Eur J Clin Pharmacol (2008) 64:841–850
DOI 10.1007/s00228-008-0515-5

REVIEW ARTICLE

Cytochrome P450 and gene activation—from pharmacology to cholesterol elimination and regression of atherosclerosis

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Received: 30 January 2008 / Accepted: 20 May 2008 / Published online: 17 July 2008

Abstract
Background Lipoproteins are closely associated with the atherosclerotic vascular process. Elevated levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein AI (apo AI) in plasma indicate a low probability of coronary heart disease (CHD) together with enhanced longevity, and elevated levels of low-density lipoprotein-cholesterol (LDL-C) and apo B indicate an increased risk of CHD and death. Studies linking gene activation and the induction of cytochrome P450 with elevated plasma levels of apo AI and HDL-C and lowered plasma levels of LDL-C presented a new potential approach to prevent and treat atherosclerotic disease.
Objective and methods This is a review aimed at clarifying the effects of P450-enzymes and gene activation on cholesterol homeostasis, the atherosclerotic vascular process, prevention and regression of atherosclerosis and the manifestation of atherosclerotic disease, particularly CHD, the leading cause of death in the world.
Results P450-enzymes maintain cellular cholesterol homeostasis. They respond to cholesterol accumulation by enhancing the generation of hydroxycholesterols (oxysterols) and activating cholesterol-eliminating mechanisms. The CYP7A1, CYP27A1, CYP46A1 and CYP3A4 enzymes generate major oxysterols that enter the circulation. The oxysterols activate—via nuclear receptors—ATP-binding cassette (ABC) A1 and other genes, leading to the elimination of excess cholesterol and protecting arteries from atherosclerosis. Several drugs and nonpharmacologic compounds are ligands for the liver X receptor, pregnane X receptor and other receptors, activate P450 and other genes involved in cholesterol elimination, prevent or regress atherosclerosis and reduce cardiovascular events.
Conclusions P450-enzymes are essential in the physiological maintenance of cholesterol balance. They activate mechanisms which eliminate excess cholesterol and counteract the atherosclerotic process. Several drugs and non-pharmacologic compounds induce P450 and other genes, prevent or regress atherosclerosis and reduce the occurrence of non-fatal and fatal CHD and other atherosclerotic diseases.

Keywords ATP-binding cassette A1 · Coronary heart disease · Cytochrome P450 · HDL cholesterol · Liver X receptor–pregnane X receptor · Oxysterol

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Introduction

In the 1960s, cytochrome P450 was known as a hepatic enzyme directly involved in the metabolism of drugs and other foreign compounds [1–3]. Studies in the 1970s linked liver microsomal P450-induction with elevated levels of plasma apolipoprotein AI (apo AI) and high-density lipoprotein cholesterol (HDL-C) [4, 5], which then were identified as powerful predictors of coronary heart disease (CHD), cerebrovascular and other atherosclerotic diseases [6, 7]. This was followed by the discovery that plasma levels of LDL cholesterol (LDL-C) decreased with increasing P450 activity in the liver [8, 9]. High plasma HDL-C and apo AI indicate a low probability of CHD together with enhanced longevity, and individuals with high LDL-C or apo B have an increased risk of CHD and death [6, 7, 10]. The results from the original studies on P450, cholesterol

fractions, proteins and induction suggested a novel approach to atherosclerosis—i.e. activation of P450 and other genes coding proteins which regulate cholesterol balance in the body— and directed research to new avenues [5, 9, 11].

By 1980, the first P450 isoenzymes were identified [12] and in the following years, dozens of P450 genes were found to code enzymes catalysing diverse metabolic processes in humans [13]. In addition to foreign compounds, P450-enzymes metabolize endogenous substrates, including vitamins, steroid hormones, cholesterol and bile acids [13]. Several P450-enzymes metabolize cholesterol to hydroxycholesterols (oxysterols), which have been identified as ligands for nuclear receptors in the induction of genes involved in cholesterol elimination [14, 15]. A number of drugs and nonpharmacologic compounds also induce P450 and other genes coding for proteins involved in lipid metabolism, including apo AI, the predominant apolipoprotein of HDL. This article reviews studies on P450-enzymes and gene activation and gene-activating compounds acting in cholesterol elimination and the prevention and regression of atherosclerotic cardiovascular disease, particularly CHD, which has been identified as the leading cause of death in the world [16].

