Pharmacology & Therapeutics 163 (2016) 58–73

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Renoprotective approaches and strategies in acute kidney injury

Yuan Yang [a], Meifang Song [a], Yu Liu [a], Hong Liu [a], Lin Sun [a], Youming Peng [a], Fuyou Liu [a,**], Manjeri A. Venkatachalam [b], Zheng Dong [a,c,*]

[a] Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China
[b] Department of Pathology, University of Texas Health Science Center at San Antonio, TX, USA
[c] Department of Cellular Biology and Anatomy, Medical College of Georgia at Augusta University and Charlie Norwood VA Medical Center, Augusta, GA, USA

ARTICLE INFO

Available online 22 April 2016

Keywords:
Acute kidney injury
Kidney protection
Kidney repair
Renoprotection
Ischemia–reperfusion
Nephrotoxicity

ABSTRACT

Acute kidney injury (AKI) is a major renal disease associated with high mortality rate and increasing prevalence. Decades of research have suggested numerous chemical and biological agents with beneficial effects in AKI. In addition, cell therapy and molecular targeting have been explored for reducing kidney tissue damage and promoting kidney repair or recovery from AKI. Mechanistically, these approaches may mitigate oxidative stress, inflammation, cell death, and mitochondrial and other organellar damage, or activate cytoprotective mechanisms such as autophagy and pro-survival factors. However, none of these findings has been successfully translated into clinical treatment of AKI. In this review, we analyze these findings and propose experimental strategies for the identification of renoprotective agents or methods with clinical potential. Moreover, we propose the consideration of combination therapy by targeting multiple targets in AKI.

Contents

Abbreviations: ACTH, Adrenocorticotropic hormone; AIF, Apoptosis inducing factor; AKI, Acute kidney injury; BMSC, Bone marrow derived stem cells; CIN, Contrast-induced nephropathy; COMP-Ang1, Cartilage oligomeric matrix protein-angiopoietin-1; CysLT1R, Cysteinyl leukotriene-1 receptor; DMARD, Disease-modifying antirheumatic drugs; eNOS, Endothelial nitric oxide synthase; eEPCs, Endothelial progenitor cells; HDAC, Histone deacetylase; HSPC, Hematopoietic stem and progenitor cells; IRI, Ischemia–reperfusion injury; ICAM-1, Intercellular adhesion molecule-1; JNK, c-Jun N-terminal kinase; KIF3B, Kinesin family member 3B; KIM-1, Kidney injury molecule 1; MAPK, Mitogen-activated protein kinase; MCP-1, Monocyte chemotactic protein-1; α-MSH, Alpha-melanocyte-stimulating hormone; MFG-E8, Milk fat globule-epidermal growth factor-factor VIII; MPT, Mitochondrial permeability transition; MSCs, Mesenchymal stem cells; NGAL, Neutrophil gelatinase-associated lipocalin; MDM2, Murine double minute-2; MMP-2, Matrix metallopeptidase 2; mTOR, Mammalian target of rapamycin; PI3K, Phosphatidylinositol-3 kinase; PACAP, Pituitary adenylate cyclase activating polypeptide; RAAS, Renin–angiotensin–aldosterone system; RANTES, Regulated upon activation normal T-cell expressed and secreted; RIP1, Receptor-interacting protein 1; TNF-α, Tumor necrosis factor-alpha; TWEAK, TNF-like weak inducer of apoptosis; VDRA, Vitamin D receptor agonist.

* Correspondence to: Z. Dong, Department of Cellular Biology and Anatomy, Medical College of Georgia and Charlie Norwood VA Medical Center, 1459 Laney Walker Blvd, Augusta, GA 30912, USA. Tel.: 706 721 2825; fax: 706 721 6120.
** Corresponding author.
E-mail addresses: lfy2061@163.com (F. Liu), zdong@augusta.edu (Z. Dong).

http://dx.doi.org/10.1016/j.pharmthera.2016.03.015
0163-7258/

1. Introduction

Acute kidney injury (AKI) is a syndrome characterized by the rapid loss of renal function resulting in the accumulation of end products of nitrogen metabolism (urea and creatinine) and/or decreased urine output (KDIGO, 2012). In clinic, AKI occurs mainly as the clinicopathological outcome of renal or extra-renal surgery, bacterial infection, and nephrotoxicity. Large epidemiological studies show a high incidence of AKI in hospitalized patients and in general population (Bellomo et al., 2012; Hsu et al., 2007; Lameire et al., 2013). AKI is considered as an important independent risk factor for mortality (Uchino et al., 2006). Patients with uncomplicated AKI have a mortality rate of up to 10%. In contrast, patients presenting with AKI and multiorgan failure have been reported to have mortality rates of over 50%. If renal replacement therapy is required, the mortality rate rises further to as high as 80% (Liaño et al., 1998; Shusterman et al., 1987). In addition, AKI is an important factor in the development and progression of chronic kidney disease (CKD) (Chawla et al., 2014; Venkatachalam et al., 2015).

