Endothelial Dysfunction and Hypertension in Rats Transduced With CYP4A2 Adenovirus

David R. Harder, Richard J. Roman

Given that the area of cytochrome P450 genetics (CYP-P450) is relatively new and is now experiencing an exponential rise in publications, it will be helpful to give some historical perspective relative to this editorial. With respect to arachidonic acid (AA) metabolism, we know most about the first two pathways of AA metabolism—cyclooxygenase (COX) and lipoxygenase enzymes—which metabolize AA to 5-, 12-, and 15-hydroxyeicosatetraenoic acid (HETE), prostaglandins, prostacyclin, thromboxane, and leukotrienes. These molecules modulate peripheral vascular function, regulate vascular tone, act as cytokines, and function in inflammatory processes.1-4 Approximately 20 years ago manuscripts began emerging which defined a third pathway for AA metabolism and metabolite formation. This pathway was via formation of particulate, inducible, cytochrome-linked proteins.5,6 Unlike the COX and leukotriene pathways, this system involved literally hundreds of genes, clustered into families, many of which had been previously studied as xenobiotic enzymes of drug metabolism in the liver and kidney. This third pathway was first studied by Capdevila,6 Oliw,7 and a number of others. AA was metabolized by cytochrome enzymes with an absorption spectra of 450 nM and labeled as the cytochrome P450 (CYP P450) pathway of AA metabolism. Since that time, well over a thousand articles have been published defining the physiologic functions of CYP P450 AA metabolites. These initial reports were largely ignored, however, and over the last decade a great deal of attention has been given to these metabolites, which function as receptor ligands and signaling molecules governing a variety of vascular phenomenon. The Figure depicts the three major pathways for metabolism of AA.

The CYP P450 family of compounds is composed of two major classifications, namely, epoxygenation of AA across the double bonds and termed epoxyeicosatrienoic acids (EETs), and the corresponding diols DiHETES, and hydroxylation of AA, broken down into hydroxylation at any of the double bonds and termed epoxyeicosatrienoic acids (HETEs). These two families of AA metabolites have radically different actions. EETs are vasodilators and mediate antiinflammatory actions, whereas 20-HETE is a potent vasoactive molecule found mainly in vascular muscle, where it is responsible for pressure-induced myogenic tone and autoregulation of renal and cerebral blood flow. Additionally, both EETs and HETEs have mitogenic properties, function as factors in hypertension, and regulate ion channels.8-10 The main target for both EETs and HETEs is large conductance calcium activated K channel (BKCa); however, both EETs and HETEs modulate BKCa in a yin-yang manner. EETs activate KCa and hyperpolarize vascular and endothelial membranes, whereas 20-HETE inhibits KCa and depolarizes vascular muscle cells.

From this very brief synopsis of CYP P450 biochemistry, the reader of the article by Wang et al11 in this issue of Circulation Research will be better informed to understand and draw individual conclusions regarding the relative importance of the data presented. The CYP P450 family of compounds consists of two main categories. The report by Wang et al uses an adenoviral (adviral) approach for overexpression of CYP 4A2 and concomitant elevation of 20-HETE in the vascular wall and parenchyma. Data within the Wang et al article are both confirmatory and seminal. The data are confirmatory in that they demonstrate in vivo that 20-HETE is procontractile as seen by elevation of arterial pressure through increasing total peripheral resistance (TPR). However, absolute confirmation of the elevation in TPR would have been measurement of cardiac output. Reduction in endothelial compensation further confirms the notion that 20-HETE increases TPR. The seminal observations are that 20-HETE appears to uncouple eNOS; however, some of these actions may result from adviral mediated inflammation.

Wang et al speculate that 4A2 expression is extra vascular muscle; support from the present findings in this regard is somewhat premature. The location of the adviral construct in endothelial and parenchymal tissue does not confirm that CYP 4A2 is “normally” expressed outside vascular muscle. However, reports that state that CYP 4A2 expression occurs in endothelial cells and adventitial tissue give credence to such an assumption.

The major observations lie in the finding that 20-HETE, through its enzymatic genesis and via increase in gp91phox, demonstrates that CYP 4A2 activity could be an in vivo source of O2 . From these data it can be argued that any study of the actions of in vivo 20-HETE needs to wrestle with possible concomitant generation of ROS. The multiple actions of ROS as signaling molecules greatly expand the cellular actions of CYP 4A2 activity and cloud discussion regarding the action of 20-HETE. For example, when conducting experiments on the influence of blood flow regulation...
in the brain or kidney with respect to mediation by 20-HETE, the confounding roles of ROS must be considered.

The impact of the report by Wang et al would be nicely augmented through use of a transgenic mouse model overexpressing 20-HETE, which would put the experiments in a “clearer light.” The ability of CYP 4A2 to epoxygenate AA needs in vivo confirmation. It is also necessary to elucidate the differences between overexpression of CYP 4A2 versus enhancing levels of 20-HETE. A number of genes in the CYP 4A family, ie, CYP 4F3, can catalyze formation of 20-HETE using AA as the substrate. However, until such experiments are done, this part of the report by Wang et al will remain controversial.

In general, this article by the Schwartzman laboratory has made a significant contribution regarding the role of 20-HETE with specific reference to its ability to alter vascular function, both through direct actions as well as through the seminal finding that 20-HETE functions to enhance ROS within the vascular wall. As discussed, there are multiple CYP P450 genes within the vasculature. What has yet to be investigated is the other side of the coin with 20-HETE and ROS. If there is upregulation of gp91phox, what will the action of 20-HETE be compared with control? Furthermore, will the induction of CYP P450 genes be altered? This manuscript not only makes significant contributions to vascular biology but opens many new questions as well.

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References


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