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Review

Mechanisms of epoxyeicosatrienoic acids to improve cardiac remodeling in chronic renal failure disease

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ABSTRACT

Both clinical and basic science studies have demonstrated that cardiac remodeling in patients with chronic renal failure (CRF) is very common. It is a key feature during the course of heart failure and an important risk factor for subsequent cardiac mortality. Traditional drugs or therapies rarely have effects on cardiac regression of CRF and cardiovascular events are still the first cause of death. Epoxyeicosatrienoic acids (EETs) are the products of arachidonic acids metabolized by cytochrome P450 epoxygenases. It has been found that EETs have important biological effects including anti-hypertension and anti-inflammation. Recent data suggest that EETs are involved in regulating cardiomyocyte injury, renal dysfunction, chronic kidney disease (CKD)-related risk factors and signaling pathways, all of which play key roles in cardiac remodeling induced by CRF. This review analyzes the literature to identify the possible mechanisms for EETs to improve cardiac remodeling induced by CRF and indicates the therapeutic potential of EETs in it.

Contents

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1. Introduction

Cardiac remodeling is one of the most common cardiac abnormalities in chronic renal failure (CRF) patients (Salvetti et al., 2007). About 70% to 80% patients with stage 4–5 chronic kidney disease (CKD) have some manifestations of left ventricular hypertrophy before the initiation of dialysis. In fact, cardiac remodeling has already occurred during the early stage of CKD (Essig et al., 2008). Although cardiac remodeling is traditionally considered to be an adaptive response during the early stage of heart diseases, it can cause severe complications such as heart failure, arrhythmia and sudden cardiac death (Haider et al., 1998; Levy et al., 1990). And it has been demonstrated that a higher left ventricular mass index is associated with a higher mortality and more adverse cardiovascular outcomes in patients receiving hemodialysis (Zoccali et al., 2004). Owing to the complex risk factors for CKD (Cerasola et al., 2011), it is still in the preliminary stage to identify effective drugs and therapies to treat cardiac remodeling induced by CRF.

Epoxyeicosatrienoic acids (EETs) are the products of arachidonic acids metabolized by cytochrome P450 (CYP) epoxygenases. Recent data show that EETs can attenuate cardiac remodeling (Ai et al., 2009; Li et al., 2009; Xu et al., 2006) and may become new therapeutics to improve patients' survival. However, the studies about the effects of EETs on regulating cardiac remodeling induced by CRF were limited and the mechanisms for these effects are largely unknown. Although it must be acknowledged that the direct evidence has not been obtained, the current data do support the hypothesis that EET upregulation improves cardiac remodeling induced by CRF. Recently, more and more scientists noticed that the dysfunction in the heart or kidneys can cause dysfunction in the other organ, Elmarakby (2012) summarized the reno-protective effect of EETs in cardiovascular disease in depth (Elmarakby, 2012), and provided four possible reno-protective mechanisms of EETs in cardiovascular disease (hypotensive and hypoglycemic effects, inhibit vascular smooth muscle cells proliferation and anti-inflammatory properties). And that raised another question—Whether EETs improve the cardiac remodeling in patients with CRF? In this study, in light of the complexity of cardiac remodeling induced by CRF (primary and secondary cardiac remodeling), here we focus on (1) EETs ameliorate cardiac remodeling induced by CRF through cardiomyocyte protection; (2) EETs ameliorate cardiac remodeling induced by CRF through regulating renal function; (3) EETs regulate CKD-related risk factors to improve cardiac remodeling induced by CRF; and (4) possible signaling pathways affected by EETs to improve cardiac remodeling induced by CRF.

2. Biological characters of epoxyeicosatrienoic acids

The metabolism of arachidonic acids forms three classes of eicosanoid biomediators: products of cyclooxygenase, lipoxygenase, and CYP epoxygenases, respectively (Brash, 2001). cyclooxygenase and lipoxygenase metabolic pathways have been detailed studied. CYP pathway, the third eicosanoid pathway, contains two enzymatic pathways, catalyzed by the hydroxylases and epoxygenases (Imig and Hammock, 2009). The hydroxylase CYP enzymes convert arachidonic acids into hydroxyeicosatetraenoic acids (HETEs), while CYP epoxygenases generate EETs. It is found that different species have different CYP epoxygenases (Imig, 2012). In fact, CYP epoxygenases is also expressed in an organ- and tissue-specific manner (Roman, 2002; Wu et al., 1997).

CYP epoxygenases produce four EET regioisomers from arachidonic acids: 5, 6-EET, 8, 9-EET, 11, 12-EET and 14, 15-EET. Once EETs are formed, they will be esterified into membrane phospholipids and bind to proteins. Subsequently, they are metabolized into shorter chain molecules by β-oxidation or metabolized to the corresponding dihydroxyeicosatrienoic acids (DHETs) by soluble epoxide hydrolase (sEH). Hydroxylation to DHETs by sEH is the main metabolic pathway for EETs (Fang et al., 1995; Zeldin et al., 1993) (Fig. 1).

Since the first descriptions of biological actions of EETs and the identification of EETs as endothelium-derived hyperpolarizing factors, there has been growing interest in EETs. Meanwhile, various types of functional effects produced by EETs have widely been found, for example, regulating peptide hormone secretion, ion transport, blood pressure, inflammation, cell proliferation, and cardiac remodeling (Roman, 2002; Zeldin, 2001) (Fig. 1). Considerable evidence has indicated that it will be a promising strategy to treat cardiac remodeling induced by CRF with EETs.

3. EETs ameliorate cardiac remodeling induced by CRF through cardiomyocyte protection

Cardiac remodeling induced by CRF is multiple factors involved consequence (Cerasola et al., 2011; Strozecki et al., 2001). And EETs play an important role in both primary cardiac remodeling and secondary cardiac remodeling induced by CRF. Considerable evidences have showed that EETs have direct cardio-protective effects for improving primary cardiac remodeling induced by CRF. Myocardium ischemia is a serious injury of

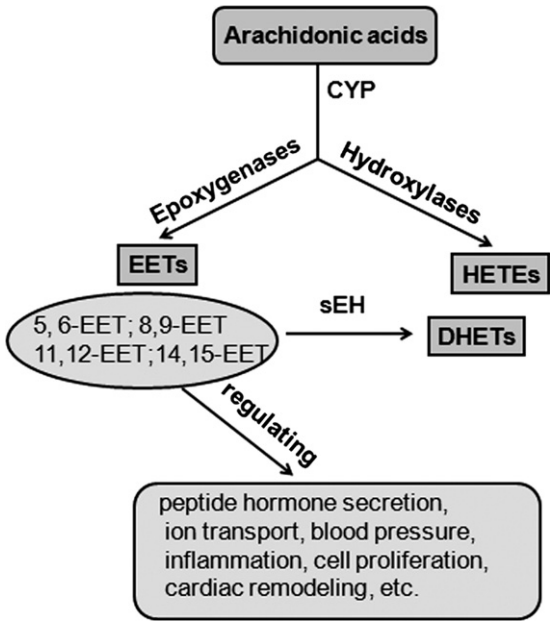

Fig. 1. Metabolism and biological characters of epoxyeicosatrienoic acids.