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Roles of the epoxygenase CYP2J2 in the endothelium

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Abstract

Cytochrome p450 (CYP)2J2 is an epoxygenase enzyme that metabolises arachidonic acid to epoxyeicosatrienoic acids (EETs). EETs are inactivated by soluble epoxide hydrolase (sEH), which converts them in to their corresponding dihydroxyeicosatrienoic acids (DHETs). CYP2J2 is highly expressed in cardiovascular tissue including the heart and vascular endothelial cells. CYP2J2 and the EETs it produces have been shown to have a diverse range of effects on the vasculature, including the regulation of inflammation, vascular tone, cellular proliferation, angiogenesis, and metabolism. This review will examine these established and emerging roles of CYP2J2 in the biology of vascular endothelial cells.

Keywords

endothelial; epoxygenase; inflammation; metabolism; angiogenesis; dilation

Introduction

Endothelial cells provide an anti-thrombotic surface, regulate vascular tone, and control the activity of circulating inflammatory cells. In the microcirculation endothelial cells provide the local supply of oxygen, and are the interface for recruitment of inflammatory cells. Endothelial cells are therefore a critical component of virtually every tissue in the body. Indeed, because we are so vascular, it is estimated that the total mass of endothelial cells is equivalent to an organ the size of the liver [1]. Endothelial cells therefore have a central role in homeostasis as well as the adaptive processes that occur during chronic inflammation, cancer, and cardiovascular diseases.

Endothelial cells are known to produce eicosanoids, lipid metabolites of arachidonic acid, particularly from the cyclooxygenase (COX)-1 and COX-2 pathways [2], the best characterised of which being prostacyclin (PGI_2; [3]). Prostacyclin is released constitutively from endothelial cells and acts as a potent anti-platelet agent, and vasodilator [4]. In addition

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to COX enzymes, endothelial cells also express eicosanoid generating epoxygenase CYP2C8, CYP2C9 and CYP2J2 [5, 6]. Epoxygenase enzymes metabolise arachidonic acid to form epoxyeicosatrienoic acids (EET)s [5]. This epoxygenase reaction [7] incorporates one atom of molecular oxygen into one of the four double bonds of arachidonic acid yielding four the potential EETs: 5,6-EET, 8,9-EET 11,12-EET or 14,15-EET. Furthermore, each EET can be present in either the S/R or R/S stereo-configuration, and each epoxygenase produces it own specific prolife of EETs. By example, CYP2C8 and CYP2C9 are 77% identical at the amino acid level [8], but CYP2C8 produces 14,15-EET and 11,12-EET at a 1.25:1 ratio, while CYP2C9 produces 14,15-EET, 11,12-EET and 8,9-EET at a ratio of 2.3:1:0.5. CYP2C8 is 81% selective for the 11(R),12(S)-EET, whereas CYP2C9 is 70% selective for the 11(S),12(R)-EET [8].

The CYP family is critical for their detoxification and elimination by oxidation of a variety of endogenous substances, as well as xenobiotics. 57 putative CYPs have been identified in man, 103 in mouse and 89 in rats, divided into 15 families [9]. Although 12 human CYP genes have been reported to possess epoxygenase activity, the most important appear to be the CYP2C and CYP2J families. In vitro, CYP1A2,2E1 and 4X1 [10] can produce epoxygenase products, CYP2D6 has no activity, while CYPs 2A6, 3A3, 3A4, 3A5, CYP2B1 and CYP2B2 [11], CYP2B12 [12], CYP2D18 [13] CYP2N1 and CYP2N2 [14], have some limited epoxygenase activity [15], [16]. CYP2C9 is more highly expressed than CYP2J2 in endothelial cells, and, in contrast to CYP2J2, CYP2C9 has a propensity to uncouple and generate reactive oxygen species (ROS). ROS increases NF-κB activity and leads to a pro-inflammatory profile [17]. CYP2J2 therefore remains a strong candidate for a vascular protective lipid metabolising epoxygenase.

CYP2J2

CYP2J2 was originally cloned from a human liver cDNA library, and found to be highly expressed in the human heart [18]. Recombinant CYP2J2 protein metabolises arachidonic acid to all four *cis*-EETs and is highly enantio-selective for 14R, 15S-EET [18]. Subsequently, CYP2J2 and its rat homologue (CYP2J3) were found expressed at high levels in the lung [19], particularly in ciliated epithelial cells lining the airway, in non-ciliated airway epithelial cells, bronchial and pulmonary vascular smooth muscle cells, pulmonary vascular endothelium, and alveolar macrophages [19]. CYP2J2 is also expressed in a variety of vascular tissue including the coronary artery [20], aorta [21], and in varicose veins [22]. CYP2J2 expression is also found in the kidney, liver and skeletal muscle [18], monocytes and macrophages [23], and to a lesser extent in the gut [24]. Relatively speaking CYP2J2 > CYP2C8 levels are in the heart while CYP2C9> CYP2J2> CYP2C8 is the order of expression in vascular tissue [21]. We and others do find however CYP2J2 can be induced by stimuli such as LPS in vascular tissue (authors unpublished observations), so these steady state levels of CYP2J2 may not fully represent its role under different conditions.

