Role of Arachidonic Acid-Derived Cyp450 Metabolites In Acute Kidney Injury

Ao Ding#, Ye Zhu#, You Zuo, Si-Rui Liu, Xuehong Li and Cheng Wang*

Department of Nephrology, 5th Affiliated Hospital of Sun Yat-Sen University, China

# These authors contributed equally

*Corresponding author: Cheng Wang, MD, Department of Nephrology, 5th Affiliated Hospital of Sun Yat-Sen University, China

ARTICLE INFO

Received: March 09, 2020
Published: March 17, 2020

Citation: Ao Ding, Ye Zhu, You Zuo, Si-Rui Liu, Cheng Wang, et al., Role of Arachidonic Acid-Derived Cyp450 Metabolites In Acute Kidney Injury. Biomed J Sci & Tech Res 26(4)-2020. BJSTR. MS.ID.004384.

Abstract

Acute Kidney Injury (AKI) remarkably affect public health and need higher healthcare costs, which is life-threatening and characterized of acute decline with function. Arachidonic Acid (AA), the precursor for synthesis of various biologically active molecules and be involved in regulation of homeostasis and metabolism. Recent studies have shown that the AA cytochrome P450 (CYP450) pathway contribute to the development of AKI by EETs (the product of catalyzing epoxidation reactions), 20-HETE (the product of omega-hydroxylation reactions) and maybe potent key for the prevention and treatment of AKI. This review summarizes recent advances in AA metabolites in AKI.

Keywords: Arachidonic Acid; Epoxyeicosatrienoic Acids; 20-Hydroxyeicosatetraenoic Acid; Acute Kidney Injury (AKI); Cytochrome P450 (CYP450)

Introduction

Acute kidney injury (AKI) is a common clinical syndrome that results in the accumulation of serum creatinine and urea nitrogen, mostly caused by Ischemia/Reperfusion (I/R), and its morbidity and mortality have increased within the last years [1-3]. Recent preclinical studies suggest that Arachidonic Acid (AA) metabolites generated by Cytochrome P450 (CYP) enzymes play an important role in the development of I/R-induced organ injury, especiially the heart and brain [4,5]. This review provide promising target for treatment with AKI by investigating the role of AA derivatives.

Mechanism of AA Derivatives

The formation of 20-Hydroxyeicosatetraenoic Acid (20-HETE) is mainly generated by CYP4A and CYP4F families, while a set of regio- and stereoisomeric Epoxyeicosatrienoic Acids (EETs) is produced through the action of CYP 2J and 2C enzymes [6]. EETs are produced in vascular endothelial cells and activate calcium-activated potassium (BK) channels in the underlying vascular smooth muscle cells, eventually leading to vasorelaxation [7-9]. While 20-HETE, which is produced by renal vascular smooth muscle cells, acts as a potent vasoconstrictor of small arteries and arterioles (<100 µm) such as renal interlobular and afferent arterioles [6]. The proportional distribution of 20-HETE and EETs could potentially influence fluid homeostasis and vascular tone and become a key determinant for controlling blood pressure [10]. Apart from the regulation of renal vascular response, the role of CYP-dependent AA metabolites in the control of sodium excretion has emerged as a dynamic new field [11]. 20-HETE and EETs are formed in different segments of the nephron and mediate tubular function with the net effect of inhibiting sodium reabsorption [12,13]. Overall, in the kidney, the eicosanoids (20-HETE and EETs) have concordant effects on sodium reabsorption but contradictory effects on vascular reactivity [14].

Impact of AA Derivatives in Aki

There are few reports that have addressed the role of 20-HETE on renal I/R-injury. In vitro experiments showed that 20-HETE overproduction can significantly exacerbate the cytotoxic and
pro-apoptotic effects of chemical hypoxia on cultured renal tubular epithelial cells [15]. Moreover, Hoff et al. concluded that ischemia-induced 20-HETE generation and action are primarily responsible for initiating the pathophysiological cascade leading to I/R-induced kidney injury [16]. This conclusion is also in line with a recent clinical study on renal transplantation showing that the extent of 20-HETE released within the first 5min of allograft reperfusion is a negative predictor of post-transplant allograft function [17]. In contrast, there is definite evidence to indicate that EETs have significant effect of decreasing inflammatory cell infiltration, limiting of leukocyte adhesion, reducing apoptosis and vasodilatation [18,19]. Accordingly, Hoff et al. also suggested that ischemia could cause the imbalance between 20-HETE and EETs, while they play opposite role in kidney. Administration of exogenous EET analogue exert better protective impact and compensate the lack of endogenous EET in ischemia-induced AKI [20].

Conclusion

This review focus on the current evidence about the critical effect of AA metabolites in AKI and provide efficacious therapeutic targets in AKI. Considering all the evidence, ischemia-induced AKI leads to the imbalance between 20-HETE and EETs, overproduced 20-HETE and the lack of endogenous EET, which support that AA metabolites play a critical role in regulating the pathophysiology processes of AKI. Thus, targeting the formation and action of CYP-dependent eicosanoids will probably have beneficial effects on the prevention of ischemic AKI in clinical setting.

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