Liver P450, lipids and proteins and the fate of cholesterol—effect of gene activation

The first studies on P450, apo AI, HDL and LDL evaluated the effects of gene-activating agents on lipids and proteins in the atherosclerotic vascular process (reviewed in [10]). Persons undergoing therapy with drugs such as phenobarbital, primidone or phenytoin, alone or in combination, showed an increase in protein and phospholipid concentrations and P450-induction in the liver as well as a concurrent and parallel elevation in apo AI and HDL-C levels in the plasma implying an upregulation of apo AI and HDL synthesis [11,17]. Further studies revealed that P450- inducing compounds such as phenobarbital [18], fenofibrate [19] and gemfibrozil [20] induce apo AI synthesis, and P450-inhibitors such as ketoconazole and metyrapone [10,20] prevent it. Studies in transgenic animals demonstrated that an activation of human apo AI gene elevates plasma levels of HDL-C and prevents atherogenesis [21]. Ketoconazole also inhibits cholesterol synthesis, reduces LDL cholesterol level [22], and by counteracting the induction of P450 suppresses the generation of oxysterols and activation of nuclear receptor and transporter genes which are involved in the elimination of cholesterol [23]. In contrast to ketoconazole, a high-dose itraconazole therapy has been found raise plasma HDL cholesterol [24]. The inducing effect of itraconazole on apo AI synthesis in Caco-2 cells in vitro suggested a mechanism for the elevation of HDL-C. From the clinical point of view it is significant, that a deficient P450-hydroxylase activity affects the fate of cholesterol leading to cellular cholesterol accumulation [25], hypercholesterolemia [26], and enhanced manifestation of atherosclerotic disease.

P450-isoenzymes and cholesterol

Accumulation of excess cholesterol in cells may have serious consequences; in the arterial wall it can progress to atherosclerotic disease. P450-enzymes are essential in the finely tuned physiological system which controls cell cholesterol balance and takes care of the elimination of excess cholesterol. They are needed in the synthesis of oxysterol and bile acid metabolites of cholesterol and in the activation of the cholesterol-eliminating mechanisms (Fig. 1) [14, 15, 27]. The oxysterols are endogenous signal compounds, which via liver X receptors (LXR) induce genes acting in cholesterol efflux, transport, excretion and absorption [28]. Hydroxylation of cholesterol to oxysterols is necessary for the natural activation of these genes; free cholesterol and cholesterol esters do not have similar ability [29].

From the quantitative point of view, CYP7A1, CYP27A1, CYP46A1 and CYP3A4 are the most important P450-isoenzymes in the formation and metabolism of oxysterols in man [30] (Fig. 1). CYP7A1 is a hepatic key P450-enzyme in maintaining cellular cholesterol balance. It is the rate-limiting enzyme in the most significant pathway for bile acid synthesis. It generates 7α-hydroxycholesterol [31] which is further metabolized to bile acids. CYP8B1 is needed in the synthesis of cholate [32]. CYP27A1, a mitochondrial P450-enzyme, is expressed in most tissues and cell types, including macrophages. It generates 27-hydroxycholesterol which, via the liver X receptor (LXR) activates genes coding transporter proteins that shuttle intracellular cholesterol to outer cell membranes for elimination [33]. A direct secretion of 27-hydroxycholesterol contributes to cholesterol efflux [27]. 27-Hydroxycholesterol is further hydroxylated by oxysterol 7α-hydroxylase, CYP7B1, and also CYP7A1 [34]. CYP46A1 has an active role in cholesterol metabolism

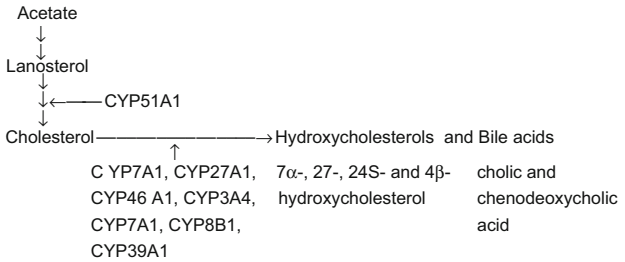

Fig. 1 P450-enzymes involved in the synthesis of cholesterol and major hydroxycholesterols and bile acids [30, 41]

in the brain [35]. It generates 24S-hydroxycholesterol, which readily passes the blood brain barrier and thus transports cholesterol from the brain. This metabolite is also a ligand for LXR and may regulate cholesterol balance through transcriptional mechanisms; it may also activate the apo AI-dependent cholesterol efflux from brain endothelial cells [36]. Hepatic CYP39A1 and possibly also CYP7A1 and CYP27A1 convert 24S-hydroxycholesterol to bile acids [35]. CYP3A4, which is expressed particularly in the liver and intestine, is the most common hepatic P450-enzyme. It metabolizes about half of all pharmaceutical agents and also acts on cholesterol and bile acid metabolism. It generates 4β-hydroxycholesterol [30].

