Effect of Cardiovascular Drugs on the Plasma Levels of Lipoprotein-Associated Phospholipase A_2 (Lp-PLA_2)

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Abstract: Several lines of evidence suggest that the lipoprotein-associated phospholipase A_2 (Lp-PLA_2) plays an important role in the pathogenesis of atherosclerotic disease. From a pathophysiological point of view the enzyme bound to apolipoprotein-B-containing lipoproteins (which corresponds to more than 90% of plasma enzymatic activity) may play a proatherogenic role since it generates lysophosphatidylcholine and oxidized fatty acids, molecules that have been shown to promote atherogenesis. On the other hand, the enzyme associated with high-density lipoprotein (HDL) may play an antiatherogenic role since it protects low-density lipoprotein (LDL) from oxidation and diminishes the biological functions of oxidized LDL. Several large-scale, prospective studies have shown that both plasma Lp-PLA_2 mass and activity represent important predictors of future cardiovascular risk in primary and secondary prevention populations. In this review, we summarize the current knowledge on the effect of drugs used in the treatment of cardiovascular disease on the plasma levels of Lp-PLA_2. This information may help clinicians to design safe and effective therapeutic strategies for the prevention and treatment of atherosclerotic disease.

Keyword: Lipoprotein-associated phospholipase A2, cardiovascular drugs, statins, fibrates.

INTRODUCTION

The plasma type of platelet-activating factor (PAF)-acetylhydrolase is a Ca^{2+}-independent phospholipase A_2 (PLA_2) that circulates in complex with lipoprotein particles. Due to this property, this enzyme is also referred to as lipoprotein-associated phospholipase A_2 (Lp-PLA_2) [1]. In human plasma, Lp-PLA_2 is mainly associated with low-density lipoprotein (LDL) as well as with high-density lipoprotein (HDL). Lp-PLA_2 is also bound to very low-density lipoprotein (VLDL) and to intermediate-density lipoprotein (IDL) as well as to lipoprotein (a) [Lp(a)] [2]. It is well documented by *in vitro* studies, by studies in animal models *in vivo* as well as by clinical trials that Lp-PLA_2 is implicated in atherosclerosis and cardiovascular disease. However, recent evidence suggests that the role of this enzyme in atherogenesis is significantly affected by the nature of its lipoprotein carrier [2]. In this context, it has been hypothesized that the modulation of the activity of Lp-PLA_2 may represent an important new therapeutic target that may affect the natural history of atherosclerotic disease. In this review, we summarize the current knowledge on the effect of drugs used in the treatment of cardiovascular disease on the plasma levels of Lp-PLA_2.

EFFECT OF ANTIOBESITY DRUGS ON Lp-PLA_2

Previous studies have shown that abdominal obesity is characterized by increased plasma concentration and activity of Lp-PLA_2. Indeed, Okada T *et al*. have shown, in a group of 17 obese children, that Lp-PLA_2 mass was significantly correlated with the measures of adiposity (relative weight, weight/height ratio and subscapular/triceps ratio); multiple regression analysis in the same study revealed that LDL-cholesterol levels and waist/height ratio were the most important determinants of Lp-PLA_2 mass explaining 68.8% of the Lp-PLA_2 concentration variability [3]. More recently, Detopoulou P *et al.* confirmed the association of Lp-PLA_2 activity with the measures of upper and total adiposity in a group of otherwise healthy adult individuals. In addition, we have shown that the presence of metabolic syndrome (a disorder closely related to abdominal obesity) is characterized not only by increased activity of plasma Lp-PLA_2 but also by decreased activity of the HDL-associated enzyme [4]. In this context, a study in experimental animals revealed that cholesterol feeding is followed by an enhancement of the secretion of the enzyme by monocyte-derived macrophages which, in turn, results in an increase in LDL-associated Lp-PLA_2 activity and in plasma lyso-PC concentration [5]. Interestingly, we have previously demonstrated that a low-calorie diet associated with weight loss in obese women resulted in a significant reduction of the plasma Lp-PLA_2 activity. This reduction was correlated with the decrease in VLDL-cholesterol levels, but not with the changes of other lipid parameters or anthropometric variables [6].