Although humans only contain CYP2J2 as its sole CYP2J family member, CYPs show a great divergence in a species dependant manner. In rabbits (CYP2J1), primates and dogs (CYP2J2), like man, only one CYP2J has been identified. Rats (CYP2J3, CYP2J4, CYP2J10, CYP2J13, CYP2J16) and mice (CYP2J5, CYP2J6, CYP2J8, CYP2J9, CYP2J11, and CYP2J12) have multiple CYP2J isoforms and pseudogenes (CYP2J7, CYP2J14 and CYP2J15) [25]. Although homologues to CYP2J2, it must be stated a number of these rat isoforms do not possess epoxygenase activity.

Alternative fatty acid metabolites

In addition to arachidonic acid CYP2J2 can metabolise linoleic acid in to EPOMEs [5], and fish oil omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid

(DHA); see table 1. Dietary EPA/DHA supplementation causes a profound shift of the cardiac CYP-eicosanoid profile from AA- to EPA- and DHA-derived epoxy- and hydroxy-metabolites [26]. CYP2J2 preferentially acts in the ω-3 double bond of both EPA and DHA to form 17,18-epoxy-eicosatetraenoic acid and 19,20-epoxy-eicosapentaenoic acid [26]. Moreover these novel CYP2J2 products are active showing highly potent antiarrhythmic properties in neonatal cardiomyocytes [26].

Soluble Epoxide Hydrolase

EETs are rapidly metabolised in the body. The main pathway for EET removal is considered to be their conversion into dihydroxyeicosatrienoic acid (DHETs) by soluble epoxide hydrolase (sEH; ephx2) [27]. DHETs are generally considered to be less active than EETs; however they have been shown to exert some vasodilator effects on coronary arteries [28], and inhibit monocyte migration [29]. In support of the importance of endogenous endothelial epoxygenases, upregulation of sEH in endothelial cells promotes a pro-inflammatory environment [30]. In contrast, elevating the levels of endogenous CYP products by removing sEH (sEH knockout mice) or inhibiting soluble epoxide hydrolase reduces neointima formation [31], atherosclerosis and abdominal aortic aneurysm development, and lowers blood pressure [32] in different mouse models. A number of sEH inhibitors have now been developed and are moving towards clinical trials for a variety of disorders related to cardiovascular disease.

Alternative substrates/Inhibitors

In addition to the metabolism of fatty acids, CYP2J2 may also be involved in the detoxification of xenobiotics. Of a screen of a 139 marketed therapeutic agents, albendazole, amiodarone, cyclosporine A, danazol, mesoridazine, nabumetone, tamoxifen, and thioridazine could all act as CYP2J2 substrates [33]. In a similar drug screen for CYP2J2 inhibition, although not found to be substrates for CYP2J2, the angiotensin II receptor antagonist telmisartan and the Ca2+ channel blocker flunarizine were shown to inhibit CYP2J2. Telmisartan and flunarizine inhibited CYP2J2 with IC50 values of 0.42 and 0.94 μM, respectively, showing at least a 10-fold selectivity against the other major metabolizing CYPs [34]. Since they were shown as substrates for CYP2J2, the histamine H1 receptor antagonists terfenadine [35] and ebastine [36] have been used as the parent compounds to generate a series of structural based CYP2J2 inhibitors with K(i) values as low as 160nM (compound 4; [35]). The production and development of these selective inhibitors will greatly aid our understanding of the CYP2J2 system.

Roles of CYP2J2

Hypoxia and reperfusion injury

Hypoxia is blood pressure caused either by blockage of blood vessels restricting oxygen delivery, or by remodelling and growth of tissue. Upon blockage removal, reperfusion of the tissue itself can result in tissue injury via free radical production. This process occurs, for example, in a heart attack, where a thrombosis blocks the blood supply to the heart. I*n vitro,* in bovine aortic endothelial cells, transfection of CYP2J2, or the addition of EETs or a sEH inhibitor prevents hypoxia-reperfusion-induced cell death, oxidant stress and superoxide generation [37].