CYP51A1 (lanosterol-14α-demethylase) is ubiquitously expressed and is the only P450 enzyme participating in cholesterol synthesis [37]. It demethylates lanosterol to cholesterol in a reaction that produces oxysterols, which inhibit hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase and sterol synthesis [37, 38]. Squalene, an intermediate in cholesterol synthesis, is metabolized to 24S,25 epoxycholesterol in a shunt pathway; this product is an activator of LXR [15] and may act against cholesterol accumulation.

Oxysterol binding protein (OSBP) and 11 related compounds form a cytoplasmic family of OSBP-related-proteins (ORPs) [39]. These compounds bind intracellular oxysterols, which are mainly generated by P450-enzymes. Recent studies suggest that ORPs are lipid sensors in the integration of lipid and sterol metabolism and transport and the regulation of cell signalling [39].

Nuclear receptors, ABC transporters, apolipoproteins and P450-enzymes

Nuclear LXR receptors LXRα and LXRβ, are cholesterol sensors that mediate the expression of multiple genes involved in the regulation of cellular cholesterol homeostasis [28]. They are activated by physiological concentrations of several oxysterols. LXRα is expressed at high levels in the liver and to lesser extent in the intestine, adipose tissue and macrophages, whereas LXRβ is ubiquitously expressed. The LXR induces transcription of ATP-binding cassette (ABC) transporters, such as ABCA1, G1, G4, G5 and G8, which act in intracellular cholesterol transport, apolipoproteins in the cluster of apo E, CI, CII and CIV, which have been shown to participate in the ABCA1-mediated cholesterol efflux [28], and of apo IV, which may contribute to the latter [40]. In addition, LXR influences the expression of several lipoprotein remodelling enzymes, sterol regulatory binding proteins (SREBPs) and also hepatic scavenger receptor B1 (SR-B1), which selectively uptakes HDL-associated cholesterol esters to the liver [28].

Pregnane X receptor (PXR), which is expressed predominantly in the human liver and to a lesser extent in the small intestine, is a master regulator of P450 enzymes in the metabolism of xenobiotic compounds and affects the fate of cholesterol [31, 41]. It mediates the induction of CYP3A4 and other P450-enzymes and can be activated by numerous structurally diverse compounds including statins, anticonvulsants and hyperforin, a constituent of the herb St John`s wort [42–45], and bile acid and epoxycholesterol metabolites of cholesterol [46]. The compounds include several PXR agonists [42–45, 47–49] that induce P450 and elevate plasma levels of apo AI and HDL-C [10, 11, 45]. A PXR agonist has been recently found to upregulate CYP27A1 and generate 27-hydroxycholesterol in the intestine, suggesting a LXRα-mediated activation of cholesterol efflux from intestinal cells to apo AI and HDL [50].

Peroxisome proliferator-activated receptors PPARα, PPARγ and PPARδ, are transcription factors which affect the development of atherosclerosis in many ways. They mediate the induction of apo AI synthesis and co-operate with LXR receptors and ABC transporters in cholesterol elimination [51, 52].

ATP-binding cassette A1 ABCA1, is a key regulator of cellular lipid efflux. It transfers cholesterol and phospholipids to the plasma membrane where apo AI picks up them [53]**.** Liver ABCA1 has been identified as a main factor [54] and intestinal ABCA1 as a contributory factor [55] in the generation of HDL-C levels in the circulation. Intestinal ABCA1 also controls the absorption of cholesterol by effluxing it from the enterocytes back to the intestinal lumen [56]. A genetic defect in ABCA1 causes Tangier disease, which is characterized by a near or complete absence of HDL, accumulation of cholesterol esters in tissues, and enhanced manifestation of cardiovascular disease [57].