Pathogenetically, AKI is generally described as the injury of renal tubular epithelial cell and vasculature, accompanied by the activation of a robust inflammatory response (Bonventre & Yang, 2011; Linkermann et al., 2014; Molitoris, 2014). In addition, depending on its severity and duration, the damage may spread to glomerulus and interstitium resulting in a full blown, lasting disease. Along with the mechanistic research, a number of agents have been shown for their renoprotective effects in AKI models (Tables 1–5), which include some clinical drugs, herbs, active chemicals, hormones, cytokines and growth factors. Moreover, molecular and cell therapies have been attempted with some promising results. In experimental models, these agents and approaches protected kidneys by suppressing inflammation, preserving vasculature, and/or directly preventing tubular cell injury and death (Fig. 1). However, up-to-date none of them has been successfully translated to the bedside or the use in patients (Jo et al., 2007). In this review, we have summarized the main renoprotective agents and analyzed their effects in AKI models and relevant mechanisms. We have also discussed the experimental strategies for the discovery of efficacious therapies for AKI, including the use of comorbid models and the test of combination therapies.

2. Chemical renoprotectants

2.1. Clinical drugs

Some clinical drugs have been shown to be protective in experimental models of AKI. These include disease-modifying antirheumatic drugs (DMARD), cholesterol-cutting statins, neuroprotective agents for cerebral infarction, selective vitamin D receptor agonist (VDRA), tetracycline antibiotics, phosphodiesterase-5 (PDE5) inhibitors, angiotensin II receptor antagonist, mammalian target of rapamycin (mTOR) inhibitor, immunosuppressant drug, and steroid hormones (Table 1). A notable advantage of clinical drugs is that they have been thoroughly tested for safety in human use and, if effective, they can be relatively rapidly applied for AKI treatment.

2.1.1. Antirheumatic and statin drugs

Leflunomide is known as an immunomodulating drug for the treatment of chronic inflammatory conditions, such as rheumatoid arthritis. In a rat model of renal ischemia–reperfusion injury (IRI), leflunomide markedly attenuated renal dysfunction and morphological alterations, and reduced oxidative stress (OS) (Karaman et al., 2006). Similarly, etanercept (a soluble tumor necrosis factor-alpha (TNF-α) receptor) showed anti-inflammatory and anti-apoptotic effects by lowering the expression of TNF-α and monocyte chemotactic protein-1 (MCP-1) in ischemic AKI rats (Choi et al., 2009). For statins, early postoperative statin use was associated with lower incidence of AKI after a cardiac surgery and decreased mortality risk as compared to preoperative statin use or acute statin withdrawal (Billings et al., 2010; Molnar et al., 2011). Several mechanisms have been suggested to contribute to the renoprotective effects of statins in AKI. Statins with their antioxidant, anti-inflammatory and anti-apoptotic effects may protect kidney against gentamicin-, cisplatin- and cyclosporine-induced nephrotoxicity, beyond their lipid-lowering capacity (Dashti-Khavidaki et al., 2013; Kostapanos et al., 2009). They may also block the activation of mitogen-activated protein kinase (MAPK) and the redox-sensitive NF-κB and activator protein-1 (AP-1) (Gueler et al., 2002). Also statins may ameliorate AKI by directly affecting renal vasculature, an observation that is particularly relevant to sepsis-associated AKI (Yasuda et al., 2006).

Table 1
Clinical drugs with renoprotective effects in AKI.

No	Name	Characteristics	Tested AKI model	Mechanism
1	Leflunomide	Pyrimidine synthesis inhibitor used in immunosuppressive diseases such as rheumatoid arthritis and psoriatic arthritis	IRI in rat	Reduce oxidative stress
2	Etanercept	TNF-α inhibitor used to treat autoimmune diseases	IRI in rat	Lower expression of TNF-α and MCP-1
3	Statins drugs	Inhibitors of HMG-CoA reductase used to lower cholesterol	Drug-, septic- and ischemic-induced AKI in rat or mice	Antioxidant, anti-inflammatory and anti-apoptotic
4	Edaravone	Neuroprotective agent in acute brain ischemia and subsequent cerebral infarction	IRI in rats	Increase Bcl-2 expression
5	Paricalcitol	Analog of vitamin D2 active form, VDR agonist	IRI in male C57BL/6 mice	Upregulate COX-2 and PGE2
6	Tadalafil, sildenafil	Phosphodiesterase type 5 inhibitor	Contrast-induced AKI in rabbits	Inhibit protein kinase G
7	Milrinone	Phosphodiesterase type 3 inhibitor	IRI in mice	Inhibit NF-κB activation
8	Fidarestat	Aldose reductase inhibitor for diabetic complications	LPS-induced endotoxic AKI	Suppress inflammation
9	Telmisartan	Angiotensin II receptor antagonist used in hypertension	IRI in rats	Decrease MDA, TNF-α, NO and homocysteine
10	Adrenomedullin	A potent endogenous vasodilatory peptide hormone	Contrast induced AKI in rats	Negative regulation of the RAAS
11	Rituximab	Monoclonal antibody against CD20 used in autoimmunity	IRI in mice	Suppression of inflammation
12	Cyclosporin A	Immunosuppressant used in transplant medicine	FA-induced AKI in mice	Block TWEAK expression and NF-κB activation
13	Mycophenolate mofetil	Immunosuppressant used in transplant or autoimmune diseases	IRI in rats	Attenuate the increase of cytokines RANTES and AIF
14	Temsirolimus	Inhibitor of mammalian target of rapamycin (mTOR)	Septic-AKI in older adult mice	Induce autophagy
15	Doxycycline	Tetracycline antibiotics for treating infections or inflammation	IRI in a rat model of ACS	Decrease IL-1β, TNF-α and MMP-2
16	Auramin	An antiparasitic drug used in treatment of trypanosomiasis	IRI in mice	Reduce tubular apoptosis and infiltrating leukocytes
17	Geranylgeranylacetone	An antiulcer drug used in treatment of gastric ulcers	IRI in rats	Induction of Hsp70