ischemic and toxic tissue damage. Prog Clin Biol Res. 1987;282:235-59.
72. Plotnikov E, Kazachenko A, Vyssokikh MY, Vasileva A, Tcvirkun D, Isaev N, et al. The role of mitochondria in oxidative and nitrosative stress during ischemia/reperfusion in the rat kidney. Kidney Int. 2007;72:1493-502.
73. Szeto HH, Liu S, Soong Y, Wu D, Darrah SF, Cheng FY, et al. Mitochondria-targeted peptide accelerates ATP recovery and reduces ischemic kidney injury. J Am Soc Nephrol. 2011;22:1041-52.
74. Cho J, Won K, Wu D, Soong Y, Liu S, Szeto HH, et al. Potent mitochondria-targeted peptides reduce myocardial infarction in rats. Coron Artery Dis. 2007;18:215-20.
75. Davis EJ, Davis-van Thienen W. Control of mitochondrial metabolism by the ATPADP ratio. Biochem Biophys Res Commun. 1978;83:1260-6.
76. Erecinska M, Stubbs M, Miyata Y, Ditre CM, Wilson

DF. Regulation of cellular metabolism by intracellular phosphate. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 1977;462:20-35.
77. Zager R. Gentamicin effects on renal ischemia/reperfusion injury. Circ Res. 1992;70:20-8.
78. Kanner J, Harel S, Rina G. Nitric oxide as an antioxidant. Arch Biochem Biophys. 1991;289:130-6.
79. Granger DN, Kubes P. Nitric oxide as antiinflammatory agent. Methods Enzymol. 1996;269:434-42.
80. Phillips L, Toledo AH, Lopez-Neblina F, Anaya-Prado R, Toledo-Pereyra LH. Nitric oxide mechanism of protection in ischemia and reperfusion injury. Investigative Surgery. 2009;22:46-55.
81. Viñas JL, Sola A, Genescà M, Alfaro V, Pí F, Hotter G. NO and NOS isoforms in the development of apoptosis in renal ischemia/reperfusion. Free Radic Biol Med. 2006;40:992-1003.
82. Hernandez-Pando R, Schön T, Orozco E, Serafin J, Estrada-Garcia I. Expression of inducible nitric oxide synthase and nitrotyrosineduring the evolution of experimental pulmonary tuberculosis. Exp Toxicol Pathol. 2001;53:257-65.
83. Heeringa P, Steenbergen E, Van Goor H. A protective role for endothelial nitric oxide synthase in glomerulonephritis. Kidney Int. 2002;61:822-5.
84. Chang B, Mathew R, Palmer LS, Valderrama E, Trachtman H. Nitric oxide in obstructive uropathy: role of endothelial nitric oxide synthase. J Urol. 2002;168:1801-4.
85. Peresleni T, Noiri E, Bahou WF, Goligorsky MS. Antisense oligodeoxynucleotides to inducible NO synthase rescue epithelial cells from oxidative stress injury. American Journal of Physiology-Renal Fluid and Electrolyte Physiology. 1996;39:F971.
86. Goligorsky MS, Noiri E, editors. Duality of nitric oxide in acute renal injury. Seminars in nephrology; 1999.
87. Kucuk A, Yucel M, Erkasap N, Tosun M, Koken T, Ozkurt M, et al. The effects of PDE5 inhibitory drugs on renal ischemia/reperfusion injury in rats. Mol Biol Rep. 2012 ;39:9775-82.
88. Milsom A, Patel N, Mazzon E, Tripatara P, Storey A, Mota-Filipe H, et al. Role for endothelial nitric oxide synthase in nitrite-induced protection against renal ischemia–reperfusion injury in mice. Nitric Oxide. 2010;22:141-8.
89. Lauer T, Preik M, Rassaf T, Strauer BE, Deussen A, Feelisch M, et al. Plasma nitrite rather than nitrate reflects regional endothelial nitric oxide synthase activity but lacks intrinsic vasodilator action. Proceedings of the National Academy of Sciences. 2001;98:12814-9.
90. Millar TM, Stevens CR, Benjamin N, Eisenthal R, Harrison R, Blake DR. Xanthine oxidoreductase catalyses the reduction of nitrates and nitrite to nitric oxide under hypoxic conditions. FEBS letters. 1998;427:225-8.
91. Duranski MR, Greer JJ, Dejam A, Jaganmohan S, Hogg N, Langston W, et al. Cytoprotective effects of nitrite during in vivo ischemia-reperfusion of the heart and liver. J Clin Invest. 2005;115:1232-40.