ATP-binding cassette G1 ABCG1, which acts in several tissues, and ABCG4, which acts in the brain, transfer cholesterol to the HDL [53, 58]. The ABCG5 and ABCG8 transporters promote biliary cholesterol secretion and reduce the absorption of dietary cholesterol [59]. Mutations in the ABCG5 or ABCG8 gene cause sitosterolemia, a rare genetic disorder of sterol metabolism characterized by hypercholesterolemia, xanthomas and premature coronary atherosclerosis [60].

Bile acids, nuclear receptors and P450-enzymes

Oxysterols are precursors of bile acids (Fig. 1) which, as ligands for nuclear receptors, such as FXR (farnesoid X receptor), PXR, CAR (constitutive androstane receptor) and VDR (vitamin D3 receptor), activate mechanisms control-

ling cellular bile acid balance [31, 41]. The FXR has a central role in the regulation on bile acid levels. Accumulation of bile acids stimulates the FXR-mediated suppression of CYP7A1 and CYP8B1, which are key enzymes in the synthesis of bile acids. The FXR also induces the expression of CYP3A4, which in turn detoxifies bile acids by oxidizing them. The PXR and VDR regulate the metabolism of secondary bile acids in the liver and intestine. They mediate the expression of the CYP3A4 gene and the detoxification of bile acids. The PXR also downregulates CYP7A1 in response to the elevation of intracellular bile acid levels. The CAR affects the metabolism of xenobiotic compounds and also detoxifies bile acids.

Drugs and nonpharmacologic compounds, gene activation and the fate of cholesterol

Many drugs and other compounds activate genes that affect the fate of lipids. These include drugs indicated for the treatment of lipid disorders, such as statins, fibrates, cholestyramine and niacin (Table 1), as well as drugs for other indications.

Statins inhibit HMGCoA reductase and cholesterol synthesis and via enzyme-, receptor- and transporter-mediated mechanisms enhance cholesterol elimination, and raise plasma apo AI and HDL-C and reduce apo B and LDL-C. The drugs are ligands for PXR receptor which is a key mediator of the induction of P450 enzymes including CYP3A4 [42–45]. The statins have been identified as P450 inducing agents [10, 42–44, 47–49], and the effects of PXR agonists on HDL-C and apo AI have been linked with their ability to induce CYP3A in rodents [45]. The drugs have been shown to induce PPARα and apo AI synthesis [61, 62] and to activate PPARγ, LXR, ABCA1 and ABCG1 genes in cholesterol-loaded macrophages [63] and ABCA1 in HepG2 cells [64] as well as to increase the cholesterol efflux to apo AI and HDL [63]. Statins can act differently in nonloaded macrophages, inhibiting the synthesis of oxysterol ligand for LXR and downregulating ABCA1 gene and cholesterol efflux [65]. Such effects, however, have not been seen in vivo.

Fibrates are P450-inducing PPARα agonists, which stimulate apo AI synthesis, raise plasma apo AI and HDL-C levels and reduce levels of LDL-C and triglycerides [10, 52, 66, 67]. They activate the LXR and ABCA1 genes and promote cholesterol efflux to apo AI [52]. An inhibition of P450 prevents fibrate-caused oxysterol generation and the induction of genes acting in cholesterol elimination, such as LXRα, PPARα, ABCA1 [23] and apo AI [20].

Cholestyramine induces CYP7A1, the rate-limiting enzyme of bile acid synthesis, leading to a depletion of hepatic cholesterol pool, and consequently to an upregulation of the LDL receptor pathway and lowering of plasma LDL-C level [68]. The drug also induces apo AI synthesis and raises plasma apo AI and HDL-C [69]. Niacin similarly raises apo AI and HDL-C levels and reduces LDL-C [70], but it differs from many other compounds that elevate HDL-C levels in that it does not increase P450 activity and apo AI synthesis. Instead, it has been found to inhibit hepatic uptake of apo AI, activate the PPARγ, LXRα and ABCA1 genes and stimulate HDL-dependent cholesterol efflux from monocytoid cells [70].