I*n vivo* and *ex vivo* CYP2J2 over expression has been examined in ischemia-reperfusion of the mouse heart. Unlike cardiac-specific CYP2J2 expression [38], endothelial-specific expression of CYP2J2 did not improve ventricular function in ischemia-reperfusion injury in isolated mouse heart [39]. In contrast to CYP2J2, highlighting the differences between vascular epoxygenases, endothelial-specific CYP2C8 over-expression was detrimental to

cardiac recovery, increasing reactive oxygen species formation and the production of damaging linoleic acid products of epoxygenases (and sEH) the DHOMEs [39].

Although not effective in the isolated heart model of ischemia-reperfusion injury, these endothelial specific CYP2J2 expressing mice do protect against global cerebral ischemia induced by bilateral common carotid artery occlusion [40]. These endothelial-specific CYP2J2 expressing mice compared to wild-type mice demonstrated increased cerebral blood flow and microvascular density (indicative of angiogenesis), decreased reactive oxygen species, infarct size and apoptosis [40].

Inflammation

Activation of endothelial cells mediates inflammatory responses by the production of pro-inflammatory cytokines, chemoattractants/chemokines and the expression of adhesion molecules. In human and bovine endothelial cells, physiological concentrations of EETs or over-expression of CYP2J2 decreases TNFα-induced endothelial vascular cell adhesion molecule (VCAM-1) expression [20] and VCAM-1 promoter activity [41]. Recent studies using newly generated epoxygenase/sEH pathway transgenic and knockout models have now looked at acute inflammation *in vivo*. Endotoxin-induced lung [42] and liver [43] inflammation and inflammation in isolated endothelial cells has been compared in wild-type and transgenic mice with endothelial expression of the human CYP2J2 and CYP2C8 epoxygenases or sEH knockout mice [42]. Endothelial cell CYP2J2, or CYP2C8 transgenic mice, or sEH knockout mice each exhibited a significantly reduced activation of NFκB signalling, e-selectin, MCP-1 *in vitro*, and IL1β, IL-6,MCP-1, and e-selectin mRNA and NFκB signalling, and neutrophil infiltration in to the lung *in vivo* [42]. A comparable protective effect of endothelial CYP2J2 expression and sEH-1 knockout to the lung was also seen in the liver of endotoxin treated mice [43].

Smooth muscle migration and proliferation are a characteristic of vascular disease such as atherosclerosis and restenosis. CYP2J2 or 11,12-EET inhibits rat aortic smooth muscle cell migration across transwell filters in a cAMP/protein kinase A-dependent manner [44]; an affect which was independent of proliferation of the smooth muscle cells. Migration and ultimate stability of vascular lesions is governed by the activities of matrix degrading enzymes, the matrix metalloproteinases (MMPs). Hyperhomocysteinemia is also associated with atherosclerotic events. In mouse aortic endothelial cells homocysteine down-regulated CYP2J2 protein expression,, increased NF-κB activation and induced MMP-9 activity. Both NFκB and MMP-9 upregulation were reversed by either CYP2J2 transfection or 8,9-EET treatment [45].

Angiogenesis

EETs have all been shown to induce angiogenesis, proliferation, migration and survival in various *in vitro* and *in vivo* models [46–49]. The potential mechanisms of EET-induced angiogenesis include inhibition of the forkhead transcription factor to down-regulate p27Kip1 [50], crosstalk to growth factors epidermal growth factor receptor [51], induction of FGF2 [52], and VEGF [53], often demonstrated via Akt activation [50–52], SRC-activation of STAT-3 [53], the activation of sphingosine kinase-1 [54], and the induction of endothelial nitric oxide synthase (eNOS; [55])

CYP2J2 has been directly implicated as a pro-angiogenic EET producer. CYP2J2 over-expression using recombinant adeno-associated viruses (rAAV) in bovine aortic endothelial cells promotes cell proliferation, migration, *in vitro* wound healing assays, and enhanced capillary tubule formation in the chicken embryo chorioallantoic membrane assays and tube formation matrigel assays [55]. I*n vivo*, in a rat ischemic hind-limb model, rAAV-CYP2J2

infection induced angiogenesis, and hind-limb protection [55]. Angiogenesis is required to provide sufficient oxygen delivery during growth of 'normal' tissue. However, in cancer, angiogenesis supports the growth and metastasis of the tumour. Overexpression of CYP2J2 in endothelial cells increases both primary tumor growth and metastasis in multiple tumor models [56]. Over-expression of CYP2J2 in MDA-MB-231 human breast cells implanted in athymic BALB/c mice showed 60% more lung metastases and enhanced angiogenesis in and around primary tumours compared with control cells [57].

CYP2J2 is therefore a target for therapeutic angiogenesis as well as cancer metastasis. sEH inhibition is considered a potential therapy for many chronic diseases such as hypertension and type 2 diabetes. Whether, the pro-angiogenic/metastatic actions of EETs will limit the long-term effects of sEH inhibition for these chronic conditions remains to be seen, but is clearly now a concern as these drugs get translated in to man.