92. Jung KH, Chu K, Ko SY, Lee ST, Sinn DI, Park DK, et al. Early intravenous infusion of sodium nitrite protects brain against in vivo ischemia-reperfusion injury. Stroke. 2006;37(11):2744-50.
93. Lii P, Liu F, Yao Z, Wang CY, Chen DD, Tian Y, et al. Nitrite-derived nitric oxide by xanthine oxidoreductase protects the liver against ischemia-reperfusion injury. Hepatobiliary Pancreat Dis Int. 2005;4:350-5.
94. Tripatara P, Patel NS, Webb A, Rathod K, Lecomte FM, Mazzon E, et al. Nitrite-derived nitric oxide protects the rat kidney against ischemia/reperfusion injury in vivo: role for xanthine oxidoreductase. J Am Soc Nephrol. 2007;18:570-80.
95. Gladwin MT. Nitrite as an intrinsic signaling molecule. Nat Chem Biol. 2005;1(5):245-6.
96. Kontogiannis J, Burns KD. Role of AT1 angiotensin II receptors in renal ischemic injury. Am J Physiol Renal Physiol1998;274:F79-F90.
97. Yang XH, Wang YH, Wang JJ, Liu YC, Deng W, Qin C, et al. Role of angiotensin-converting enzyme (ACE and ACE2) imbalance on tourniquet-induced remote kidney injury in a mouse hindlimb ischemia–reperfusion model. Peptides. 2012;36:60-70.
98. Robinette J, Conger JD. Angiotensin and thromboxane in the enhanced renal adrenergic nerve sensitivity of acute renal failure. J Clin Invest. 1990;86:1532.
99. López B, Salom MG, Arregui B, Valero F, Fenoy FJ. Role of superoxide in modulating the renal effects of angiotensin II. Hypertension. 2003;42:1150-6.
100. Kim SM, Kim YG, Jeong K-H, Lee SH, Lee TW, Ihm CG, et al. Angiotensin II-induced mitochondrial Nox4 is a major endogenous source of oxidative stress in kidney tubular cells. PloS One. 2012;7:e39739.
101. Zou XJ, Yang L, Yao SL. Endoplasmic reticulum stress and C/EBP homologous protein-induced Bax translocation are involved in angiotensin II-induced apoptosis in cultured neonatal rat cardiomyocytes. Exp Biol Med (Maywood). 2012;237:1341-9.
102. Iwai M, Horiuchi M. Devil and angel in the renin–angiotensin system: ACE–angiotensin II–AT1 receptor axis vs. ACE2–angiotensin-(1–7)–Mas receptor axis. Hypertens Res. 2009;32(7):533-6.
103. Ferrario CM. ACE2: more of Ang-(1–7) or less Ang II? Curr Opin Nephrol Hypertens. 2011;20:1-6.
104. Mackie FE, Campbell DJ, Meyer TW. Intrarenal angiotensin and bradykinin peptide levels in the remnant kidney model of renal insufficiency. Kidney Int. 2001;59:1458-65.
105. Barroso LC, Silveira KD, Lima CX, Borges V, Bader M, Rachid M, et al. Renoprotective effects of AVE0991, a nonpeptide Mas receptor agonist, in experimental acute renal injury. Int J Hypertens. 2012;2012.
106. Tikellis C, Bernardi S, Burns WC. Angiotensin-

converting enzyme 2 is a key modulator of the renin–angiotensin system in cardiovascular and renal disease. Curr Opin Nephrol Hypertens. 2011;20:62-8.
107. Kostenis E, Milligan G, Christopoulos A, Sanchez-Ferrer CF, Heringer-Walther S, Sexton PM, et al. G-protein–coupled receptor Mas is a physiological antagonist of the angiotensin II type 1 receptor. Circulation. 2005;111:1806-13.
108. Barrilli A, Molinas S, Petrini G, Menacho M, Elías MM. Losartan reverses fibrotic changes in cortical renal tissue induced by ischemia or ischemia-reperfusion without changes in renal function. Mol Cell Biochem. 2004;260:161-70.
109. Pazoki-Toroudi HR, Hesami A, Vahidi S, Sahebjam F, Seifi B, Djahanguiri B. The preventive effect of captopril or enalapril on reperfusion injury of the kidney of rats is independent of angiotensin II AT1 receptors. Fundam Clin Pharmacol. 2003;17:595-8.
110. Morganti A, Lonati C. Aliskiren: the first direct renin inhibitor available for clinical use. J Nephrol. 2011;24:541-9.
