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Commentary

Inhibition and inactivation of human CYP2J2: Implications in cardiac pathophysiology and opportunities in cancer therapy ☆

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ABSTRACT

Extrahepatic cytochrome P450 enzymes (CYP450) are pivotal in the metabolism of endogenous substrates and xenobiotics. CYP2J2 is a major cardiac CYP450 and primarily metabolizes polyunsaturated fatty acids such as arachidonic acid to cardioactive epoxyeicosatrienoic acids. Due to its role in endobiotic metabolism, CYP2J2 has been actively studied in recent years with the focus on its biological functions in cardiac pathophysiology. Additionally, CYP2J2 metabolizes a number of xenobiotics such as astemizole and terfenadine and is potently inhibited by danazol and telmisartan. Notably, CYP2J2 is found to be upregulated in multiple cancers. Hence a number of specific CYP2J2 inhibitors have been developed and their efficacy in inhibiting tumor progression has been actively studied. CYP2J2 inhibitor such as C26 (1-[4-(vinyl)phenyl]-4-[4-(diphenyl-hydroxymethyl)-piperidinyl]-butanone hydrochloride) caused marked reduction in tumor proliferation and migration as well as promoted apoptosis in cancer cells. In this review, we discuss the role of CYP2J2 in cardiac pathophysiology and cancer therapeutics. Additionally, we provide an update on the substrates, reversible inhibitors and irreversible inhibitors of CYP2J2. Finally, we discuss the current gaps and future directions in CYP2J2 research.

1. Introduction

Extrahepatic cytochrome P450 enzymes (CYP450) play a dominant role in xenobiotic metabolism and organ-specific toxicity [1]. For example, skatole or 3-methylindole, that is derived from the colonic hydration of tryptophan and present in cigarette smoke, is dehydrogenated by lung-specific CYP2F1 to highly reactive 3-methyleneindolenine [2]. This reactive metabolite intercalates with DNA and is cytotoxic to bronchial epithelial cells in humans [3]. CYP2J2 is a CYP450 expressed predominantly in the heart [4] although it has been measured in liver [5], gastrointestinal tract [6], pancreas [7], lungs [8], brain [9] and other tissues. CYP2J2 is the only isoform of CYP2J family found in humans. CYP2J2 is primarily found in cardiomyocytes, coronary arterial endothelial cells and to a lesser extent in vascular smooth muscles cells and aorta [10,11]. Compared to the atria, the ventricles have higher expression of CYP2J2 mRNA, while the levels are equal between the two ventricles [12]. CYP2J2 metabolizes endogenous polyunsaturated fatty acids (PUFAs) such as arachidonic acid (AA) [13] and linoleic acid (LA) [14] as well as xenobiotics such as terfenadine [15] and astemizole [16]. CYP2J2 has garnered

Abbreviations: 2-AG, 2-arachidonylglycerol; 17-ODYA, 17-octadecynoic acid; APD, action potential duration; AA, arachidonic acid; AEA, arachidonyl ethanolamide; BK_{ca}, calcium-dependent potassium channels; CYP2J2 transgenic, CYP2J2-TG; CYP450, cytochrome P450 enzyme; DHETs, dihydroxyeicosatrienoic acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EDHF, endothelial-derived hyperpolarising factors; EDPs, epoxydocosapentaenoic acids; EEQs, epoxyeicosatetraenoic acids; EET-EA, epoxyeicosatrienoic acid ethanolamide; EETs, epoxyeicosatrienoic acids; EOAs, epoxyoctadecenoic acids; HETE-EA, hydroxyeicosatetraenoic acid ethanolamide; LA, linoleic acid; MBI, mechanism-based inactivation; MI complex, metabolite-intermediate complex; miRNAs, microRNAs; $mitoK_{ATP}$, mitochondrial ATP-dependent potassium channels; MAPK, mitogen-activated protein kinase; NDBD, *N*-desbutyldronedarone; NDEA, *N*-desethylamiodarone; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; 17-ODYA, 17-octadeynoic acid; PPARγ, peroxisome proliferator-activated receptor gamma; PI3K, phosphatidylinositide 3-kinase; PUFAs, polyunsaturated fatty acids; SERCA2a, sarcoplasmic/endoplasmic reticulum calcium ATPase; sEH, soluble epoxide hydrolase; TNFα, tumor necrosis factor alpha; TKIs, tyrosine kinase inhibitors; MMP, matrix metalloproteinases.

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increased attention in recent years as it was discovered to be upregulated in haematological malignancies [17] and certain carcinomas [18]. This has led to an explosion of new research in the field of cancer therapeutics with novel CYP2J2 inhibitors. Since CYP2J2 enzyme straddles between endobiotic and xenobiotic metabolic pathways, researchers are evaluating the perturbation of its endobiotic pathways due to CYP2J2 inhibition or induction.

Like CYP2D6, a number of single nucleotide polymorphisms of CYP2J2 have been discovered. CYP2J2*7 is the most commonly found SNP with marginally reduced CYP2J2 expression while CYP2J2*8 (rs150461093) polymorphism (heterozygote) exhibits complete loss of metabolic activity. Although CYP2J2*7 has been associated with incidence of hypertension in Russian and Saudi populations, strong correlation between CYP2J2*7 and hypertension across gender and race has not been established. Similarly, no significant correlation between CYP2J2*7 and coronary artery disease is proven. It is currently unknown whether carriers of other CYP2J2 polymorphisms are predisposed to cardiovascular diseases. CYP2J2 polymorphisms and their implications in cardiovascular diseases such as hypertension, coronary artery disease and myocardial infarction have been comprehensively reviewed [19].