Regulation of blood pressure

Renal CYP-derived EETs regulate sodium transport and blood pressure [58]. Endothelial CYP-derived EETs are considered potent vasodilators. Intravenous or intra-arterial infusion of 14,15-EET decreases mean arterial blood pressure in normal and spontaneously hypertensive rats by up to 45 mmHg [59]. CYP2J3 and EETs are increased in spontaneously hypertensive rat kidney, and after high salt diet [60]. High-salt intake can change the effect of adenosine on arterial tone in mice. The high salt diet caused an upregulation of the adenosine A(2A) receptor which triggered vascular relaxation through ATP-sensitive (K(+)) channels via the induction and activation of CYP2J3 [61].

I*n vitro* CYP2J2 transfected cultured bovine aortic endothelial cells demonstrated increased eNOS protein expression, activity and Thr495 phosphorylation via mitogen-activated protein kinase, and protein kinase C [62]. Mice with endothelial expression of CYP2J2 exhibit attenuated resistant vessel constriction to endothelin-1 and enhanced dilatation to acetylcholine [32]. These endothelial CYP2J2 transgenic mice by themselves demonstrated modest, but not significantly, lower mean arterial pressure. However, when endogenous production of vasodilator products NO and prostanoids were inhibited by co-administration of N-nitro-L-arginine methyl ester and indomethacin, mean arterial pressure was significantly lower in endothelial CYP2J2 transgenic mice compared to wild-type controls [32]. Similar was seen when the mice were given a high-salt diet or subcutaneous angiotensin II [32]. The subsequent increase in systolic blood pressure, proteinuria, and glomerular injury, were significantly attenuated in the endothelial CYP2J2 transgenic compared to wild-type mice [32]. Long-term expression of CYP2J2 can also be achieved in spontaneously hypertensive rats (SHR) using a type 8 recombinant adeno-associated virus [63]. In CYP2J2-expressing SHR rats, systolic blood pressure was significantly decreased, cardiac output was improved, cardiac collagen content was reduced and the ANP levels increased in the myocardium and plasma [63].

Although EETs and CYP2J2 have been associated with a reduction in mean arterial blood pressure, EETs and epoxygenases induce vasoconstriction in certain vascular beds. Recently CYP2J2, 5,6-EET and 14,15-EET, and the corresponding DHETs were found to be up-regulated in preeclamptic placenta, deciduae and plasma respectively [64]. In rat models of preeclampsia or uterine arterial rings *in vitro* non-specific epoxygenase inhibition reduced blood pressure and caused dilation [64]. Although CYP2J was increased in placenta, it must be noted that these constrictor effects although attributed to CYP2J were not directly shown to be via CYP2J (as opposed to alternative epoxygenase) enzymes.

EETs have been shown to be both constrictors and dilators in the pulmonary circulation. In the monocrotaline-induced development of progressive pulmonary hypertension, CYP2J2

expression increased tissue EET production and reduced pulmonary artery thickening and muscularization, along with the reduction in right ventricular pressure [65]. In human donor lungs, sEH is expressed in pulmonary arteries [66]. However, sEH was absent in samples from patients with pulmonary hypertension [66]. In isolated lungs from WT mice, acute hypoxic vasoconstriction was potentiated by sEH inhibition and attenuated by an EET antagonist [67]. In normoxic sEH knockout mice, acute hypoxic vasoconstriction and small artery muscularization were greater than that in WT lungs. Enhanced muscularization was accompanied with decreased voluntary exercise capacity [67]. These constrictor actions of 11,12-EET in the pulmonary circulation are via transient receptor potential C6 channels [68] and BK channel α and β(1) subunits in mitochondria [69]. Different epoxygenases appear to act differently even though they all produce EETs [39]. Whether, CYP2J and CYP2C isoforms have different roles in the pulmonary circulation similar to the coronary circulation [39] is not clear. So far CYP2C9/CYP2C29 have been implicated in inducing hypoxic (though not experimentally monocrotaline-induced; [65]) pulmonary vasoconstriction and remodelling [70]. Whether CYP2J2 acts in the same manner is not known, but again the development of sEH inhibitors may be limited if pulmonary hypertension becomes a common side-effect.