Anticonvulsants, such as phenobarbital, phenytoin and carbamazepine, are PXR agonists which upregulate P450-enzymes, including CYP3A4 [42–44], and raise plasma apo AI and HDL-C levels proportionately to P450-induction

Table 1 Effect of drugs and alcohol on: increase (+) in P450 and ABCA1 activity and apo AI synthesis (S) and decrease (↓) in CHD mortality and CHD/cardiovascular morbidity

Drug	P450	ABCA1	Apo AI-S	Mortality	Morbidity	References
Statin	+	+	+	↓	↓	10, 42–44, 47–49, 61, 63, 64, 100–102
Fibrate	+	+	+	↓[a]	↓[a, b]	10, 19, 52, 66, 67, 92, 93, 103
Cholestyramine	+	?	+		↓	10, 68, 69, 92
Niacin	-	+	-		↓	70
Anticonvulsant	+	?	+	↓[c]		10, 42–45, 104
Glitazone	+	+	+		↓[d]	43, 44, 51, 52, 72–75, 106
Alcohol	+	+	+	↓[e]	↓[e]	10, 76–80, 96, 97, 105

P450, Cytochrom P450; ABC, ATP-binding cassette; CHD, Coronary heart disease; Apo AI, apolipoprotein AI
[a] Gemfibrozil [103]
[b] Fenofibrate [92], bezafibrate [93]
[c] Anticonvulsant therapy (phenytoin ± carbamazepine ± barbiturate), case-control study [104]
[d] Pioglitazone, cardiovascular events in type 2 diabetics [106]
[e] Moderate alcohol consumption [105]

[10, 11]. Phenobarbital induces hepatic apo AI mRNA [18], and a recent study linked the effect of phenobarbital and other PXR agonists on apo AI and HDL-C with their ability to induce CYP3A in mice [45]. Anticonvulsants also enhance the generation of 4β-hydroxycholesterol [71], a LXR agonist which may—via transcriptional mechanisms—increase cholesterol efflux and raise HDL-C. The inverse relation of LDL-C level to the induction [8, 9] probably reflects the inhibiting effect of oxysterols on cholesterol synthesis and enhanced LDL-C elimination via the upregulated LDL receptor pathway.

Glitazones are PPARγ and PXR agonists and P450-inducing agents [43, 44, 72–74] that increase apo AI synthesis, raise plasma HDL-C levels [75] and, via activation of the LXRα, ABCA1, ABCG1, apo E and SR-B1 genes, promote cholesterol efflux from macrophages [51, 52].

Alcohol enhances P450 activity [10, 76] and apo AI synthesis [10, 77], and persons using alcohol regularly show an elevation of plasma apo AI and HDL-C [76–79] levels that is proportional to the increase in P450 [78]. Alcohol also promotes ABCA1- and cAMP-mediated cholesterol efflux from macrophages [80].

Vitamin A derivates—retinoids—upregulate several genes involved in reverse cholesterol transport, such as CYP27A1, LXRα, PPARγ, ABCA1, ABCG1 and the apolipoproteins CI, CII, CIV and E [73, 81]. Hypertriglyceridemia and other adverse effects have limited the clinical usage of retinoids. Calcium channel blockers also have the potential to induce P450 [44]. Verapamil, nifedipine and nicardapine were found to induce ABCA1 expression and increase apo AI-dependent cholesterol efflux from macrophages [82]. Telmisartan, an angiotensin receptor blocker, has been shown to enhance both apo AI- and HDL-mediated cholesterol efflux from macrophages by increasing ABCA1, ABCG1 and SR-B1 expression via PPARγ-dependent and LXR-dependent/-independent pathways [83]. Angiotensin-converting enzyme (ACE) inhibitors can also affect the fate of cholesterol [84, 85]. Adenosine A2A receptor agonists have been found to upregulate CYP27A1 and ABCA1 expression and prevent the formation of foam cells [86] and biphosphonate, to inhibit foam cell formation [87], to induce ABCA1 transcription and to stimulate cholesterol efflux from monocytoid cells [88].

Drugs and other compounds against atherosclerosis

Several drugs prevent or retard the progression, or even regress, atherosclerosis, as assessed by angiography, ultrasonography or histological/ biochemical analysis. These include statins, such as rosuvastatin [89], atorvastatin [90] and simvastatin [91], which have been shown to regress coronary atherosclerosis. Positive results have also been obtained with lovastatin, fluvastatin, gemfibrozil, fenofibrate [92], bezafibrate [93] and cholestyramine [10]. Niacin was recently found to reduce carotic intimal media thickness in persons with metabolic syndrome [94].