In this commentary, we first discuss the substrates, inhibitors, and mode of inhibition of CYP2J2. Secondly, we present biological roles of CYP2J2 and its AA metabolites, along with the implications of CYP2J2 inhibition in cardiac pathophysiology. Thirdly, we discuss the role and consideration of CYP2J2 inhibitors in cancer therapeutics. Lastly, we highlight the current gaps in CYP2J2 research and provide directions for future research.

2. Substrate and inhibition of CYP2J2

2.1. Endogenous substrates of CYP2J2

CYP2J2 is an epoxygenase enzyme metabolizing a number of polyunsaturated omega-6 (ω-6) fatty acids such AA and LA and omega-3 (ω-3) fatty acids such as eicosapentaenoic acid (EPA) [20] and docosahexaenoic acid (DHA) [21]. CYP2J2 metabolizes AA to regioisomeric and stereoselective epoxyeicosatrienoic acids (EETs) namely 5,6-EET, 8,9-EET, 11,12-EET and 14,15-EET; LA is converted to epoxyoctadecenoic acids (EOAs) such as 12,13-EOA and 9,10-EOA; EPA forms epoxyeicosatetraenoic acids (EEQs) such as 17,18-EEQ and DHA yields epoxydocosapentaenoic acids (EDPs) such as 19,20-EDP (Table 1) [21,22]. CYP2J2-mediated metabolism of AA has garnered a lot of attention in recent years owing to the cardioprotective roles of EETs. Nevertheless, it is noteworthy that the metabolic turnover rates for CYP2J2 for EPA (0.943 nmol/min/nmol CYP2J2) and DHA (0.228 nmol/min/nmol CYP2J2) are higher than LA (0.105 nmol/min/nmol CYP2J2) and AA (0.065 nmol/min/nmol CYP2J2) [20,22,23]. This reflects the different intrinsic clearances of the endogenous substrates by CYP2J2. Recently, Arnold et al. performed extensive studies to determine the Michaelis-Menten kinetic parameters of CYP2J2-mediated metabolism of the polyunsaturated fatty acids (PUFAs) [24]. The K_m value for AA metabolism was found to be 131 μM while that for xenobiotics such as astemizole and terfenadine are 0.65 μM and 0.4 μM respectively. This difference in the substrate affinities (K_m values) between endogenous and exogenous substrates suggests that CYP2J2 may preferentially metabolize xenobiotics in the presence of endogenous substrates. Considering CYP2J2 is an extrahepatic CYP450 and heart is not the main xenobiotic elimination organ, this knowledge is clinically insightful. Apart from CYP2J2, CYP2C8 and CYP2C9 are involved in EET biosynthesis in the heart and this information has been reviewed previously [25]. It is noteworthy that EETs are readily metabolized by soluble epoxide hydrolase (sEH) to their respective regioisomeric vicinal diols, dihydroxyeicosatrienoic acids (DHETs) [26]. DHETs exhibit similar physiological actions as EETs but are significantly less potent compared to EETs [27]. Besides PUFAs, CYP2J2 metabolizes vitamin D2 and D3 to 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 respectively [28]. Since CYP2J2 expression in skin and liver is limited, the physiological implication of CYP2J2-mediated bioactivation of vitamin D needs further investigation. Lastly, the perturbation of the endocannabinoid system is linked to cardiovascular, gastrointestinal and immunological disorders [29]. McDougle et al. discovered that two endocannabinoids namely arachidonyl ethanolamide (AEA) and 2-arachidonylglycerol (2-AG) undergo metabolism by CYP2J2 to form predominantly epoxyeicosatrienoic ethanolamide (e.g. 14,15-EET-EA) and epoxyeicosatrienoic glycerol (e.g. 14,15-EET-G) [30]. In a similar study, other metabolites of AEA such as 11,12-EET-EA, 8,9-EET-EA, 5,6-EET-EA, 20-hydroxyeicosatetraenoic ethanolamide (20-HETE-EA) and 19-HETE-EA were determined in

Table 1
Regioisomeric metabolites deriving from human CYP2J2 metabolism of arachidonic acid, linoleic acid, eicosapentaenoic acid and docosahexaenoic acid.

(Substrate) Regioisomeric Metabolites	% of total	% of R, S	% of S, R	References
(Arachidonic acid)				
5, 6-EET	4	n.d.	n.d.	[13]
8, 9-EET	28	60	40	[13]
11, 12-EET	27	62	38	[13]
14, 15-EET	41	43	57	[13]
(Linoleic acid)				
12,13-EOA	59	n.d.	n.d.	[14]
9,10-EOA	41	n.d.	n.d.	[14]
(Eicosapentaenoic acid)				
5,6-EEQ	3	n.d.	n.d.	[22]
8,9-EEQ	15	n.d.	n.d.	[22]
11,12-EEQ	15	n.d.	n.d.	[22]
14,15-EEQ	16	n.d.	n.d.	[22]
17,18-EEQ	50	65	35	[22]
(Docosahexaenoic acid)				
4,5-EDP	n.d.	n.d.	n.d.	[22]
7,8-EDP	7	n.d.	n.d.	[22]
10,11-EDP	8	n.d.	n.d.	[22]
13,14-EDP	8	n.d.	n.d.	[22]
16,17-EDP	n.d.	n.d.	n.d.	[22]
19,20-EDP	77	75	35	[22]

n.d.: not determined.