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Cytochrome P450-derived eicosanoids and heart function

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ABSTRACT

The cytochrome P450 monooxygenase system (CYP) is a multigene superfamily of enzymes, which are important in the metabolism of foreign and endogenous compounds. CYP isoforms metabolize a number of n-3 and n-6 polyunsaturated fatty acids (PUFA), including linoleic acid (18:2n6, LA), arachidonic acid (20:4n6, AA), ecosapentaenoic acid (20:5n3, EPA) and docosahexaenoic acid (22:6n3, DHA) into bioactive lipid mediators, termed eicosanoids. CYP-derived eicosanoids have numerous effects toward physiological and pathophysiological events within the body, which depends on the type, quantity and timing of metabolites produced. Alterations in fatty acid composition and concentrations have been shown to have a role in cardiovascular disease (CVD). The functional role of CYP isozymes and CYP-derived eicosanoids toward physiological and pathophysiological processes in the heart is a rapidly expanding field of research. Numerous studies have investigated the beneficial and detrimental effects of CYP epoxygenase derived metabolites of AA, epoxyeicosatrienoic acids (EET) and CYP ω-hydroxylase products, hydroxyeicosatetraenoic acids (HETE), toward both cardiac and vascular function and disease. Emerging research is revealing the importance of other lipid mediators generated from CYP isozymes, such as epoxyeicosatetraenoic acids (EEQ) and epoxydocosapentaenoic acids (EDP), formed from the metabolism of EPA and DHA and metabolites of LA. Important determinants such as genetics, gender and age have a role in regulating the CYP-derived eicosanoids produced from the metabolism n-3 and n-6 PUFA. Obtaining a better understanding of the complex role CYP-derived eicosanoids have within the heart will provide valuable insight for both basic and clinical researchers investigation CVD.

Contents

Abbreviations: AA, arachidonic acid; ACS, acute coronary syndrome; ALA, alpha-linolenic acid; AMI, acute myocardial infarction; AMPK, 5′ adenosine monophosphate-activated protein kinase; Ang II, angiotensin II; ANP, atrial natriuretic peptide; BaP, benzo(α)pyrene; BK_{Ca}, large $Ca2^{+}$ sensitive potassium channels; CAD, coronary artery disease; CHD, coronary heart disease; COX, cyclooxygenase; CVD, cardiovascular disease; CYP-450, cytochrome *p*-450; DCM, diabetic cardiomyopathy; DDMS, *N*-methylsulfonyl-12,12-dibromododec-11-enamide; DHA, docosahexaenoic acid; DHET, dihydroxyeicosatrienoic acid; DiHOME, dihydroxyoctadecenoic acid; DM, diabetes mellitus; EDP, epoxydocosapentaenoic acids; EEQ, epoxyeicosatetraenoic acids; EET, epoxyeicosatrienoic acids; EET-B, (N-(5-((2-acetamidobenzo[*d*]thiazol-4-yl)oxy) pentyl)-N isopropylheptanamide); EEZE, epoxyeicosa-5(*Z*)-enoic acids; EPA, ecosapentaenoic acids; *EPHX2*, gene encoding soluble epoxide hydrolase enzyme; EpOME, epoxyoctadecamonoenic acid; GPCR, G-protein coupled receptor; GSK2256294, (1*R*,3*S*)-N-(4-cyano-2-(trifluoromethyl)benzyl)-3-((4-methyl-6-(methylamino)-1,3,5-triazin-2-yl)amino)cyclohexane-1-carboxamide; HET0016, N-hydroxy-N′-(4-butyl-2-methylphenyl)-formamidine; HETE, hydroxyeicosatetraenoic acid; HF, heart failure; HO-1, heme oxygenase-1; HR, hypoxia/reoxygenation; INH, isoniazid; IR, ischemia reperfusion; ISO, isoproterenol; LA, linoleic acid; LAD, left anterior descending coronary artery; LOX, lipoxygenase; LPS, lipopolysaccharide; LV, left ventricle; LVDP, left ventricular developed pressure; MAG, monoacylglyceride; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; MPTP, mitochondrial permeability transition pore; NF-κB, nuclear factor kappa B; NICM, non-ischemic cardiomyopathy; NO, nitric oxide; PI3K, phosphatidylinositol-3 kinase; PIP, phosphatidylinositol; PKB, (AKT) Protein kinase B; PLA2, phospholipases A2; PPAR, proliferative peroxisome activated receptor; PUFA, polyunsaturated fatty acid; RAS, renin-angiotensin system; ROS, reactive oxygen species; sEH, soluble epoxide hydrolase; sEHi, soluble epoxide hydrolase inhibitor; SFA, saturated fatty acid; SHR, spontaneously hypertensive rat; SIRT, sirtuin; SNP, single nucleotide polymorphisms; SPZ, sulfaphenazole; STZ, streptozotocin; TAC, transverse aortic constriction; t-AUCB, 4-[[trans-4-[[(tricyclo[3.3.1.13,7]dec-1-ylamino) carbonyl]amino] cyclohexyl]oxy] benzoic acid; TGFβ1, transforming growth factor beta 1; TNF-α, tumor necrosis factor alpha; TP, thromboxane; TUPS, 1-(1-methanesulfonyl-piperidin-4-yl)-3-(4-trifluoro-methoxy-phenyl)-urea; UA-8, 13-(3-propylureido)tridec-8-enoic acid; VSMC, vascular smooth muscle cells.

