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Protective Effects of Angiotensin-Converting-Enzyme-2 on Renal Dysfunction in Obstructive Jaundice

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Abstract

Acute renal failure occurring in patients with obstructive jaundice after surgery is still a serious clinical complication. Renin-angiotensin-aldosterone system (RAAS) plays a key role in the progression of kidney disease. Previous studies have demonstrated that angiotensin-converting-enzyme-2 (ACE2), a component of the RAAS system, acts as a local regulator for renal protection, and has a beneficial effect on renal fibrosis. This review will summarize the role of ACE2 and the protective effects on renal dysfunction in obstructive jaundice.

Introduction

Obstructive jaundice is a common clinical manifestation in hepatobiliary surgery. The pathophysiological changes in obstructive jaundice remain to be complex. Hyperbilirubinemia in patients with obstructive jaundice induces various clinical complications and increased morbidity and mortality including acute renal failure and endotoxemia[1,2].

Acute renal failure occurs in 8 to 10% of patients with obstructive jaundice. However, the mortality rate of this complication is reaching up to 70%–80%[1]. Accumulating evidences support that the increase of total bilirubin (Tbil) and serum creatinine (Scr) level in postoperative patients with obstructive jaundice relates to acute renal failure[3,4].

A correlation was suggested between endotoxins and the complications in patients with obstructive jaundice[1,5]. Released cytokines due to endotoxin cause renal vasoconstrictive effect, acute tubular necrosis, fibrin deposition and systemic inflammatory response, which impact the short-term outcome[6]. Impaired immune function caused by obstructive jaundice contributes to the release of inflammatory cytokine TNF-α, IL-1, IL-6[7].

The experimental animal model for obstructive jaundice is established by bile duct ligation (BDL)[8]. It has contributed to a better understanding of pathophysiology and the assessment of therapeutic strategy.

This review will explore the protective effects of RAAS (Renin-angiotensin-aldosterone system) on renal dysfunction in obstructive jaundice.

The RAAS and Renin Inhibition

The RAAS has a crucial role in the regulation of blood pressure, fluid balance, and renal homeostasis[9]. Accumulating evidences have

shown that the progression of renal disease is associated with RAAS[10,11]. Independent regulation of the intrarenal RAAS and inappropriate activation of this system contributes to the development and maintenance of renal disease[12]. Blockade of the RAAS by renin inhibition is an effective way to prevent progressive renal dysfunction, manifesting as reduced blood pressure, kidney fibrosis and inflammation, but at high risk of renal disease[13,14].

The Role of ACEI/ARBs

Previous research mainly focused on the effect of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blockers (ARBs) on renal function. ACEI prevents the conversion of Angiotensin I to Angiotensin II by inhibiting the angiotensin-converting enzyme and decreases aldosterone secretion. Mishina *et al.* reported that renal dysfunction was improved after benazepril (an ACEI) was administered, which showed a protective effect in preventing the progression of renal disease[15]. ARBs block the attachment of Angiotensin II to its receptor. Similar to ACEI, ARBs decreased blood pressure and albuminuria, produced renal protective effect[16]. And, ACEI and ARBs are all recommended for the treatment of diabetic nephropathy[17].

The Role of ACE2 and Aldosterone

Angiotensin-converting enzyme 2 (ACE2) is an exopeptidase that catalyzes the conversion of angiotensin II to angiotensin-(1-7) and is expressed abundantly in the kidney. It was found to have an important regulatory role in RAAS and was demonstrated to be a therapeutic target in renal disease. Studies have demonstrated the interplay between ACE2 and the kidney under normal and pathological conditions and pointed out the crucial role of ACE2 plays in the modulation of renal injury[18,19]. Clarke *et al.* concluded that the upregulation of ACE2 results in a significant protective effect on renal function in both diabetic patients and animal models[20]. Liu *et al.* studied the mechanisms of renoprotective role of ACE2 and demonstrated that enhanced Ang II-mediated TGF-β/Smad and NF-κB signaling may be the mechanisms by which loss of ACE2 enhances renal fibrosis and inflammation[21].

Studies using type 2 diabetes models have shown that ACE2 expression increased at an early stage, and reduced in the kidney with diabetic nephropathy developing[22]. Similarly, the ACE2 expression is elevated in early and decreased in the late stage of diabetic nephropathy in type 1 diabetes models[23]. Aldosterone is a steroid hormone produced by zona glomerulosa of the adrenal cortex in the adrenal gland. It is part of the RAAS and is related with the development and progression of the cardiovascular and renal disease. It was proved that aldosterone in the circulation indirectly promotes the development of renal diseases by inducing inflammation, fibrosis, and necrosis[24]. Mechanism studies of aldosterone-induced inflammation provided the rationale for an expanded therapeutic role for mineralocorticoid receptor antagonists and aldosterone synthase inhibitors[25]. Fukuda *et al.* suggested that aldosterone induces kidney injury via activation of NF-κB and mineralocorticoid receptor, and decreased ACE2 expression may play an important role in aldosterone-induced kidney injury[26]. Animal experiments showed that aldosterone administration could reduce the expression of ACE2. Nevertheless, aldosterone antagonists could reverse the pathological changes[27].

Aldosterone Antagonist: Spironolactone

Spironolactone, a non-selective aldosterone antagonist, is commonly used in clinical practice which interferes with RAAS. The administration of spironolactone could abolish the effect of aldosterone.

de Sousa *et al.* showed that the treatment with spironolactone appears to be effective in controlling proteinuria and with a protective effect on renal fibrosis[28]. A meta-analysis evaluated the benefits and potential adverse effects of spironolactone on renoprotective treatment in patients with diabetic nephropathy and concluded that spironolactone could be used to prevent or slow diabetic nephropathy progression by reducing proteinuria[29]. Agrawal *et al.* concluded that ACEI and ARBs have been shown to suppress RAAS ineffectively, and they supported the use of spironolactone for more comprehensive suppression of the RAAS, which improved mortality outcomes in patients with chronic kidney disease[30].

Some animal experiments related with spironolactone have been conducted. Zhou H *et al.* proved that spironolactone may prevent renal fibrosis by inhibiting the endothelial-mesenchymal transition in rats[31]. Jeewandara *et al.* showed that inhibition of aldosterone via spironolactone was able to retard both renal and cardiac disease progression in a rodent model of kidney disease[32]. Another study showed that spironolactone administration after mild ischemia may be a useful therapeutic strategy to prevent the detrimental effect on renal function[33].

In our previous study, we found that down-regulation of the ACE2 expression in the kidney of the BDL group was significant. Interestingly, the ACE2 expression is negatively correlated with Scr/Tbil. Further investigation showed that spironolactone intervention could significantly improve the renal fibrosis induced by obstructive jaundice. We also discovered that the ACE2 expression of BDL group could be upregulated by spironolactone. It implied that spironolactone could induce feedback regulation of RAAS, thereby affecting the expression of ACE2 and improving the renal function[8]. Nevertheless, the mechanism that leads to the expression change of ACE2 in obstructive jaundice is unclear and needs further study.

Summary

In conclusion, the change of ACE2 expression was correlated with the renal dysfunction in obstructive jaundice. Spironolactone not only improved the progression of renal fibrosis but also upregulated ACE2 expression in the kidney of obstructive jaundice.

Conflict of Interests

Authors declared no conflict of interests.

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