Orlistat is the first of a class of antiobesity agents, the lipase inhibitors. We have previously shown that the combination of orlistat with a low-calorie diet is followed by a significant reduction in plasma Lp-PLA_2 activity as well as by an increase in the activity of HDL-associated enzyme (by 14% and 11% respectively) [7]. These changes were correlated with the changes in lipid and anthropometric values and were more pronounced when orlistat was combined with

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the lipid-lowering agent fenofibrate. More specifically, the reduction in plasma Lp-PLA_2 activity was positively correlated with the decreases in LDL-cholesterol and small, dense LDL subfraction concentrations as well as with the changes in boby mass index (BMI) values. On the other hand, the increase in HDL-associated enzyme activity showed a significant negative correlation with the reduction in triglyceride levels [7].

ESTROGEN REPLACEMENT AND THYROID SUBSTITUTION THERAPY

The effect of hormonal replacement therapy on the determination of future cardiovascular risk remains controversial [8-10]. Observational studies have shown that postmenopausal women exhibit significantly higher plasma activity of Lp-PLA_2 compared to premenopausal ones [11]. In addition, experiments in ovariectomized rats showed that the administration of estrogens significantly reduced the plasma activity of Lp-PLA_2 [12]. Taken together these results indicate that sex steroid hormones may play important roles in the regulation of the activity of this enzyme. In this context, Yoshimura T *et al.* have shown that estrogen replacement therapy significantly reduced the activity of Lp-PLA_2 (by approximately 25%) in a group of 8 otherwise healthy postmenopausal women [11]. This reduction was associated with a significant improvement in the overall lipid profile (reduction of total and LDL-cholesterol, increase in HDL- cholesterol) and thus the authors suggested that the estrogen-induced decrease in the concentration of LDL particles may represent the most important mechanism underlying the reduction in Lp-PLA_2 activity [11]. Similar results were obtained when mestranol, a steroid with estrogen-like activity, was given in adult men [13]. On the other hand, the administration of steroids with progesterone-like activity has the opposite effect since it increases the plasma activity of Lp-PLA_2 and may offset the potentially protective effect of estrogens on LDL metabolism and Lp-PLA_2 enzymatic activity [12].

Subclinical hypothyroidism is a common disorder that has been associated with an increased incidence of coronary heart disease [14,15]. In a previous study we showed that individuals with this disease are characterized by an adverse lipid profile (elevated total and LDL- cholesterol values, increased concentrations of triglycerides and apolipoprotein B) as well as by significant alterations in Lp-PLA_2 activities [16]. Indeed, patients with subclinical hypothyroidism display increased activity of total plasma Lp-PLA_2 and decreased activity of HDL-associated Lp-PLA_2 compared to healthy individuals [16]. Interestingly, the administration of thyroid substitution therapy and the resulting restoration of euthyroidism are accompanied by a significant increase in the activity of the HDL-associated enzyme, whereas the total plasma Lp-PLA_2 remains unaffected [16].

