

Lingoversity

Yong-Hsin Valerie Ng

Cytochrome P450 Eicosanoids Regulate Vascular Function Via Peroxisome Proliferator-activated Receptor Alpha Yong-Hsin Valerie Ng, 2005

Eicosanoids generated from the metabolism of arachidonic acid by cytochrome P450 (CYP) metabolism are mediators of diverse biological functions including the regulation of vascular tone, cellular proliferation, and inflammation. The major products of CYP-catalyzed arachidonic acid metabolism are 20-hydroxyeicosatetraenoic acid and the regio- and stereospecific epoxyeicosatrienoic acids, which can be further metabolized by soluble epoxide hydrolase (sEH) into their corresponding dihydroxyeicosatrienoic acids. Regulation of CYP eicosanoid levels is determined by numerous factors including the expression and function of the CYP enzymes responsible for their formation. Induction and repression of CYP and sEH can be mediated by the nuclear receptor peroxisome proliferator-activated receptor alpha (PPARalpha). Ligands for PPARalpha include fatty acids, eicosanoids, and fibrate drugs. Given that eicosanoids are PPARalpha agonists, and that PPARalpha can regulate CYP eicosanoid levels, the overall hypothesis tested in this dissertation is that components of the CYP-catalyzed pathway of arachidonic acid metabolism affect and/or mediate biological effects via PPARalpha-associated transcriptional signaling. CYP eicosanoids and a class of urea-based inhibitors of sEH are identified as novel PPARalpha ligands that alter the transcription of PPARalpha-responsive genes. The latter group of

compounds consists of urea-based alkanolic acids which potentially attenuate smooth muscle cell proliferation, an action that requires PPARalpha expression. In smooth muscle cells, CYP eicosanoids also induced the expression of cyclooxygenase-2 (COX-2) via increased NF-kappaB signaling and in a PPARalpha-dependent manner. Upregulation of COX-2 resulted in the surprising attenuation of inflammatory prostaglandin release, showing that cross-talk between the cyclooxygenase and CYP-catalyzed pathways of arachidonic acid metabolism may have anti-inflammatory effects. In vivo, CYP and sEH expression, especially in small diameter vessels and the heart, are altered after treatment with a PPARalpha agonist, demonstrating that these enzymes are responsive to PPARalpha activation physiologically. In summary, these results suggest that CYP eicosanoids and urea-based inhibitors of sEH favorably affect vascular function and mediate their effects through PPARalpha. Further investigations into the actions of these molecules may be helpful in the design of pharmacological modulators for the treatment of inflammation and vasculoproliferative diseases.

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