111. Wang Z, Liu Y, Han Y, Guan W, Kou X, Fu J, et al. Protective effects of aliskiren on ischemia–reperfusion-induced renal injury in rats. Eur J Pharmacol. 2013;718:160-6.
112. Kilgore KS, Friedrichs GS, Homeister JW, Lucchesi BR. The complement system in myocardial ischaemia/reperfusion injury. Cardiovasc Res. 1994;28:437-44.
113. Arumugam TV, Shiels IA, Woodruff TM, Granger DN, Taylor SM. The role of the complement system in ischemia-reperfusion injury. Shock. 2004;21:401-9.
114. De Vries B, Matthijsen RA, Wolfs TG, van Bijnen AA, Heeringa P, Buurman WA. Inhibition of complement factor C5 protects against renal ischemia-reperfusion injury: inhibition of late apoptosis and inflammation1. Transplantation. 2003;75:375-82.
115. Williams JP, Pechet TT, Weiser MR, Reid R, Kobzik L, Moore Jr FD, et al. Intestinal reperfusion injury is mediated by IgM and complement. J Appl Physiol (1985). 1999;86(3):938-42.
116. Bonventre JV. Complement and renal ischemia-reperfusion injury. Am J Kidney Dis. 2001;38:430-3.
117. Wetsel RA, Kildsgaard J, Haviland DL. Complement anaphylatoxins (C3a, C4a, C5a) and their receptors (C3aR, C5aR/CD88) as therapeutic targets in inflammation. Therapeutic interventions in the complement system; 2000. p. 113-53.
118. Foreman K, Glovsky M, Warner RL, Horvath S, Ward PA. Comparative effect of C3a and C5a on adhesion molecule expression on neutrophils and endothelial cells. Inflammation. 1996;20:1-9.
119. Foreman K, Vaporciyan A, Bonish B, Jones M, Johnson K, Glovsky M, et al. C5a-induced expression of P-selectin in endothelial cells. J Clin Invest. 1994;94:1147.
120. Hattori R, Hamilton K, McEver R, Sims P. Complement proteins C5b-9 induce secretion of high molecular weight multimers of endothelial von Willebrand factor and translocation of granule membrane protein GMP-140 to the cell surface. J Biol Chem. 1989;264:9053-60.
121. Arumugam TV, Shiels IA, Strachan AJ, Abbenante G, Fairlie DP, Taylor SM. A small molecule C5a receptor antagonist protects kidneys from ischemia/reperfusion injury in rats. Kidney Int.2003;63:134-42.
122. Zheng X, Zhang X, Sun H, Feng B, Li M, Chen G, et al. Protection of renal ischemia injury using combination gene silencing of complement 3 and caspase 3 genes. Transplantation. 2006;82:1781-6.
123. Zhou W, Farrar CA, Abe K, Pratt JR, Marsh JE, Wang Y, et al. Predominant role for C5b-9 in renal ischemia/reperfusion injury. J Clin Invest. 2000;105:1363-71.
124. Dirnagl U, Simon RP, Hallenbeck JM. Ischemic tolerance and endogenous neuroprotection. Trends Neurosci. 2003;26:248-54.
125. Kinsey GR, Huang L, Vergis AL, Li L, Okusa MD. Regulatory T cells contribute to the protective effect of ischemic preconditioning in the kidney. Kidney Int. 2010;77:771-80.
126. Chen H, Xing B, Liu X, Zhan B, Zhou J, Zhu H, et al. Ischemic postconditioning inhibits apoptosis after renal ischemia/reperfusion injury in rat. Transpl Int. 2008;21:364-71.
127. Fan LH, He L, Cao ZQ, Xiang J, Liu L. Effect of ischemia preconditioning on renal ischemia/reperfusion injury in rats. Int Braz J Urol. 2012;38:842-54.
128. Chen X, Liu X, Wan X, Wu Y, Chen Y, Cao C. Ischemic Preconditioning Attenuates Renal Ischemia-Reperfusion Injury by Inhibiting Activation of IKKβ and Inflammatory Response. Am J Nephrol. 2009;30:287-94.
129. Liu G, Thornton J, Van Winkle D, Stanley A, Olsson R, Downey J. Protection against infarction afforded by preconditioning is mediated by A1 adenosine receptors in rabbit heart. Circulation. 1991;84:350-6.
130. Meldrum DR. Mechanisms of cardiac preconditioning: ten years after the discovery of ischemic preconditioning. J Surg Res. 1997;73:1-13.
131. Lee HT, Emala CW. Protective effects of renal ischemic preconditioning and adenosine pretreatment: role of A1 and A3receptors. Am J Physiol Renal Physiol. 2000;278:F380-F7.