EFFECT OF ANTIHYPERTENSIVE AND GLUCOSE-LOWERING THERAPY ON Lp-PLA_2

So far, little is known about the relationship between Lp-PLA_2 activities and the presence of essential hypertension. In a previous study, Satoh K *et al.* showed that hypertensive patients may exhibit significantly higher activity of plasma Lp-PLA_2 compared to individuals with normal blood pressure values [17]. These findings were also supported by subsequent studies showing that women with pregnancy-induced hypertension had higher plasma Lp-PLA_2 compared to normotensive ones of the same gestational age [18,19]. Although the hormonal changes that take place during pregnancy complicate the interpretation of these later findings, all the above mentioned results, taken together, suggest a positive association between blood pressure values and plasma Lp-PLA_2 activity. However, it is well-known that hypertension is usually associated with the presence of other comorbid conditions (such as obesity, dyslipidemia and metabolic syndrome) known to affect the enzymatic activity of Lp-PLA_2. Thus, it is far from clear whether the alterations in Lp-PLA_2 activity that characterize the hypertensive individuals are due to hypertension per se or must be attributed to the presence of other comorbidities. In any case, studies in hypertensive individuals have shown that the conventional doses of various antihypertensive medications (such as eprosartan, varnidipine, valsartan, lacidipine, atenolol, benazepril and indapamide), although sufficiently reduce both systolic and diastolic blood pressure values, have no significant effect on plasma and HDL-associated Lp-PLA_2 activities [20-22]. It must be noted that none of the above-mentioned drugs significantly affected serum lipids and lipoproteins except for indapamide that induced a slight increase in total cholesterol and triglyceride values [22].

The effect of glycaemic control on the Lp-PLA_2 activity remains controversial. Thus, some studies indicated that subjects with non-insulin dependent diabetes mellitus are characterized by increased activity of plasma Lp-PLA_2 compared to non-diabetic individuals [23,24]. However, it must be noted that in these studies no adjustments for potential confounders (such as BMI, smoking habits and lipid levels) were performed. On the other hand, Iwase M *et al.* found no differences in plasma Lp-PLA_2 activity between type 2 diabetic patients and control individuals with similar lipid values [25]. The picture seems to be more clear in individuals with insulin-dependent diabetes mellitus. All the studies conducted in this patient group revealed increased plasma Lp-PLA_2 activities compared to non-diabetic subjects [26-28], a finding that can be attributed to the preferential enrichment of electronegative LDL particles in enzymatic activity [29]. Interestingly, the optimization of glycaemic control with insulin therapy reduced the proportion of electronegative LDL as well as the enzymatic activity associated with electronegative LDL particles in this patient population [29]. On the contrary, the effect of oral hypoglycaemic drugs on Lp-PLA_2 activities remains ill defined. Thus, a study conducted in type 2 diabetic patients revealed no effect of pioglitazone and glipizide on plasma Lp-PLA_2 activity [30], whereas another study showed that pioglitazone administration may enhance plasma Lp-PLA_2 activity [31]. It is clear that further studies are needed to delineate the role of glucose-lowering therapy in the modulation of Lp-PLA_2 activities.

EFFECT OF LIPID-LOWERING THERAPY ON Lp-PLA_2 MASS AND ACTIVITY

Statins

Statins represent the most widely used class of hypolipidemic drugs. Several large-scale, placebo-controlled trials