The recent ASTEROID trial demonstrated that rosuvastatin therapy, which effectively reduced LDL-C and apo B and raised HDL-C and apo AI, resulted in a significant regression of atherosclerosis in coronary arteries of CHD patients [89]. A post-hoc analysis combining data from four prospective intravascular ultrasonography–statin trials revealed, in particular, that patients whose HDL-C levels increased by more than 7.5% in addition to effective LDL-C lowering exhibited the most profound regression of atherosclerosis [95]. The increases in HDL-C levels were found to be an independent predictor of a beneficial outcome with statin therapy.

Many compounds used for other purposes than dyslipidemia also have antiatherogenic effects. Phenobarbital prevents cholesterol accumulation and the formation of atherosclerotic lesion in arterial wall [10], and those persons using alcohol moderately show less carotic [96] and coronary [97] atherosclerosis. Pioglitazone and etidronate have been found to reduce carotic intima-media thickness in type 2 diabetic subjects [98] and those with osteopenic type 2 diabetes, respectively [99].

Drugs and other compounds and cardiovascular events

Several trials have evaluated the effects of statins and other compounds on the occurrence of cardiovascular events (Table 1). Statins reduce coronary events, strokes and all-cause mortality [100, 101]. A meta-analysis of data on more than 90,000 participants revealed that the change in total mortality reflects a decrease in coronary mortality [101]. A recent atorvastatin study found that a relatively small increase (mean 7%) in HDL-C level independently of LDL-C lowering is linked with a reduced risk of major coronary events and stroke [102]. An analysis of 18-years of follow-up data from the Helsinki Heart Study revealed that gemfibrozil reduces both CHD mortality and total mortality in the subgroup of persons with dyslipidemia related to the metabolic syndrome [103]. In type 2 diabetic subjects, bezafibrate has been shown to reduce the incidence of coronary events [93], niacin, that of myocardial infarctions [92] and fenofibrate, that of non-fatal myocardial infarctions [92]. A follow- up survey conducted 9 years after the completion of a niacin trial, showed a 11% lower total mortality in patients originally treated with niacin compared with placebo-treated patients [70]. Cholestyramine reduces the risk of CHD death and/or non-fatal myocardial infarction [92], a reduced death rate from CHD has been reported also for people undergoing anticonvul-

sant therapy [104], and population studies show that moderate alcohol consumption reduces CHD morbidity and mortality, and also total mortality [105].

Pioglitzone has been found to reduce cardiovascular events in type 2 diabetics [106], whereas a meta-analysis reported an increase in the risk of myocardial infarction and an increase cardiovascular death of borderline significance with rosiglitazone [107]. This controversy led to the warning stating that rosiglitazone is not recommended in CHD and/or peripheral artery disease, and that it is contra-indicated in acute coronary syndrome [EMEA, European Medicines Agency].

Mutation and inhibition of P450, enhanced atherogenesis and cardiovascular events

A mutation in the P450 gene affects the fate of cholesterol and enhances the atherosclerotic process. A defect in the CYP27A1 gene causes cerebrotendinous xanthomatosis, CTX, a genetic disease characterized by xanthoma formation and premature atherosclerosis [25], and a mutation in the CYP7A1 gene can lead to hypercholesterolemia and enhance atherogenesis [26]. A low P450 activity could also impede oxysterol generation and LXR-mediated activation of the proteins participating in cholesterol transport, such as ABC transporters, apolipoproteins, lipoprotein-modifying enzymes, SREBPs and SR-B1.

An exogenous inhibition of P450 can similarly promote cholesterol accumulation. Carbon monoxide (CO) binds to ferrous heme of P450, consequently blocks oxidative reactions [3], and promotes cholesterol accumulation and formation of atherosclerotic lesions in arterial walls [108]. The effect of CO on P450 could contribute to the increased incidence of cardiovascular events and deaths observed with increasing CO exposure in smokers [109]. Early studies with interferon showed a decrease in plasma HDL-C and apo AI level [110] and, later on, interferon γ was found to reduce P450 and ABCA1 activity, impede reverse cholesterol transport and promote atherogenesis [111, 112]. Ketoconazole prevents P450-induction, and consequently oxysterol generation and the activation of genes involved in reverse cholesterol transport, such as LXRα, PPARα, ABCA1 [23].