Anti-thrombotic actions

In vascular endothelial cells, physiological concentrations of EETs, particularly 11,12-EET, or over-expression of CYP2J2, increased tissue plasminogen activator (t-PA) expression and activity, without affecting plasminogen activator inhibitor-1 expression [71]. Platelet aggregation induced by arachidonic acid is inhibited by all EET isomers with no evidence of stereospecificity [72]. EETs can compete with arachidonic acid in the COX binding site, which can reduce prothrombotic TXA_2 generation. However, inhibition of aggregation was not uniformly associated with inhibition of TXA_2, suggesting alternative mechanisms TXA_2 pathway inhibition [72]. Different EET regioisomers hyperpolarize platelets down to −69+/−2 mV (from −58+/−9 mV), which is prevented by the non-specific potassium channel inhibitor charybdotoxin and calcium-activated potassium channels of large conductance (BK(Ca) channels), iberiotoxin [73]. EETs also inhibit platelet adhesion to endothelial cells under static and flow conditions. Exposure of platelets to EETs inhibited platelet P-selectin expression in response to ADP [73]. Human platelets incubated with 11,12-EET increased platelet NOS activity, nitrite production, cGMP content, and the platelet uptake of L-^{3}H-arginine in a concentration-dependent manner [74]. In addition, 11,12-EET attenuated intracellular free Ca(2+) accumulation stimulated by collagen, which was at least partly mediated by this EET-activated L-arginine/NOS pathway [74].

Metabolism

Recently the xenosensing nuclear receptor PXR was found in endothelial cells along with a variety of drug metabolising CYP2 enzymes and transporters [75, 76]. These findings suggest the vasculature may have a far greater role in drug metabolism than previously thought. CYP2J2 plays important roles in the metabolism of therapeutic drugs, such as astemizole and ebastine, as well as endogenous fatty acids. Terfenadine, ebastine, and astemizole have been identified as substrates for CYP2J2 [33]. Ebastine undergoes extensive metabolism to form desalkylebastine and hydroxyebastine. Hydroxyebastine is subsequently metabolized to carebastine. In human liver microsomes, these hydroxylation reactions of ebastine are preferentially catalyzed by CYP2J2 [77]. 139 marketed therapeutic agents and compounds were screened and eight novel substrates were identified including amiodarone, cyclosporine, albendazole, astemizole, thioridazine, mesoridazine, and danazol [33]. Interestingly, amiodarone 4-hydoxylation appears to be a specific CYP2J2-catalyzed reaction with no CYP3A4, or other drug-metabolizing enzyme involvement [78]. Although the CYP2J2 active site can accommodate large substrates, it may be narrower than the

classical xenobiotic drug metabolising CYP3A4. This data does suggest that CYP2J2 may be an unrecognized participant in first-pass metabolism, but its contribution is minor relative to that of CYP3A4.

CYP2J2 is the most abundant isoform in all human heart. Incubation of verapamil with heart microsomes led to the formation of nine CYP450-dependent metabolites: a major finding was the observation that stereoselectivity was reversed compared to human liver microsomes, in which the *R*-enantiomer is metabolized to a greater extent [79]. Similarly, verapamil can be metabolised by coronary artery endothelial cells, which also are also known to contain CYP2J2, along with CYP1A1, CYP2A6/7, CYP2A13, CYP2B6/7, CYP2C8, and CYP2E1 [80].

Rat CYP2J3 has been identified as a principal vitamin D 25-hydroxylase [81]. Human CYP2J2 exhibits 25-hydroxylation activity, although its activity is weaker than rat CYP2J3 [81]. Moreover, CYP2J2 and CYP2J3 exhibit distinct preferences toward vitamin D3 and D2 respectively [81]. CYP2J2 is also able to release NO production from (NO-aspirin) NCX-4016 as well as the commonly prescribed organic nitrates nitroglycerin and isosorbide dinitrate [82]; again suggestive of a direct metabolic activity directly relevant to endothelial cell biology.

Polymorphisms of CYP2J2 also appear to regulate its ability to metabolise xenobiotics. Twelve genetic variations of CYP2J2 including the two novel nonsynonymous mutations G312R and P351L were identified from 93 Korean subjects [83]. The recombinant CYP2J2 G312R variant, found in 1.6% of Korean subjects, showed almost complete loss of enzymatic activity, as determined by CYP2J2-catalysed astemizole O-demethylation and ebastine hydroxylation [83]. The CYP2J2 P351L variant showed enzymatic activities that were comparable with the wild-type CYP2J2. The CYP2J2 G312R variant was not found in 192 Chinese, 99 African-Americans, 100 Caucasians and 159 Vietnamese subjects [83].