have shown that the administration of these drugs is followed by an impressive reduction in the future cardiovascular risk in both primary and secondary prevention populations [32,33]. Although the reduction in LDL-cholesterol concentration may represent the most important cardioprotective effect of these drugs, it has been proposed that statins also exert additional lipid-independent mechanisms of action that may alter the natural history of the atherosclerotic process [34]. Several years ago, we showed for the first time in the literature that atorvastatin (20mg/day) sufficiently reduces plasma Lp-PLA_2 activity in patients with primary dyslipidemias of types IIA and IIB (by 28.6 and 42.4%, respectively) [35]. More specifically, atorvastatin significantly reduced the enzyme activity associated with the VLDL and IDL subfraction as well as with each LDL subfraction in both patient groups [35]. Remarkably, a significant reduction was also observed in the enzyme activity (expressed either per milligram of protein or per milligram of lipoprotein mass) in the dense LDL subfractions (ie, LDL-4 and LDL-5); this phenomenon was not observed in the other apoB-containing lipoprotein subfractions. On the other hand, atorvastatin had no significant effect on the HDL-associated activity of the enzyme in both patient groups. Since in this study atorvastatin did not reduce the production of the enzyme by peripheral blood monocyte-derived macrophages, it can be hypothesized that the enhancement in the rate of LDL removal from the circulation may represent the main mechanism by which atorvastatin reduces plasma Lp-PLA_2 activity. This is also supported by the positive correlation observed between the reduction of plasma LDL-cholesterol levels and that of plasma Lp-PLA_2 activity [35]. In a subsequent study, we found that the effect of rosuvastatin on Lp-PLA_2 activities was similar to that of atorvastatin [36]. More specifically, the administration of rosuvastatin in patients with type IIA dyslipidemia resulted in a significant parallel decrease in plasma Lp-PLA_2 mass and activity. Lipoprotein subfractionation revealed that these changes were due to the decrease in enzyme mass and activity in all LDL subfractions. Finally, the drug had no effect on HDL-associated enzymatic activity and mass [36]. Our observation that the reduction in plasma Lp-PLA_2 activity after atorvastatin and rosuvastatin therapy is closely related to their LDL-lowering effects implies that Lp-PLA_2 lowering may represent a class effect of statins. In this context, in another study we showed that conventional doses of fluvastatin also reduce plasma Lp-PLA_2 activity (by 25%) without affecting the HDL-associated enzyme [22]. On the contrary, other studies revealed inconsistent results on the effect of the other statins (such as lovastatin, pravastatin and simvastatin) on the Lp-PLA_2 activity [25,37-41].

Fibrates

Fibrates represent an important class of hypolipidemic drugs. These compounds exert their metabolic effects by modulating the expression of several genes involved in lipoprotein metabolism. In addition, numerous studies suggest that fibrates may also affect the progression of the atherosclerotic process by several lipid-independent mechanisms [42]. In a previous study, we tested the effect of micronized fenofibrate administration on the Lp-PLA_2 activities in patients with dyslipidemias of type IIA, IIB and IV [43]. Fenofibrate induced a significant decrease in plasma Lp-PLA_2 activities in all patient groups. Interestingly, in Type IIA patients, this reduction was mainly due to a fall in enzyme activity associated with the dense LDL subspecies, whereas in Type IIB and Type IV patients, it was due to the decrease in Lp-PLA_2 activity associated with both the VLDL+ IDL and dense LDL subfractions. More importantly, and in contrast to that observed after statin administration, fenofibrate therapy in Type IIB and Type IV patients significantly increased the HDL-associated Lp-PLA_2 due to the increase in enzyme activity associated with the HDL-3c subfraction [43]. To shed more light in these effects Saougos V *et al.* concomitantly determined Lp-PLA_2 activity and mass in both plasma and HDL before and after fenofibrate administration in 50 subjects with type IV dyslipidemia [36]. Interestingly, fenofibrate reduced both enzyme mass and enzymatic activity in total plasma. Lipoprotein subfraction analysis revealed that fenofibrate significantly reduced the Lp-PLA2 activity and mass associated with the VLDL+IDL subfraction. In addition, fenofibrate did not affect the activity, and mass of the enzyme associated with large and intermediate LDL particles (LDL-1 to LDL-4); however, it significantly reduced the enzyme activity and mass associated with LDL-5. HDL subfractionation revealed that the drug significantly increased both the enzymatic activity and mass associated with HDL-3c particles without affecting the specific activity associated with this subfraction [36].

Other studies confirmed the efficiency of fenofibrate in reducing plasma Lp-PLA_2 mass [44], and showed that this may represent a property of all fibric acid derivatives, since ciprofibrate displays similar to fenofibrate behavior [22]. Furthermore, although the addition of orlistat to fenofibrate has an additive effect in terms of plasma Lp-PLA_2-lowering [7], the recently published DIACOR (Diabetes and Combined Lipid Therapy Regimen) study revealed that the simvastatin-fenofibrate combination is no more effective than either form of monotherapy [45].

