Having a heart attack? Avoid the “HETE”!

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CYP metabolize endogenous arachidonic acid into vasoactive products, such as EETs (5,6-EET; 8,9-EET; 11,12-EET; and 14,15-EET) by epoxygenases and 20-HETE by ω-hydroxylation. EETs can be further metabolized by epoxide hydrolase into dihydroxyeicosatetraenoic acids, which are only weakly vasoactive. EETs contribute to coronary vasorelaxation in the absence of nitric oxide, possibly through the activation of Ca2+-activated potassium channels and subsequent hyperpolarization of vascular smooth muscle cells (2). Conversely, 20-HETE primarily induces vasoconstriction (16, 25), although the opposite has also been suggested in certain models (24). The role of ω-hydroxylation in cardiac I/R has been studied in canines. These studies revealed that the ω-hydroxylation metabolite 20-HETE was abundantly released into the plasma during I/R (20). Subsequently, the cardioprotective effects of several specific and nonspecific ω-hydroxylation inhibitors were assessed (21). ω-Hydroxylation inhibition was shown to reduce both 20-HETE formation and infarct size (21). Thus 20-HETE and perhaps other CYP ω-hydroxylation products may play a deleterious role in cardiac injury. Whether this is due to a direct effect on cardiac myocytes or on postischemic vasoconstriction requires further elucidation but appears to involve ATP-sensitive potassium channels (9).

As opposed to HETEs, EETs may have a cardioprotective effect against I/R. The epoxygenase CYP2J2 is expressed predominantly in the heart and is abundant in cardiac myocytes (36). In addition to the CYP2C subfamily, CYP2J2 plays a role in the biosynthesis of EETs and postischemic functional recovery (27). CYP2J2 transgenic mice have increased arachidonic acid epoxygenase activity compared with wild-type hearts and also exhibit improved recovery of left ventricular developed pressure (LVDP) after I/R (27). Addition of the epoxygenase inhibitor MS-PPOH before ischemia abolishes the improvement in LVDP observed in the CYP2J2 transgenic hearts (27). Thus it would appear that EETs are cardioprotective. However, cocaine upregulates CYP2J2 but greatly increases the risk of myocardial infarction (32).

In this issue of The American Journal of Physiology-Heart and Circulatory Physiology, Nithipatikom et al. (22) assess the cardioprotective roles of 11,12-EET and 14,15-EET against I/R in canines. In this study, administration of 11,12-EET or 14,15-EET 30 min before occlusion or for 5 min at the beginning of reperfusion was able to reduce infarct size to a similar extent as one 5-min cycle of ischemic preconditioning. Epoxygenase inhibition did not prevent the cardioprotective effects of preconditioning, suggesting that EET production does not play a role in cardiac preconditioning. Interestingly, inhibition of epoxygenase activity was effective in blunting the cardioprotection conferred by ω-hydroxylation inhibition. This would suggest that EETs are necessary for the cardioprotective effects of ω-hydroxylation inhibition and that perhaps the formation or the action(s) of EETs is favored when the production of EETs and HETEs by CYP as well as leukotrienes and prostacyclins by lipooxygenases and cyclooxygenases.

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ISCHEMIA-REPERFUSION (I/R) injury plays a major role in the pathogenesis of cardiac complications, such as myocardial infarction, acute angina, heart transplantation, coronary artery bypass surgery, and balloon angioplasty. Increasing evidence has emerged that implicates cytochrome P-450 enzymes (CYPs) and their metabolites in cardiac I/R injury (8–10, 12–14, 20–22, 35). CYPs are responsible for the metabolic activation or inactivation of xenobiotics. Of the sixty-three different CYP isorforms that have been identified in humans, only a handful, primarily the CYP2 and -4 subfamilies, are believed to play a role in cardiovascular physiology and disease (5). Recent studies (8, 21, 27) have revealed a role for CYP in ischemic injury and cardioprotection. Interindividual variation in the activities of CYP isorforms due to polymorphisms affects xenobiotic metabolism, detoxification and/or clearance, and risk for hypertension and atherosclerosis and may influence the risk and severity of a myocardial infarction (3, 6, 14, 15, 28, 29, 33). Additionally, CYP activity is also affected by factors such as age, ethnicity, diet, drugs, hormones, sex difference, development, and inflammation (7, 13, 18, 19, 23).

CYP epoxygenases and ω-hydroxylases are responsible for the formation of epoxyeicosatrienoic acids (EETs) and HETEs (1). In addition to the production of EETs and HETEs, certain CYPs also generate significant levels of reactive oxygen species (5, 8, 12). Determining which of these factors contribute to I/R injury and their effects on vascular endothelium and cardiomyocytes has been a topic of intense research in recent years.

Arachidonic acid metabolism is increased during myocardial I/R (11). Increased arachidonic acid metabolism results from elevated phospholipase A2 (PLA2) activity, which catalyses the hydrolysis of arachidonic acid from membrane phospholipids, thereby increasing free arachidonic acid concentration in the cytosol (31). Arachidonic acid metabolism is detrimental during I/R, because inhibition of PLA2 (Ca2+-dependent or -independent) is cardioprotective (26, 31, 34). The cyclooxygenase and CYP pathways are primarily responsible for the metabolism of arachidonic acid after I/R. Arachidonic acid or its metabolites can induce oxidative stress in multiple cell types (4, 17, 30). In addition, CYP-mediated superoxide production has been demonstrated in renal microsomes (5) and may contribute to vascular and cardiac postischemic superoxide production (8, 12). Increased arachidonic acid metabolism also results in the production of EETs and HETEs by CYP as well as leukotrienes and prostacyclins by lipooxygenases and cyclooxygenases.
of CYP-derived HETEs is blocked. Conversely, because arachidonic acid is also metabolized by cyclooxygenases and lipoxygenases, it is possible that there is a shift toward increased leukotriene or prostacyclin production. Changes in arachidonic acid production favoring prostacyclin or EET formation would significantly enhance postischemic vasodilation as observed when hearts were treated with N-methylsulfonyl-12,12-dibromododec-11-enamide in the observed study (22). The observation that ω-hydroxylation inhibition doubled transmural blood flow during reperfusion would suggest that attenuation of postischemic vascular dysfunction might be a mechanism warranting further investigation. However, combined inhibition of epoxygenases and ω-hydroxylases resulted in a further elevation in transmural blood flow but a loss of cardioprotection, possibly associated with a shift in arachidonic acid metabolism toward cyclooxygenase-mediated prostacyclin production. Though there is still much to understand, the present study has provided additional evidence to support the concept of therapeutic targeting of CYP to attenuate I/R injury.

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