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1. Introduction

Cardiovascular disease (CVD) remains a major cause of illness, disability and death in both Western societies and developing nations. As populations' age and co-morbidities such as obesity and diabetes become more prevalent both the human health cost and economic burden of these conditions will increase. The ability to manage risk factors such as dietary fat intake has an important role in reducing the development of CVD. The long-chain n-3 and n-6 polyunsaturated fatty acids (PUFA) are important fatty acids obtained from dietary sources. These fatty acids are required components of phospholipid membranes and serve as precursors to large family of eicosanoids. The metabolism of n-3 and n-6 PUFA into a plethora of bioactive eicosanoids occurs through three primary enzymatic systems such as cyclooxygenases (COX), lipoxygenases (LOX) and cytochrome P450 (CYP) enzymes. There is a growing understanding of the relative contribution of CYP-derived eicosanoids toward cardiac function and dysfunction suggesting the importance of these metabolites. Further elucidation of their role in both physiological and pathophysiological states of an individual's heart will provide novel therapeutic strategies to improve cardiovascular health.

The importance of dietary fatty acids in the reduction of CVD has been recognized for many years (Erkkila, de Mello, Riserus, & Laaksonen, 2008; Kritchevsky, 1998). Early studies investigating the association of serum cholesterol with coronary heart disease (CHD) suggested that unsaturated fatty acids lowered serum cholesterol levels compared to saturated fatty acids (SFA) (Keys, Anderson, & Grande, 1957; Mensink & Katan, 1992; Mensink, Zock, Kester, & Katan, 2003). Evidence demonstrates the adverse effects of both *trans* fatty acids (TFA) and SFA, whereas PUFAs are associated with a lower incidence of CVD (von Schacky, 2006, 2007; Willett, 2007). These latter studies showed a lower incidence of cardiac death, as well as decreases in blood pressure, blood viscosity, plasma triglycerides, ventricular fibrillation, arrhythmia, and myocardial infarction (heart attack, MI) (Harris, 2007; Simopoulos, 2008; von Schacky, 2006, 2007). While the exact molecular mechanisms by which fatty acids regulate cardiac function or trigger dysfunction are not fully defined, it is recognized they are pleiotropic. Beneficial and detrimental outcomes ultimately depend on the levels and type of fatty acids predominating within the body or cell. The challenge for researchers is to determine the extent fatty acids influence physical properties and biochemical processes, which provide protection toward contractile dysfunction, energetics and CVD. This review focuses on research investigating CYP-derived metabolites of n-3 and n-6 PUFA and their roles in CVD, with emphasis on the heart.

Box 1
Introduction and Overview

- Dietary fat intake of N-3 and N-6 PUFAs can affect the pathogenesis of CVD
- Linoleic acid, the primary source of essential N-6 PUFAs, is converted to arachidonic acid
- Alpha-Linolenic acid is the primary source of N-3 PUFAs, EPA and DHA
- Emerging research is demonstrating the epoxy, hydroxyl and diol metabolites derived from N-3 and N-6 PUFAs have important physiological and pathophysiological properties

1.1. Overview of cardiovascular pathophysiology

Cardiovascular disease is an all-encompassing term reflecting many pathophysiological problems impacting both vascular and cardiac function, which often lead to MI, heart failure (HF) and stroke (Scott, 2004). Influencing the development of CVD are both controllable and uncontrollable risk factors, such as age, hypertension, dyslipidemia, obesity, diabetes mellitus and smoking, all of which comprise multiple organ systems that convalesce to drive significant changes in cardiovascular structure, function, metabolism and bioenergetics (Fig. 1). The end point for many CVD patients is HF, which is characterized by decreased cardiac output. HF is not a single disease entity but a defined pathogenesis cumulating in failed systolic and/or diastolic function resulting an inability of the heart to meet the energetic demands of the body (Fletcher & Thomas, 2001). The stiffening of the vasculature resulting from prolonged endothelial dysfunction and oxidizing lipid particles, as found in atherosclerosis, is one of the greatest contributors to coronary artery disease (CAD) and coronary heart disease (CHD) (Scott, 2004). Rupture of unstable atherosclerotic plaques can cause the formation of thrombi and/or emboli, leading to myocardial ischemia, angina and acute myocardial infarction (AMI) (Reed, Rossi, & Cannon, 2017). AMI is a common outcome of persistent CHD with death usually arising from arrhythmias or left ventricular rupture (sudden cardiac death) (Reed et al., 2017). Damage immediately following AMI is typified by apoptotic and necrotic cell death, activation of inflammatory cascades, severe mitochondrial alterations in bioenergetic and cell death regulation, and ionic and metabolic disturbances (Frangogiannis, 2015). While success with early reperfusion strategies and adjuvant therapies has decreased acute mortality rates, there has been a paradoxical increase in the incidence of chronic heart failure. Deterioration of cardiac function post-AMI includes extensive ventricular remodelling involving formation of fibrotic scar tissue as damaged cardiomyocytes are replaced with myofibroblasts (Frangogiannis, 2015). This shifts the injury from an acute index event to a chronic disease were individuals live with damaged hearts, in which patients often progress to HF. HF can also arise from hypertension, where the heart attempts to contract more forcefully to account for the extra workload, resulting in compensatory hypertrophy and extensive ventricular remodelling (Fletcher & Thomas, 2001; Rogers & Bush, 2015). Eventually, the ventricular wall thins, and coupled with a dilated chamber, progresses to dilated cardiomyopathy (Fletcher & Thomas, 2001). In response to decreased output,

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