Ezetimibe

Ezetimibe is the first member of a new class of selective cholesterol absorption inhibitors. Recently published data indicate that ezetimibe inhibits the transport of cholesterol across the brush border of the intestinal wall by inhibiting the function of Niemann-Pick C 1-like protein. This inhibition decreases the cholesterol content of hepatocytes and results in an upregulation of LDL receptors which, in turn, reduces the serum concentrations of LDL-cholesterol [46]. In a previous study we have shown that ezetimibe significantly decreases total plasma Lp-PLA_2 activity and mass [36]. Lipoprotein subfractionation revealed that this reduction was due to a decrease in enzyme mass and activity associated with all apolipoprotein B-containing lipoprotein subfractions. On the other hand, ezetimibe also induced a small but significant reduction in the HDL-associated Lp-PLA_2 mass and activity; this reduction was exclusively attributed to a decrease in the enzymatic activity and mass associated with the dense HDL-3c subfraction [36].

Niacin

Niacin is a hypolipidemic drug that has long been used in the treatment of dyslipidemia and cardiovascular disease. So far, no study has tested the effect on niacin monotherapy on

Lp-PLA_2 measures. However, Kuvin JT *et al.* have recently shown that the addition of extended-release niacin to ongoing medical therapy in individuals with stable coronary disease (all patients in this study were already on statin therapy) results in a significant improvement in lipid profile (reduction in triglyceride values and increase in HDL-cholesterol concentrations) that was followed by a shift in lipoprotein subfraction distribution (for both LDL and HDL) towards larger and more buoyant particles. Interestingly, these changes were accompanied by a significant decrease (by 20%) in total plasma Lp-PLA_2 mass [47].

MARINE n-3 POLYUNSATURATED FATTY ACIDS

There is accumulating evidence that fish intake may protect against the development of cardiovascular disease. This is believed to be due to the content of long-chain n-3 polyunsaturated fatty acids (PUFA) in fish, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A recent study in individuals admitted to elective coronary angiography because of suspected coronary artery disease suggested that the plasma levels of Lp-PLA_2 mass are independently and inversely associated with the content of EPA in adipose tissue [48]. Although these results support the view that marine n-3 PUFA intake may reduce the serum concentrations of Lp-PLA_2, another study in healthy adults revealed that the administration of either high or moderate doses of these compounds has no effect on plasma levels of Lp-PLA_2 [49].

LDL APHERESIS

LDL apheresis is a process used to remove excessive LDL-cholesterol in individuals resistant to diet and medical therapy (typically patients with either homozygous or heterozygous familial hypercholesterolemia). LDL apheresis is a weekly or bimonthly process that in addition to LDL-cholesterol may also remove other mediators of systemic inflammation. In a study included 8 dyslipidemic patients, Moriarty PM *et al.* found that LDL-cholesterol was reduced by approximately 60% immediately after LDL apheresis (acute reduction) [50]. Before initial treatment, the mean baseline LDL-cholesterol level was 262 mg/dl. Three months after the initial measurement, before the last LDL apheresis treatment was administered, the mean LDL-C level was 226 mg/dl, representing an overall 14% reduction. After an initial apheresis treatment, the mean Lp-PLA_2 reduction was 32%. Unlike LDL-cholesterol, however, Lp-PLA_2 levels did not rebound to pretreatment levels, with overall levels reduced by 22% over the course of 3 months of treatment ($p< 0.003$). Interestingly, reductions in LDL-cholesterol and Lp-PLA_2 were not significantly correlated [50], suggesting that LDL apheresis may reduce the plasma concentration of Lp-PLA_2 by lipid-lowering-independent mechanisms [50]. The authors proposed that the removal of oxidized LDL particles by LDL apheresis system may represent the most important mechanism for the acute Lp-PLA_2 reduction [50].

CONCLUSION

Several drugs commonly used in everyday clinical practice for the prevention or treatment of cardiovascular disease may significantly modify Lp-PLA_2 mass and activities. The knowledge of these changes may help clinicians to design safe and effective therapeutic strategies for the prevention and treatment of atherosclerotic disease

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