Major functional polymorphisms

In vitro and animal studies have led to the speculation of whether CYP2J2 regulates human diseases (Table 2). In particular, studies have focused on cardiovascular diseases, such as coronary artery disease, which have strong inflammatory and vasomotor components. The relationships between CYP2J2 and coronary artery disease, stroke and hypertension have been examined in a number of population groups. The CYP2J2 gene, located on chromosome 1, contains nine exons, eight introns, and is approximately 40.3 kb in length [84]. A variety of CYP2J2 single nucleotide (SNP) polymorphisms have now been identified (Table 2), including a number which cause a protein coding change; e.g. Thr143Ala (called *CYP2J2*2*); Arg158Cys (*CYP2J2*3*); Ile192Asn (*CYP2J2*4*); Asp342Asn (*CYP2J2*5*); and Asn404Tyr (*CYP2J2*6*). When tested for activity *CYP2J2*2*, *CYP2J2*3* and *CYP2J2*6* mutants showed significantly reduced metabolism of both arachidonic acid and linoleic acid, while *CYP2J2*4* showed significantly reduced metabolism of arachidonic acid only. *CYP2J2*5* was similar to the metabolism of wild-type CYP2J2 for both substrates [85].

Coronary artery disease and myocardial infarction

A functional SNP has also been identified in the proximal promoter of CYP2J2 located at −50 (G-50T; *CYP2J2*7*). This G-50T mutation results in the loss of a Sp1 transcription factor binding site, and a 50% reduction in promoter activity [86]. In a cohort of 289 patients with coronary artery disease (255 controls) *CYP2J2*7* was present in 17% of coronary artery disease patients, and only 10% of control subjects (p=0.03) [86].

In addition to the incidence of coronary artery disease, *CYP2J2*7* has also been studied for an influence on myocardial infarction. A study with 512 patients with sleep apnoea and another 488 patients who were admitted for coronary angiography similarly suggested carriers of *CYP2J2*7* had significantly more myocardial infarctions compared to carriers of the wild type CYP2J2. (T/T or G/T: 21.6%; G/G: 13.7%; p = 0.026) [87]. In a case-control study of patients in Washington State, *CYP2J2* SNPs were studied for risk of myocardial infarction and ischemic stroke in 856 myocardial infarction cases, 368 stroke cases and 2688 controls [88]. Variation in CYP2J2 was associated with myocardial infarction risk (P=0.027). Although the functional consequences of these SNPs are not known, two intronic CYP2J2 tag-single nucleotide polymorphisms, rs10889160 and rs11572325 in particular were associated with an increased risk of myocardial infarction (odds ratio: 1.24, p=0.004; odds ratio: 1.27; p=0.006, respectively) [88]. No evidence of an association was found between variation in CYP2J2 and stroke in this study.

*CYP2J2*7* is not always found to be associated with risk of coronary artery disease or myocardial infarction, and has been associated with a protective phenotype.. In the Atherosclerosis Risk in Communities study (n=2065), the *CYP2J2*7* polymorphism was associated with a significantly lower risk of incident coronary heart disease in African-Americans (adjusted hazard rate ratio 0.58, p=0.036); however, no significant association was observed in Caucasians [89]. In the Chinese Han population (1344 cases and 1267 ethnically and geographically matched controls), the presence of *CYP2J2*7* showed no significant association with the incidence of coronary artery disease [90].

Hypertension

The incidence of hypertension and frequency of *CYP2J2*7* in particular appears to be highly population dependent. *CYP2J2*7* appears to be associated with an increased risk of hypertension in Russian [91], Chinese Han [92] and Saudi populations [93]. 576 unrelated Russian subjects, including 295 patients with hypertension and 281 healthy subjects were studied for the frequency *CYP2J2*7*. *CYP2J2*7* was significantly higher in patients with hypertension versus healthy controls (OR 4.03; p=0.0004) [91]. Similarly, in the Han Chinese population (841 subjects, 415 unrelated hypertensives and 426 age-, gender- and area-matched normotensives). Carriers of two copies of the *CYP2J2*7* variant in particular had significantly higher systolic blood pressure (p = 0.016) [92]. In a Saudi population of 116 cases with documented hypertension compared to that of 250 unrelated normotensive patients, hypertensive's showed a significantly higher frequency *CYP2J2*7* compared with controls (odds ratio=3.7, p=0.0003) [93].

In contrast, in the 'Malmö Diet and Cancer' study (5740 participants), the incidence of cardiovascular events (coronary events, n = 261; ischemic stroke, n = 185) monitored over 10 years of follow-up in this Swedish population showed no relationship between *CYP2J2*7* and blood pressure or hypertension [94]. Moreover, in a biethnic population from Tennessee, *CYP2J2*7* frequency was significantly higher in African-Americans versus Caucasians (14.1% versus 7.7%, P=0.01) irrespective of hypertension status [95]. In this Caucasian population the incidence of hypertension in individuals carrying the *CYP2J2*7* allele adjusted for age, gender, body mass index and family history was 0.39, suggesting a protective effect of decreased CYP2J2 activity [95].

