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Review

Stabilized epoxygenated fatty acids regulate inflammation, pain, angiogenesis and cancer

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ABSTRACT

Epoxygenated fatty acids (EpFAs), which are lipid mediators produced by cytochrome P450 epoxygenases from polyunsaturated fatty acids, are important signaling molecules known to regulate various biological processes including inflammation, pain and angiogenesis. The EpFAs are further metabolized by soluble epoxide hydrolase (sEH) to form fatty acid diols which are usually less-active. Pharmacological inhibitors of sEH that stabilize endogenous EpFAs are being considered for human clinical uses. Here we review the biology of ω-3 and ω-6 EpFAs on inflammation, pain, angiogenesis and tumorigenesis.

Contents

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1. Introduction

Arachidonic acid (ARA, 20:4ω-6) compromises a major component in the membrane phospholipids and plays a critical role in cell signaling [1–3]. Upon cellular stimulation, the incorporated ARA is released by several enzymes including diacylglycerol lipase and phospholipase A2 (PLA_2) to generate free intracellular ARA, which is rapidly metabolized by a series of enzymes to generate lipid mediators (LMs) in a process collectively termed the ARA cascade [1–3]. The lipid signaling in the ARA cascade is important because the LMs regulate many fundamental biological processes from inflammation to blood flow, and therefore are important therapeutic targets for multiple human disorders [1–3]. There are three major branches in the ARA cascade: cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP) pathways. The COX and LOX pathways generate predominately but not exclusively pro-inflammatory LMs and a variety of approved drugs target these two branches [2]. In contrast, our knowledge of the CYP pathway, which is usually regarded as the third branch of the ARA cascade, is rather limited and has not yet been exploited therapeutically [3–6]. Lipid amides and other endocannabinoids are important chemical mediators [7]. However, they are usually not considered as part of the ARA cascade and only their epoxygenated metabolites are discussed here.

The CYP branch, which was first described in 1980s, converts ARA to two major classes of LMs: CYP ω/ω-1 hydroxylases (mainly CYP4A and CYP4F) catalyze the hydroxylation of ARA to generate 19-hydroxyeicosatetraenoic acid (19-HETE) and 20-HETE [8]. In the other branch of the CYP pathway, CYP epoxygenases (mainly CYP2C and CYP2J) catalyze the epoxidation of ARA to generate epoxygenated fatty acids (EpFAs) called epoxyeicosatrienoic acids (EETs) that include four regioisomers of 5,6-, 8,9-, 11,12- and 14,15-EET [3]. 20-HETE has been shown to have an array of largely detrimental effects, inducing hypertension, endothelial dysfunction, inflammation, cardiovascular diseases, angiogenesis and tumor growth [9–14]. EETs have been investigated as autocrine and paracrine signaling molecules which have anti-inflammatory, vasodilative, anti-hypertensive, cardio-protective, renal-protective, pro-angiogenic and analgesic effects [5]. As we simplistically discuss LMs with terms such as inflammatory or anti-inflammatory and suggest beneficial or detrimental effects, it is important to remember most LMs have multiple effects that maintain a critical balance in normal physiology. Although chemically stable (other than the 5,6-EET regioisomer), EETs are highly unstable *in vivo* mainly due to the rapid metabolism by soluble epoxide hydrolase (sEH, encoded by *EPHX2*) to the less-active fatty acid diols termed dihydroxyeicosatrienoic acids (DHETs) (Fig. 1) [6]. Therefore, blocking the degradation of generally beneficial EETs by targeting sEH is pharmacologically attractive. During the past decade, pharmacological inhibitors of sEH (sEHIs) with IC_{50} values in nM–pM range and good pharmacokinetic (PK) profiles *in vivo* have been developed [4,15]. The sEHIs, which stabilize endogenous EETs, are promising drug candidates for multiple human diseases and have been evaluated in phase II human trials [4,16].

