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LETTER TO THE EDITORS

Cytochrome P450 and gene activation – cholesterol elimination and regression of atherosclerosis: author reply to the commentary

Pauli V. Luoma

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The Editorial commentary by Olavi Pelkonen and Jukka Hakkola "Cytochrome P450, induction and cholesterol – what are the connections?" [1] regarding my review article "Cytochrome P450 and gene activation – from pharmacology to cholesterol elimination and regression of atherosclerosis" [2] published in this journal gives reason for some comments.

The review does not report, as stated in the commentary, that the effects of all the compounds affecting the fate of cholesterol are partially or totally mediated through the action of cytochrome P450 enzymes. Instead, it focuses, as presented, first on the effects of P450s, and second on the effects of gene activation and gene-activating compounds.

The conclusion of the article "P450-enzymes are essential in the physiological maintenance of cholesterol balance" is according to the commentary "correct only at a very general level." There are, however, numerous studies showing that P450 enzymes are specifically involved. P450s are essential in the formation of oxysterols and bile acids, biologically active necessary signaling molecules and metabolites. A defect in CYP27A1 underlies cholesterol accumulation and clinical manifestations such as xanthomas in tendons and brain and premature atherosclerotic disease, and a defect in CYP7A1 leads to cholesterol accumulation and atherogenic hypercholesterolemia.

The commentary states that the simple hypothesis (which is three decades old) linking P450 and induction phenomenon with cholesterol metabolism, transporters and atherosclerosis "still remains a hypothesis." The statement is no longer valid. Cholestyramine, which by specifically inducing hepatic CYP7A1 reduces low-density lipoprotein cholesterol (LDL-C) and, by inducing apolipoprotein (apo) AI synthesis increases apo AI and high-density lipoprotein cholesterol (HDL-C), has been shown to regress coronary atherosclerosis (angiography) [2]. Fibrates induce P450s, including ω-hydroxylases, which generate eicosanoid ligands for peroxisome proliferator-activated receptor (PPAR)-α [3, 4]. Fibrate-caused PPAR-α activation upregulates LXR, transporters and cholesterol elimination to apo AI, and an inhibition of the fibrate-caused P450-induction prevents activation of cholesterol-lowering mechanisms [2].

Statins induce P450 enzymes, including ω-hydroxylases, in human liver microsomes [2, 5]; ω-hydroxylases generate eicosanoids, which are PPAR-α and PPAR-γ activators and also induce the expression of P450 enzymes [4]. Statin-caused PPAR activation upregulates LXR and cholesterol transporters and promotes cholesterol elimination to apo AI and HDL [2]. Statin has also been shown to induce—via SREBP-2 activation—the expression of CYP4F2 [5] and the liver-specific ABCA1 [6]. The drug reduced expression of the peripheral type of ABCA1 in vitro in an LXR-dependent manner [6] and increased LXR expression both in hepatocytes and leucocytes in vivo [2]. LXR activation has been shown to also upregulate the LDL receptor gene, and SREBP-2 activation provides a link between the regulation of CYP4F2 and LDL receptor [5].

The statement "convincing evidence linking P450s, induction, cholesterol and atherosclerosis is still lacking" does not take into account current knowledge. Deficient P450-hydroxylase activity leads to cholesterol accumulation, and gene-activating agents prevent or regress atherosclerosis They include effective compounds that, via P450 induction, affect the fate of cholesterol and act against the atherosclerotic process. The effects of both endogenous and pharmacologic gene activation have significance: coronary

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heart disease is the leading cause of death in the world and cerebrovascular disease the second leading cause.

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