There are therefore several studies which both implicate and discard polymorphisms of CYP2J2 (particularly *CYP2J2*7*), with the development of coronary artery disease, hypertension and myocardial infarction. Whether these associations or lack therefore of, of CYP2J2 with these diseases, have a polymorphic component making them specific to certain population, but not others is not known, but clearly possible. CYP2J2 does not act alone, it requires substrate to be generated. Environmental factors may therefore also play a role in

how CYP2J2 behaves, i.e. different diets in different populations for example may alter the balance and extent of the mediators CYP2J2 produces, which ultimately may affect how it behaves.

Conclusions

CYP2J2 is a vascular epoxygenase which can protect the endothelial cell and underlying tissue from hypoxia and reperfusion, it is anti-inflammatory, involved in the detoxification of xenobiotics and produces mediators that regulate vascular tone, inflammatory cell and cardiac cell function (Figure 1). CYP2J2 and the EETs it produces are pro-angiogenic, which has both therapeutic potential for ischemia, but may also potentiate the spread of cancer. EETs and sEH inhibition also potentiate hypoxic pulmonary hypertension. Although, CYP2J2 has yet to be implicated in mediating this hypoxia driven pulmonary hypertension, these findings may again limit the usefulness of sEH inhibitor therapy for example. In man, a variety of different population groups, (although not universal) indicate that polymorphism of the CYP2J2 promoter (*CYP2J2*7*) which reduces CYP2J2 expression is associated with an increased risk of coronary artery disease and hypertension. Larger population studies will be required to see how universal these polymorphic differences truly are in man. Although, there is still considerable amount to learn regarding the actual products of epoxygenases and how they mediate their actions [96], modulating the CYP2J2 pathway appears an excellent target for vascular endothelial disorders. More still needs to be done to understand how the different epoxygenases act and signal in man.

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Highlights

- The CYP2J family are a group of CYP450 lipid metabolising epoxygenases
- CYP2J are expressed in a variety of tissues including endothelial cells
- CYP2J and its products regulate tone, inflammation, metabolism and angiogenesis
- The CYP2J2*7 SNP carries increased risk of coronary artery disease and hypertension