Linoleic acid (18:2, ω-6), which is a biosynthetic precursor to generate ARA and is highly abundant in the western diet [17], is also a substrate of the CYP/sEH pathway [6]. The metabolism of linoleic acid by CYP epoxygenases generates the linoleic epoxides including 9,10-epoxyoctadecenoic acid (9,10-EpOME) and 12,13-epoxyoctadecenoic acid (12,13-EpOME), which are further metabolized by sEH to form the linoleic diols including 9,10-dihydroxyoctadecenoic acid (9,10-DiHOME) and 12,13-dihydroxyoctadecenoic acid (12,13-DiHOME) [6]. EpOMEs have been associated with multiple organ failure and adult respiratory distress syndrome in some severe burn patients [18–21]. We have shown that the sEH-mediated conversion of EpOMEs to DiHOMEs plays a critical role in the cellular toxicity of EpOMEs [22]. With a high consumption of linoleic acid in the western diet, it is critical to investigate the effects of linoleic acid metabolites on human health, in particular EpOMEs and DiHOMEs which have been demonstrated to have toxic effects.

Besides ω-6 polyunsaturated fatty acids (PUFAs), ω-3 PUFAs such as eicosapentaenoic acid (EPA, 20:5ω-3) and docosahexaenoic acid (DHA, 22:6ω-3) are also substrates of the enzymes in the ARA cascade, which convert them to the ω-3-series LMs [23–25]. A major theory to explain the health-promoting effects of ω-3 PUFAs is that they compete with ARA for the enzymatic metabolism, decreasing the formation of ω-6-series LMs that are predominately pro-angiogenic and pro-inflammatory and increasing ω-3-series LMs that have less detrimental and possibly beneficial effects [23–25]. Indeed, the metabolism of ω-3 PUFAs by COX and LOX

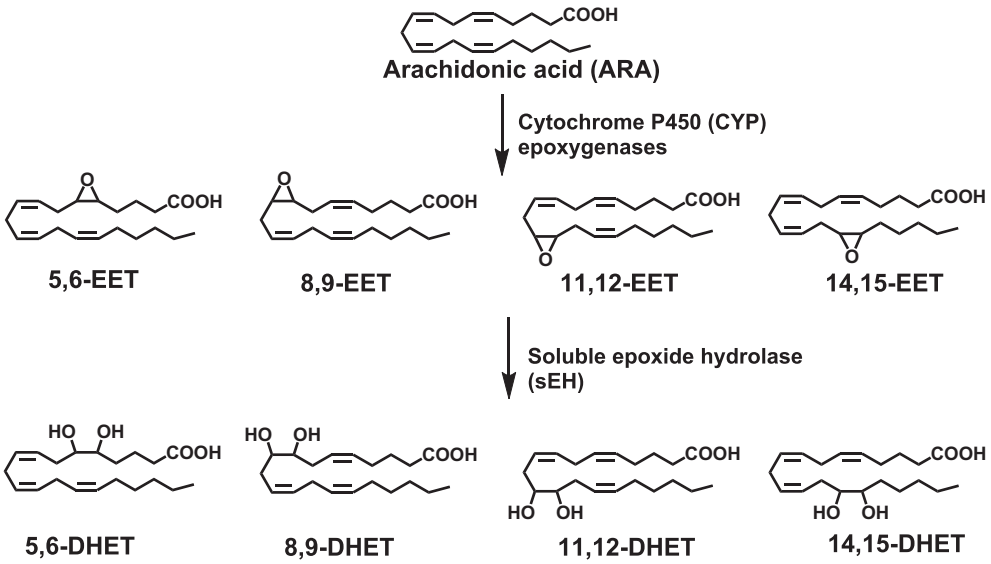

Fig. 1. The metabolism of arachidonic acid by cytochrome P450 (CYP) epoxygenases (largely CYP2C and CYP2J) leads to the formation of epoxyeicosatrienoic acids (EETs) including four regioisomers of 5,6-, 8,9-, 11,12- and 14,15-EET. EETs are further metabolized by soluble epoxide hydrolase (sEH) to form the fatty acid diols termed dihydroxyeicosatrienoic acids (DHETs) which are usually less-active or inactive.