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Review article

Epoxyeicosatrienoic acids and cardioprotection: The road to translation

Akinyemi Oni-Orisan [a,b], Nasser Alsaleh [d], Craig R. Lee [a,b,c], John M. Seubert [d,e,*]

[a] Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[b] Center for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[c] UNC McAllister Heart Institute, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[d] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada
[e] Department of Pharmacology, University of Alberta, Edmonton, AB, Canada

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ABSTRACT

Cardiovascular disease, including acute myocardial infarction (AMI), is the leading cause of morbidity and mortality globally, despite well-established treatments. The discovery and development of novel therapeutics that prevent the progression of devastating consequences following AMI are thus important in reducing the global burden of this devastating disease. Scientific evidence for the protective effects of epoxyeicosatrienoic acids (EETs) in the cardiovascular system is rapidly emerging and suggests that promoting the effects of these cytochrome P450-derived epoxyeicosanoids is a potentially viable clinical therapeutic strategy. Through a translational lens, this review will provide insight into the potential clinical utility of this therapeutic strategy for AMI by 1) outlining the known cardioprotective effects of EETs and underlying mechanisms demonstrated in preclinical models of AMI with a particular focus on myocardial ischemia–reperfusion injury, 2) describing studies in human cohorts that demonstrate a relationship between EETs and associated pathways with coronary artery disease risk, and 3) discussing preclinical and clinical areas that require further investigation in order to increase the probability of successfully translating this rapidly emerging body of evidence into a clinically applicable therapeutic strategy for AMI.

Contents

Abbreviations: $\Delta\Psi_m$, mitochondrial membrane potential; AMI, acute myocardial infarction; CAD, coronary artery disease; Cav-1, caveolin-1; Cav-3, caveolin-3; CPR, cardiopulmonary resuscitation; DHETS, dihydroxyeicosatrienoic acids; DHOMEs, dihydroxyoctadecaenoic acids; eNOS, endothelial nitric oxide synthase; EDPs, epoxydocosapentaenoic acids; EETs, epoxyeicosatrienoic acids; EPCs, endothelial progenitor cells; EpOMEs, epoxyoctadecaenoic acids; IR, ischemia-reperfusion; Kca, calcium-activated potassium channel; LAD, left anterior descending; LV, left ventricular; LVDP, left ventricular developed pressure; mitoK_{ATP}, mitochondrial K_{ATP}; mPTP, mitochondrial permeability transition pore; NF-κB, nuclear factor-kappaB; NO, nitric oxide; p42/p44 MAPK, p42/p44 mitogen-activated protein kinase; PI3K, phosphatidylinositol-3 kinase; ROS, reactive oxygen species; sarcK_{ATP}, sarcolemma K_{ATP}; sEH, soluble epoxide hydrolase; TAC, transverse aortic constriction; TNF-α, tumor necrosis factor alpha.

* Corresponding author at: Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB T6G 2N8, Canada. Tel.: +1 780 492 0007; fax: +1 780 492 1217.
E-mail address: jseubert@pharmacy.ualberta.ca (J.M. Seubert).

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1. Introduction

Despite major advances in evidence-based medical therapies, cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide. In the western world, CVD has been the leading cause of death for almost a century and its prevalence is expected to continue to rise tremendously [1,2]. Most notably, acute myocardial infarction (AMI) events, complications of CVD, are a primary source of the public health burden associated with this illness [1,2]. AMI is typically characterized by rupture of an atheromatous plaque resulting in an intracoronary thrombus and myocardial ischemia [3]. The restoration of blood flow, termed ischemia–reperfusion (IR), is imperative to prevent further myocardial cell necrosis. Paradoxically, however, IR also triggers injury to the myocardium [4]. Consequently, identification and characterization of the key pathways that regulate IR injury will facilitate the development of novel therapeutic strategies that mitigate IR injury and its pathological consequences, thereby reducing the risk of adverse outcomes following AMI.

It is now well-established that cytochrome P450 (CYP)-derived epoxyeicosatrienoic acids (EETs), endogenous lipid metabolites of arachidonic acid, elicit potent anti-inflammatory, vasodilatory, fibrinolytic, anti-apoptotic, pro-angiogenic, and smooth muscle cell anti-migratory effects in the cardiovascular system [5,6]. Furthermore, accumulating preclinical evidence from in vitro, ex vivo, and in vivo models of AMI demonstrates that EETs directly protect the myocardium following ischemia via a variety of mechanisms [7–9]. Additionally, associations between genetic polymorphisms in the CYP epoxygenase pathway and the risk of developing CVD have been reported in humans [10]. Therefore, therapeutic interventions that promote the cardioprotective effects of EETs offer considerable promise as a novel therapeutic strategy to reduce sequelae following AMI; however, key questions remain to be addressed prior to translation of EET-promoting strategies into successful proof-of-concept phase I and II clinical trials. The acute and chronic cardioprotective effects of EETs and underlying mechanisms have not been fully characterized. Furthermore, the association between genetic polymorphisms in the CYP epoxygenase–EET pathway and poor prognosis has not been studied in patients suffering from an AMI. These are currently active areas on investigation.