Discussion and conclusions

Advanced methods in molecular biology and genomics have identified diverse biological and clinical roles for isoenzymes of P450, which was once believed to be one enzyme in the hepatic detoxification system. P450s hydroxylate both endogenous and foreign substances and affect multiple metabolic processes and clinical outcomes. P450-enzymes are essential for the physiological maintenance of cholesterol homeostasis, responding to elevated cholesterol by activating mechanisms which efflux cellular cholesterol and raise plasma HDL-C and suppress cholesterol synthesis, thereby reducing LDL-C. Correspondingly, a naturally low P450 activity or a genetic defect in P450 can promote cholesterol accumulation and atherogenesis. A mutation in a transporter gene, such as ABCA1, G5, G8, or apo AI, can impede the response to activation and also enhance the atherosclerotic process.

Several drugs and nonpharmacologic compounds also induce genes with similar effects as the endogenous gene activation on lipid and proteins, and prevent or regress atherosclerosis, thereby reducing cardiovascular events. These compounds can produce a lipoprotein pattern comparable with that in familial hyper-HDL-emia, which is characterized by a low risk of CHD and enhanced longevity [10]. A recent statin study revealed that individuals who show increases in HDL-C level greater than the mean percentage change together with an effective LDL-C reduction experience the greatest degree of atheroma regression [95]. Statins increase HDL-C level up to 15% and can regress atherosclerosis, whereas torcetrapib, an inhibitor of CETP (cholesterol ester transfer protein) which raised HDL-C level up to 60%, failed to slow the progression of coronary plaques [113]. This difference emphasizes the significance of the mechanisms by which the drugs raise HDL-C.

The discovery of LXRs and oxysterols, with the latter functioning as ligands for LXRs and as secretory forms for cellular cholesterol efflux, significantly clarified the cholesterol-lowering mechanisms. The investigations that identified PXR, PPAR, FXR and several other receptors as well as ABC and other transporters—and their functions—further explained important processes in maintaining cholesterol homeostasis. The progress in studies on cholesterol regulation has greatly stimulated the search for new agents with a potential to regress atherosclerosis. Recently, a LXR agonist was found to stimulate reverse cholesterol transport by promoting cholesterol efflux from macrophages and transporting it to liver and further to feces in vivo in mice [114]. Another study showed that LXR agonist increases ABCA1 activity in atherosclerotic lesions and also induces the regression of these lesions in mice [115].

The liver is of critical importance in the metabolism and elimination of endogenous and exogenous compounds. Many natural and foreign compounds upregulate key effectors in cellular cholesterol efflux, including hepatic ABCA1 and apo AI, main factors in the generation of plasma HDL-C levels, and the LDL receptor, which leads to a lowering of LDL-C levels. Liver disease and a change in liver size can also affect the fate of cholesterol [10, 116, 117]. Patients treated with P450-inducing drugs show an elevation of plasma HDL-C and the HDL-C/LDL-C ratio

together with an increase of metabolically active liver mass [116], and the 24S-hydroxycholesterol levels reflect the balance between cerebral production capacity and the metabolic capacity in the liver [117].

An atherogenic diet upregulates hepatic P450-enzymes, hydroxycholesterols [38] and ABCA1, thereby supporting a major role for the liver in the dietary modulation of HDL-C levels [118]. In accordance with this, a recent study found that an upregulation of the hepatic LXRα protects animals on a Western diet from atherosclerosis, underlining the potential of selective activators of LXR target genes in the liver as agents against lipid disorders and atherosclerosis [119]. The PXR, a master regulator of hepatic CYP3A4 and other P450 enzymes, also protects against the toxicity caused by a high-cholesterol diet [120], and PXR agonists raise apo AI and HDL-C levels. Interestingly, a recent statin study revealed that the increases in HDL-C levels independently predict the rate of atherosclerosis regression in coronary arteries [95]. Modification of life-style factors, including the Western-type diet, together with or without effective drug therapy are key factors in the fight against atherosclerosis and the epidemic of CHD.

Acknowledgements The author is grateful for the excellent collaboration he received, especially to Eero Sotaniemi (†), Olavi Pelkonen, Markku Savolainen and Vilho Myllylä from the University of Oulu, Finland; Christian Ehnholm from the National Public Health Institute, Helsinki; and Heikki Vapaatalo from the University of Helsinki.

The studies were supported by the Academy of Finland and the Paavo Nurmi Foundation, Finland.

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