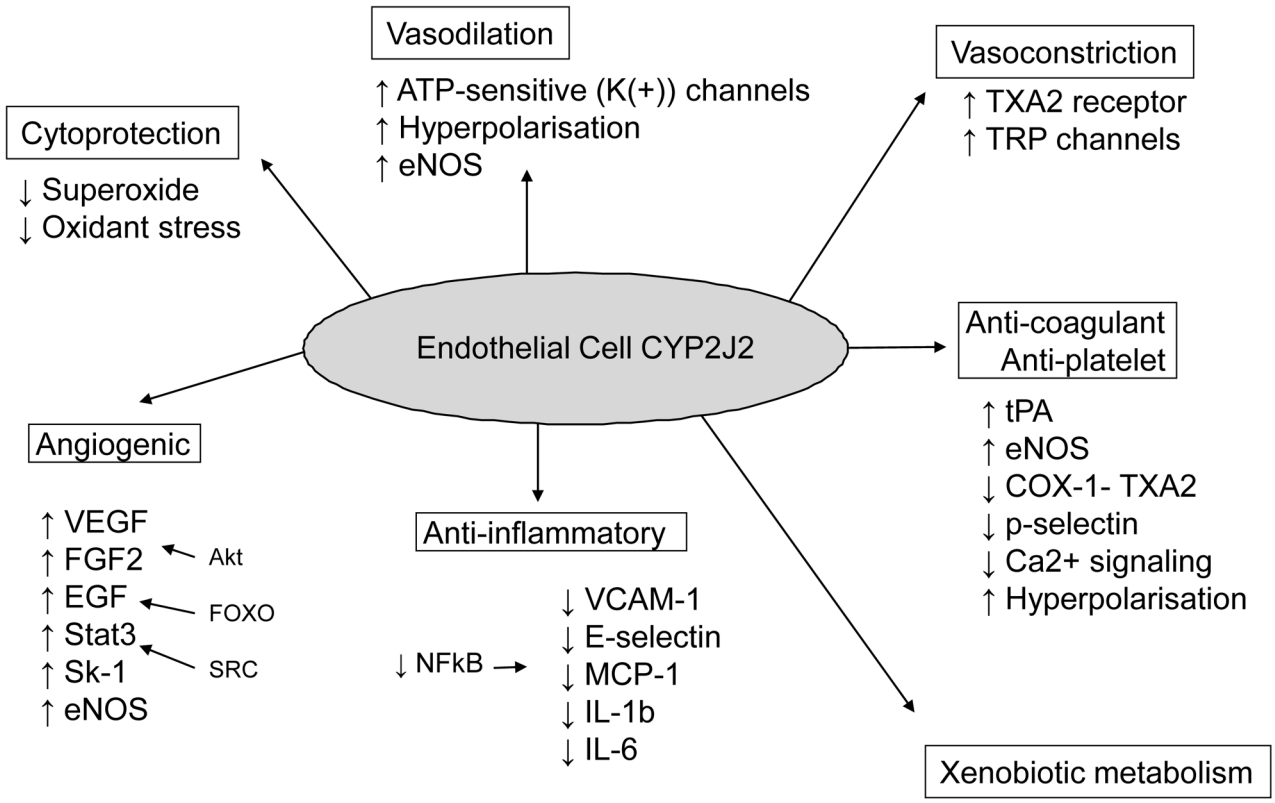

Figure 1. Actions of CYP2J2 in endothelial cells

CYP2J2 produces mediators that can vasodilate via ATP-sensitive K+ channels leading to hyperpolarisation of underlying smooth muscle cells and up-regulate endothelial nitric oxide synthase (eNOS; NOS-3) protein and activity. CYP2J products may also vasoconstrict different vascular beds by activating the thromboxane A_2 (TXA_2) receptor or via transient receptor potential (TRP) channels. In addition, CYP2J and its products have anti-platelet/anti-coagulant properties via upregulation of tissue plasminogen activator (tPA), NOS, and through a reduction in TXA_2 synthesis, a decrease in p-selectin expression, a decrease in intracellular Ca2+ and via platelet hyperpolarisation. CY2J enzymes can metabolise a variety of xenobiotics and drugs to inactivate them, and is anti-inflammatory decreasing NF-κB activation and its target genes including VCAM-1, e-selectin, monocytes chemoattractant protein (MCP)-1 (CCL2), IL-1β and IL-6. CYP2J and its products are angiogenic by increasing VEGF, FGF2, EGF, eNOS, sphingosine kinase (SK-1), and STAT-3 in part via activation of Akt, Forkhead box (FOX)O, and SRC tyrosine kinase, and is cytoprotective being associated with a reduction in intracellular superoxide generation and oxidant stress.

Table 1

Common fatty acid substrates and metabolites of CYP2J2 and sEH

Substrate	Epoxygenase Product	sEH Product
Arachidonic acid	Epoxy-eicosatrienoic acids	Dihydroxy-eicosatrienoic acids
	5,6-EET	5,6-DHET
	8,9-EET	8,9-DHET
	11,12-EET	11,12-DHET
	14,15-EET	14,15-DHET
Linoleic acid	Epoxy-octadecenoic acids	Dihydroxy-octadecenoic acids
	8,9-EpOME	8,9-DHOME
	12,13-EpOME	12,13-DHOME
Docosahexaenoic acid	Epoxy-docosapentaenoic acids	Dihydroxy-docosapentaenoic acid
	4,5-EpDPE	4,5-DHDPA
	7,8-EpDPE	7,8-DHDPA
	10,11-EpDPE	10,11-DHDPA
	13,14-EpDPE	13,14-DHDPA
	16,17-EpDPE	16,17-DHDPA
	19,20- EpDPE	19,20-DHDPA
Eicosapentaenoic acid	Epoxy-eicosatetraenoic acid	Dihydroxy-eicosatetraenoic acid
	17,18-EpETE	17,18-DHET

Table 2

CYP2J2 polymorphisms and their associations to coronary artery disease, myocardial infarction and hypertension

CYP2J2 polymorphism		Effect	Effect on population	Ref
Wild-type	CYP2J2(*1)			
Thr143Ala	*CYP2J2*2*	↓ metabolism of arachidonic acid and linoleic acid	unknown	84
Arg158Cys	*CYP2J2*3*	↓ metabolism of arachidonic acid and linoleic acid	unknown	84
Ile192Asn	*CYP2J2*4*	↓ metabolism of arachidonic acid	unknown	84
Asp342Asn	*CYP2J2*5*	Similar to wilt-type	unknown	84
Asn404Tyr	*CYP2J2*6*	↓ metabolism of arachidonic acid and linoleic acid	unknown	84
Promoter				
G-50T	*CYP2J2*7*	↓promoter activity	**Coronary artery disease**	
			↑ German	85
			↓ African American	88
			No effect	
			Caucasian Amercican	88
			Chinese Han	89
			Myocardial Infarction	
			↑ German	86
			Hypertension	
			↑ Russian	90
			↑ Chinese Han	91
			↑ Saudi	92
			↓Caucasian American	94
			No effect	
			Swedish	93
Intronic				
rs10889160		Unknown	↑ MI	87
rs11572325				
			No effect stroke	