This review aims to 1) outline the known cardioprotective effects of EETs and underlying mechanisms with a particular focus on myocardial IR injury, 2) describe studies in human cohorts that demonstrate a relationship between EETs and associated pathways with the risk of coronary artery disease (CAD), and 3) discuss preclinical and clinical areas that require further investigation in order to increase the probability of successfully translating this rapidly emerging body of evidence into a clinically applicable therapeutic strategy for AMI.

2. The CYP epoxygenase pathway

Arachidonic acid is metabolized by CYP epoxygenase enzymes to form bioactive EETs (Fig. 1) [11]. CYP2J and CYP2C epoxygenases are the primary sources of all four EET regioisomers (5,6-, 8,9-, 11,12-, and 14,15-EETs) [12]. Each regioisomer is composed of 2 different stereoisomers (R,S or S,R configuration) [12]. CYP2J2, CYP2C8 and CYP2C9 are extensively and constitutively expressed in human heart tissue [13,14]. The predominant fate of EETs is through rapid metabolism by soluble epoxide hydrolase (sEH) into dihydroxyeicosatrienoic acids (DHETs), which generally have less biological activity [6,7]. *EPHX2* codes for human sEH [15] and is expressed in a multitude of cell types [16]. Importantly, sEH is highly expressed in the myocardium [16].

In parallel, arachidonic acid is also metabolized by cyclooxygenase, lipoxygenase and CYP hydroxylase enzymes to produce biologically active metabolites that play a functional role in myocardial IR injury [17–19]. In addition to arachidonic acid-derived products, other members of the n − 6 polyunsaturated fatty acid (PUFA) family (most notably linoleic acid) and of the n − 3 PUFA family such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) play a role in cardiovascular disease [20]. CYP-dependent epoxy-derivatives of these PUFAs are also potent biological mediators in the cardiovascular system and may be subsequently metabolized into vicinal diols by epoxide hydrolases [12, 21,22]. Although these emerging data are beyond the scope of this review, we summarize select examples from the literature throughout the review that will stimulate future research in this area.

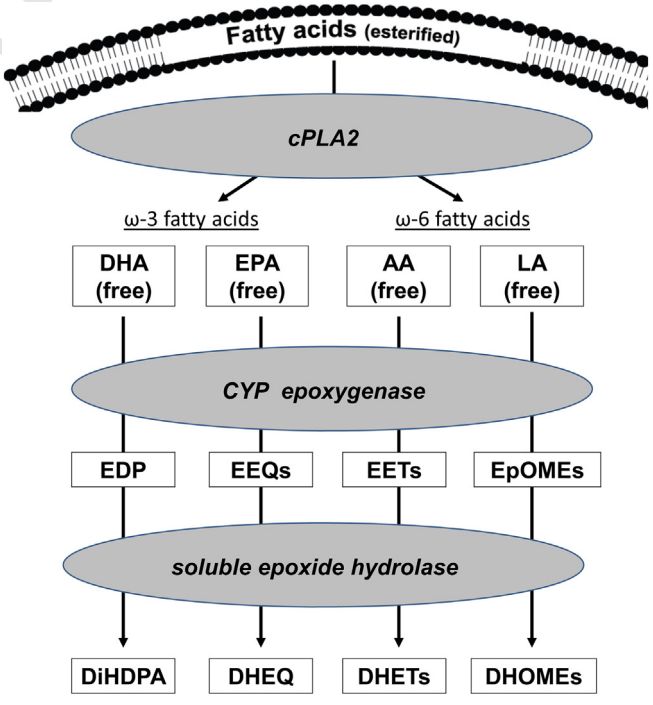

Fig. 1. Cytochrome P450 (CYP) epoxygenase–epoxyeicosatrienoic acid (EET) and parallel pathways. Through the activation of cytosolic phospholipase A2 (cPLA2) in cardiomyocytes following AMI, membrane-bound fatty acids are released into the cytosol and subsequently metabolized by CYP epoxygenases to form biologically active eicosanoids. The CYP2J and CYP2C epoxygenases produce four regioisomers of EETs from arachidonic acid (AA) that elicit various biological effects. These bioactive epoxyeicosanoids are extensively hydrolyzed by soluble epoxide hydrolase into the less biologically active dihydroxyeicosatrienoic acid (DHET) metabolites. DHA, docosahexaenoic acid; DHEQ, dihydroxy-eicosatetraenoic acid; DHOME, dihydroxyoctadecaenoic acid; DiHDPA, dihydroxy-docosapentaenoic acid; EDP, epoxydocosapentaenoic acid; EEQ, epoxyeicosatetraenoic acid; EPA, eicosapentaenoic acid; EpOME, epoxyoctadecaenoic acid; LA, linoleic acid.

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